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Comunicazioni Libere



C1

Impaired inhibitory control of saccadic eye movements in cervical dystonia: an eye tracking study

Federico Carbone, P. Ellmerer, S. Spielberger, S. Bösch, K. Seppi, W. Poewe, A. Djamshidian

Department of Neurology, Medical University Innsbruck, Innsbruck, Austria

Background: The pathophysiological mechanisms behind cervical dystonia (CD) are to date still unclear. CD has traditionally been described as a basal ganglia disorder but more recent evidence points towards a network disorder model, where several nodes other than the basal ganglia are involved [2]. Impairment of the cerebellum and superior colliculus [3], two structures heavily involved in oculomotor control, has been described in patients with cervical dystonia.

Objective: The aim of the present study was to assess the oculomotor performance in cervical dystonia patients using eye tracking saccade paradigms.

Methods: We recruited a total of 49 participants in our study (33 patients with CD and 16 age and gender matched healthy controls). Using a video-based eye tracker three different paradigms were employed. The overlap prosaccade task assesses the automatic visuomotor response (saccade to the target). In the antisaccade task, volitional oculomotor control is examined (saccade opposite to the target [1]). The countermanding task explores the saccadic response inhibition (refrain from saccade to target when the stop signal appears). For each paradigm saccadic amplitude, saccadic reaction times and error rates were recorded.

Results: CD patients showed a worse performance in all three paradigms compared to controls. CD patients showed a higher rate of premature saccades in the overlap prosaccade task, a higher directional error rate in the antisaccade task, and a higher rate of failed inhibition in the countermanding task.

Additionally, saccadic reaction times in the correctly performed antisaccade task were significantly longer in CD patients.

Conclusions: The present study highlights a loss of saccadic inhibitory control in CD patients.

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C2

Idiopathic upper limb dystonia - Time for a better understanding

*Tommaso Ercoli*¹, R. Pellicciari², G. Fabbrini^{3,4}, G. Ferrazzano⁴, M.M. Mascia¹, R. Eleopra⁵, A. Albanese⁶, R. Erro⁷, P. Barone⁷, L. Avanzino^{8,9}, R. Ceravolo¹⁰, M. Esposito¹¹, L. Bertolasi¹², C.L. Scaglione¹³, A.R. Bentivoglio^{14,15}, M.C. Altavista¹⁶, F. Bono¹⁷, P. Girlanda¹⁸, A. Pisani¹⁹, M.S. Cotelli²⁰, B. Minafra²¹, A. Castagna²², M. Zibetti²³, S. Misceo²⁴, L. Magistrelli^{25,26}, G. Cossu²⁷, M. Coletti Moja²⁸, A. Berardelli^{3,4}, G. Defazio¹

¹Dept. of Medical Science and Public Health, Institute of Neurology, University of Cagliari, Cagliari, Italy

²Dept. of Basic Science, Neuroscience and Sense Organs, Aldo Moro University, Bari, Italy

³IRCCS Neuromed, Pozzilli (IS) Italy

⁴Dept. of Human Neurosciences, Sapienza University of Rome, Rome, Italy

⁵Neurological Unit 1, Fondazione IRCSS. Istituto Neurologico “Carlo Besta”, Milan, Italy

⁶Dept. of Neurology, IRCCS Istituto Clinico Humanitas, Rozzano (Milan) Italy

⁷Dept. of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, University of Salerno, Italy

⁸Ospedale Policlinico San Martino - IRCCS, Genoa, Italy

⁹Dept. of Experimental Medicine, Section of Human Physiology, University of Genoa, Genoa, Italy

¹⁰Dip.to di Medicina Clinica e Sperimentale, Università di Pisa. Pisa, Italy

¹¹Dept of Neurosciences, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy

¹²Neurologic Unit, University Hospital, Verona, Italy

¹³IRCCS Institute of Neurological Sciences, Bologna, Italy

¹⁴Fondazione Policlinico Universitario A. Gemelli – IRCCS, Rome, Italy

¹⁵Institute of Neurology, Università Cattolica del Sacro Cuore, Rome, Italy

¹⁶Neurology Unit, San Filippo Neri Hospital ASL Roma 1, Roma, Italy

¹⁷Center for Botulinum Toxin Therapy. Neurologic Unit. A.O.U. Mater Domini, Catanzaro, Italy

¹⁸Dept. of Clinical and Experimental Medicine, University of Messina, Messina, Italy

¹⁹Neurology, Dept. of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

²⁰Neurologia, Azienda Socio-Sanitaria Territoriale Esine, Brescia, Italia

²¹Mondino Foundation IRCCS, Parkinson Disease and Movement Disorders Unit, Pavia, Italy

²²IRCCS, Fondazione Don Carlo Gnocchi, Milan, Italy

²³Dept. of Neuroscience Rita Levi Montalcini, University of Turin, Turin, Italy

²⁴Neurologic Unit, San Paolo Hospital, Bari, Italy

²⁵Movement Disorders Centre, Neurology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

²⁶PhD program in Clinical and Experimental Medicine and Medical Humanities, University of Insubria, Varese, Italy

²⁷Neurology Service and Stroke Unit, Department of Neuroscience, AO Brotzu, Cagliari, Italy

²⁸Neurology Unit, Umberto I Hospital, Turin, Italy

Introduction: Idiopathic adult-onset upper limb dystonia (ULD) may have focal onset or may be site of spread of dystonia arising in other body parts [1]. A remarkable feature of ULD is task-specificity, even though ULD may also develop as a non-task specific dystonia. No large study has evaluated the phenomenological spectrum of ULD.

Objective: This cross-sectional study examined the clinical and demographic features of ULD related to onset site, spread, and task-specificity in a large cohort of Italian patients.

Methods: Data were obtained from the Italian Dystonia Registry [2].

Results: We enrolled 182 patients with idiopathic adult-onset ULD, (92 men/90 women aged 59.4+15.05 years). Focal ULD at onset was reported in 107 patients, segmental onset with upper limb (UL) involvement in 35 patients, and onset in other body regions with later spread to the UL in 40 patients. The three groups did not differ for age at evaluation, educations, age at dystonia onset, and frequency of sensory trick and family history of dystonia. However, men predominated in the group with focal ULD at onset; the latter was also characterized by a greater frequency of task-specificity at onset; by contrast, the group with segmental ULD and focal onset elsewhere was characterized by higher age at UL involvement and greater frequency of tremor and cardiovascular diseases. Age of UL involvement was significantly lower in patients with task-specific ULD than in those who presented with non-task-specific ULD (43+15 vs. 53+16 years, $p<0.0001$). Among the 107 patients with focal ULD onset, dystonia spread to near sites (most frequently neck and face) in 35 patients over 13.5+13.7 years. Cox regression analysis revealed a significant lower risk of spread in patients who presented with task-specificity.

Conclusions: This study details the clinical presentation of adult-onset ULD with particular reference to onset site, spread, and occurrence of task-specificity.

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C3

A mutation in a novel lysosomal gene causes adult-onset generalized dystonia in an Italian patient

Edoardo Monfrini¹, F. Cogiamanian¹, S. Salani¹, L. Straniero², A. Bordoni¹, M. Aureli³, M. Garbellini¹, L. Borellini¹, E. Carsana³, S. Corti¹, G.P. Comi¹, N. Bresolin¹, S. Duga², A. Di Fonzo¹

¹Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy; Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

²Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI) Italy; Humanitas Clinical and Research Center, Rozzano (MI) Italy

³Department of Medical Biotechnology and Translational Medicine, University of Milan, Segrate, (MI) Italy

Introduction: The advent of NGS provided an impressive step forward in the identification of the genetic causes of inherited dystonias, leading to the description of many novel genes in the last ten years. The lysosomal pathway has been recently associated with the pathogenesis of several forms of inherited dystonias, such as in VPS16- and VAC14-related diseases and in some neurodegenerations with brain iron accumulations (i.e. Kufor-Rakeb and BPAN).

Objectives: Our aim is to find the genetic cause of adult-onset generalized dystonia in an Italian male patient.

Methods: A movement disorders specialist performed a neurological examination of the proband. The subject underwent brain MRI and neurophysiological studies. Blood samples were collected. Skin biopsy was obtained from the proband through a punch on the ventral part of the left forearm. Whole-exome sequencing (WES) was performed on genomic DNA of the patient. Functional studies (immunoblotting, enzymatic activities, and electron microscopy) were conducted on patient-derived fibroblasts to prove mutation pathogenicity.

Results: The family of the proband lived in a very small village in Southern Italy for many generations. The proband was born at term after an uneventful pregnancy. All the stages of psychomotor development were normal. Reportedly, from the age of 30 years, the proband developed involuntary dystonic movements, initially affecting the right limbs. After 5 years from disease onset, dystonia became generalized, involving the trunk, limbs, neck (torticollis), and vocal cords (until complete anarthria). Brain MRI displayed atrophy of basal ganglia and marked symmetrical hypointensity in T2- and T2*-weighted sequences in substantia nigra, red nucleus, nigrostriatal projections, and globus pallidus. The suspected consanguinity of the parents suggested a homozygous mutation as the cause of the disease. WES was performed on the proband. No pathogenic mutations were found in known disease genes for inherited dystonias and NBIA. A filtering analysis for rare (allele frequency <0.5%) homozygous variants with protein impact was performed. Only one candidate variant in a gene involved in lysosomal and autophagic functions was identified. Segregation analysis in the family was consistent with autosomal recessive inheritance. Functional studies on patient-derived fibroblasts showed a striking defect of lysosomal and autophagic function.

Conclusions: This work represents the first association of a mutation in a novel lysosomal gene with a form of adult-onset generalized dystonia and provides strong in vitro evidence of mutation

pathogenicity. The identification of this novel gene confirms the important role of lysosomes in dystonia pathogenesis.

C4

Slowly and rapidly progressive Parkinson's disease: a multicenter study on clinical heterogeneity

*Alberto Romagnolo*¹, A. Merola², A.K. Dwivedi³, A. Padovani⁴, D. Berge⁶, P.J. Garcia-Ruiz⁷, M. Fabbri^{1,8}, C.A. Artusi¹, M. Zibetti¹, M.G. Rizzone¹, A. Pilotto^{4,9}, S. Bonacina⁴, F. Morgante^{10,11}, K. Zeunere⁵, C. Griewing⁵, E. Schaeffer⁵, F. Rodriguez-Porcel¹², M. Kauffman¹³, P. Turcano¹⁴, L.M. de Oliveira¹⁵, G. Palermo¹⁶, E. Shanks¹⁷, F. Del Sorbo¹⁸, S. Bonvegna¹⁸, R. Savica¹⁴, R.P. Munhoz¹⁹, R. Ceravolo¹⁶, R. Cilia¹⁸, A.J. Espay¹⁷, L. Lopiano¹

¹Department of Neuroscience Rita Levi Montalcini, University of Turin, Turin, Italy

²Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

³Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA

⁴Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

⁵Department of Neurology, Christian-Albrecht-University, Kiel, Germany

⁶Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany

⁷Department of Neurology, Movement Disorders Unit, Fundacion Jimenez Diaz, Universidad Autonoma de Madrid, Madrid, Spain

⁸Laboratory of Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

⁹Parkinson's Disease Rehabilitation Centre, FERB ONLUS – S. Isidoro Hospital, Trescore Balneario (BG), Italy

¹⁰Neurosciences Research Centre, Molecular and Clinical Sciences Institute, St George's University of London, London, UK

¹¹Dipartimento di Medicina Clinica e Sperimentale, Università di Messina, Messina, Italy

¹²Department of Neurology, Medical University of South Carolina, Charleston, SC, USA

¹³Consultorio y Laboratorio de Neurogenética, Centro Universitario de Neurología "José María Ramos Mejía" y Division Neurología, Hospital J.M. Ramos Mejia, Facultad de Medicina, UBA, Buenos Aires, Argentina

¹⁴Department of Neurology, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN, USA

¹⁵Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, University Health Network, Toronto Western Hospital, Division of Neurology, University of Toronto, Toronto, Ontario, Canada

¹⁶Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

¹⁷Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

¹⁸Parkinson Institute, ASST Gaetano Pini-CTO, Milan, Italy

¹⁹Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Krembil Brain Institute, Toronto, Ontario, Canada

Introduction: Parkinson's disease (PD) presents with a heterogeneous course, ranging from very slowly progressive (VSP-PD) to rapidly progressive (RP-PD) variants.

Objective: To determine whether VSP-PD and RP-PD variants are distinguished by different demographic, clinical, and habits/occupational factors.

Methods: We retrospectively evaluated 365 patients (210 VSP-PD and 155 RP-PD). VSP-PD were defined as Hoehn and Yahr (H&Y) stage ≤ 3 , preserved cognitive function, and Schwab and England (S&E) score ≥ 70 after ≥ 20 years of PD (or ≥ 10 years if older than 60 at PD onset); RP-PD as H&Y > 3 , S&E score < 70 , and cognitive impairment within 10 years from PD onset. We performed between-group analysis of demographic, habits/occupational, and clinical features at baseline and follow-up, and unsupervised data-driven analysis of the clinical homogeneity of VSP-PD and RP-PD.

Results: At onset, VSP-PD subjects were younger (48.7 ± 10.6 vs. 69.2 ± 7.8 years), had lower severity (UPDRS-III score 9.83 ± 5.10 vs. 22.94 ± 10.70) and greater asymmetry (96.0% vs. 78.9%) of motor symptoms, and lower prevalence of depression (29.3% vs. 60.0%) than RP-PD ($p < 0.001$). VSP-PD was associated with active smoking ($p < 0.05$) and physical activity ($p < 0.001$), RP-PD with agricultural occupation ($p < 0.05$). At follow-up, VSP-PD showed higher prevalence of motor complications, and higher dosage of dopaminergic medications ($p < 0.001$); RP-PD higher prevalence of depression, hallucinations, dysautonomia, and RBD ($p < 0.001$). Data-driven analysis confirmed the independent clustering of VSP-PD and RP-PD, with age at onset emerging as a critical discriminant between the two groups (< 46 -year-old vs. > 68 -year-old); data-driven analysis also confirmed the association between VSP-PD and asymmetric clinical presentation involving the upper or lower limb, UPDRS-III at onset < 10 , and physical activity, and between RP-PD and symmetric clinical presentation involving both upper and lower limbs, UPDRS-III at onset > 20 , agricultural occupation, and history of depression.

Conclusions: There are differential distributions of demographic, clinical, age at PD onset, and habits/occupational factors among phenotypic extremes in PD.

C5

Emotional avoidance in functional movement disorders

Angela Marotta¹, M. Fiorio¹, B. Demartini^{2,3,4}, M. Riello¹, G. Tecilla¹, C. Dallochio⁵, M. Tinazzi¹

¹Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

²Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milano, Italy

³Unità di Psichiatria II, A.O. San Paolo, ASST Santi Paolo e Carlo, Milano, Italy

⁴Aldo Ravelli Research Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Milan, Italy

⁵Department of Medical Area, Neurology Unit, ASST Pavia, Italy

Background: Functional movement disorders (FMD) are characterized by motor symptoms that disappear with distraction. FMD often present with emotional difficulties, like depression or anxiety [1]. It has been recently proposed that emotions may act as risk and maintaining factor by interacting with other cognitive functions, like attention.

Aim: The current study tackled this issue by investigating the effect of emotions on attention in FMD.

Methods: 25 FMD and 25 healthy controls (HC) attended the study. A dot-probe task was used to measure emotion-related attentional bias. In each trial, a pair of faces, one emotional (happy, angry or sad) and the other neutral, was displayed on a screen. Soon after, a dot appeared in the same location previously occupied by one of the faces [2]. Participants had to press a left or right key, according to the location of the dot. Faster or slower reaction times for dot appearing in the same location as the emotional face are suggestive of attentional bias toward (i.e., hypervigilance) or away (i.e., avoidance) from emotional stimuli, respectively. All participants underwent alexithymia assessment. Patients were also tested for depression, anxiety and health status.

Results: FMD exhibited attentional bias away from emotions compared to HC. Moreover, FMD showed a specific attentional bias away from sad faces, which significantly correlated with quality of life. Alexithymia was not different between groups.

Discussion: Our study reveals a specific effect of emotions on attention in FMD, likely involving avoidance of sadness. Moreover, attentional avoidance of sadness seems to support the perception of a good quality of life, in spite of the difficulties related to the disease. Future studies are needed to disentangle role of attentional avoidance of sadness as risk and maintaining factor in FMD.

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C6

Intrinsic functional connectivity correlates of RBD in cognitively unimpaired drug-naïve Parkinson's disease patients

*Francesco Paolo Bonifacio*¹, R. De Micco¹, M. Siciliano^{1,2}, F. Di Nardo^{1,2}, S. Satolli¹, G. Caiazzo¹, F. Esposito³, G. Tedeschi¹, A. Tessitore¹

¹Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Napoli, Italy

²Neuropsychology Laboratory, Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

³Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, University of Salerno, Baronissi (SA), Italy

Introduction: REM Behavioural Disorder (RBD) is characterized by lack of skeletal muscle atonia during REM sleep and it develops in around 50% of Parkinson's disease (PD) patients. PD patients with RBD present an increased risk of worse motor progression and dementia over the disease course.

Objectives: To investigate intrinsic brain intra and inter-network connectivity correlates of RBD in a cohort of cognitively unimpaired drug-naïve PD patients and to correlate neuroimaging findings to clinical and cognitive measures.

Methods: 3T MRI images of 56 drug-naïve PD patients (25 PD-RBD and 31 PD-no-RBD) were acquired. RBD presence and severity were assessed by means of a clinical interview and the RBD Screening questionnaire (RBDSQ). Single-subject and group-level independent component analysis was used to investigate intra and inter-network functional connectivity differences within the default mode (DMN), fronto-parietal (FPN), salience (SN) and executive control (ECN) networks between patients sub-groups. Finally, linear regression analysis was used to investigate correlations between imaging and clinical data.

Results: Compared to PD-no-RBD patients, PD-RBD showed an increased connectivity within the SN and the ECN as well as a decreased connectivity within the FPN. Within the DMN, PD-RBD exhibit both an increased and a decreased connectivity compared to PD-no-RBD. This imaging pattern was found to be correlated with both RBD severity and cognitive outcomes in PD patients.

Conclusions: Our findings demonstrated that an abnormal intrinsic brain connectivity within and between the major neurocognitive networks may represent a potential neural correlate of RBD symptoms and severity in early PD patients. This aberrant connectivity is correlated with cognitive outcomes even in the absence of cognitive impairment and may potentially be proposed to develop a sensitive and early biomarker of dementia in PD.

C7

Distinctive blood alpha-synuclein profile and lysosomal alterations in sporadic and GBA1-related Parkinson's Disease

Micol Avenali^{1,2}, S. Cerri³, G. Ongari³, C. Pacchetti⁴, C. Tassorelli^{1,2}, E.M. Valente^{5,6}, F. Blandini³

¹Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

²Neurorehabilitation Unit, IRCCS Mondino Foundation, Pavia, Italy

³Laboratory of Cellular and Molecular Neurobiology, IRCCS Mondino Foundation, Pavia, Italy

⁴Parkinson's Disease and Movement Disorders Unit, IRCCS Mondino Foundation, Pavia, Italy

⁵Laboratory of Molecular Genetics and Cytogenetics, IRCCS Mondino Foundation, Pavia, Italy

⁶Department of Molecular Medicine, University of Pavia, Pavia, Italy

Objectives: Mutations in the GBA1 gene, encoding the lysosomal enzyme glucocerebrosidase (GCase), are the most frequent risk factor for Parkinson's disease (PD). The aim of this study is to characterize the blood profile of alpha-synuclein and the main lysosomal proteins of PD subjects carrying GBA1 mutations (GBA-PD), as well as their clinical features.

Methods: In this study we recruited 14 GBA-PD, 25 PD subjects without GBA1 mutations (iPD) and 31 healthy subjects (HC). We evaluated alpha-synuclein levels in peripheral blood lymphocytes, plasma exosomes and whole plasma and lysosomal alterations in lymphocytes by analyzing the expression of the main GCase-related proteins (cathepsin D, LAMP1, LIMP2, Saposin C). Moreover, we assessed motor and non-motor signs in all subjects by means of clinical questionnaires and scales (MoCA, UPSIT, RBDsq, UPDRS-III, SCOPA-AUT and BDI).

Results: GCase activity was significantly affected in PD-GBA patients compared with iPD and HC. In GBA-PD, decreased GCase activity was associated with higher alpha-synuclein levels in lymphocytes compared with iPD. Both GBA-PD and iPD patients showed increased levels of exosomal alpha-synuclein; whereas plasma exosomal α -syn/total α -syn ratio was significantly higher in iPD than in GBA-PD. Interestingly, a significant inverse correlation between GCase activity and plasma exosomal α -syn/total α -syn ratio was detected, suggesting a potential mechanism by which changes in GCase activity may affect the α -synuclein release. The GBA-PD group also displayed lower Saposin C levels and higher LIMP-2 levels compared to iPD. A prevalence of non-motor features were also observed in GBA-PD group compared to iPD.

Conclusions: This study confirms the presence of distinctive lysosomal alterations related to GCase enzyme deficiency in GBA-PD group compared to iPD and highlights that differences also exist in the blood alpha-synuclein profile between patient's group. These features could be distinctive of GBA-related condition and potentially trigger pathological conversion.

C8

Human induced pluripotent stem cells (iPSCs) as a model for the study of neural development in Parkinson's disease patients carrying GBA mutation

*Francesco Motolese*¹, A. Casamassa³, A. Vescovi³, V. Di Lazzaro¹, J. Rosati³, M. Marano^{1,2}

¹Neurology, Neurobiology and Neurophysiology Unit, University Campus Bio-Medico of Rome, Rome, Italy

²The Alberto Sordi Foundation, Università Campus Bio-Medico di Roma, Rome, Italy

³IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Objective: To study in vitro neural development of human induced pluripotent stem cells (iPSCs) [1] derived from fibroblasts of Parkinson's disease (PD) patients carrying glucocerebrosidase gene (GBA) mutation.

Background: iPSCs technology allows generating in vitro models that accurately reflect the human disease, through a source of patient's specific cells (i.e. fibroblasts) [2]. Mutations of the GBA gene are recognized as the most common risk factor for PD [3].

Methods: Dermal fibroblast derived from two PD patients carrying GBA mutation (variant p.E326K) [4] and two healthy donors were reprogrammed into iPSCs through virus-free and feeder-free protocol. All iPSCs clones, showing an uniform flat morphology, were characterized for their pluripotency, both in vitro through embryoid bodies formation and in vivo through teratoma formation assay. A new protocol was optimized to obtain iPSCs derived Neural Stem Cells (NSCs) able to spontaneously differentiate in neural cells such as astrocytes, oligodendrocytes and neurons.

Results: We successfully reprogrammed the fibroblasts into iPSCs. Neural stem cells were obtained from iPSCs lines. We analyzed these cell lines at morphological and molecular level to underline functional and biochemical differences possibly related to the mutation.

Conclusions: NSCs were obtained from two PD patients carrying GBA mutations and two healthy donors. These "induced" Neural Stem Cells had the same properties of brain derived NSCs and could differentiate in all of three neural lineages (neurons, astroglia and oligodendrocytes). Disease specific stem cells offer the unprecedented opportunity to study in vitro tissue formation and pave the way for the development of molecules reverting pathological phenotype. In this regard, since GBA mutations impair endolysosomal trafficking, likely favoring alpha-synuclein accumulation, iPSCs could be used as models to better understand GBA mutations role in PD and to study targeted treatments aimed at counteracting disease progression [5].

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C9

Progression of cardiovascular autonomic failure in Parkinson's disease from early disease stage: a prospective study

Francesca Baschieri^{1,2}, L. Sambati^{1,2}, P. Guaraldi^{2,3}, G. Barletta^{1,2}, A. Cecere^{1,2}, P. Cortelli^{1,2}, G. Calandra Buonauro^{1,2}

¹Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italia

²IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italia

³Neurology Outpatient Clinic, Department of Primary Care, Local Health Authority of Modena, Modena, Italy

Introduction: Orthostatic hypotension (OH) is reported in approximately 30% of Parkinson's disease (PD) patients [1]. However, prevalence of neurogenic OH (due to cardiovascular autonomic failure) is unknown, especially at early disease stage.

Objective: To describe changes of cardiovascular autonomic function objectively and comprehensively assessed in PD patients from early disease stage.

Methods: We analysed cardiovascular reflex tests (CRTs) of the first 90 PD patients recruited in the prospective observational study "Bologna motor and non-motor prospective study on Parkinsonism at onset". Each patient underwent a full neurological workup including CRTs (head up tilt test; Valsalva manoeuvre; deep breathing; cold face test and isometric exercise) performed according to standardized procedures [2] at baseline (T0) and after 16 months follow-up (T1). A group of 50 age- and sex-matched controls was used for comparison.

Results: At T0 (56 males, mean age 61±10 years, disease duration 19±9 months, UPDRS III 15±7) neurogenic OH was detected in 3/90 (3.3%) patients. Overshoot during Valsalva manoeuvre and systolic blood pressure (BP) increase to cold face test and isometric exercise were significantly impaired in PD ($p<0.05$ vs controls). At T1 (UPDRS III 18±8) neurogenic OH was recorded in 6/90 (6.6%) patients. Abnormal responses to CRTs observed at T0 were confirmed at T1. In addition, systolic BP in phase II of Valsalva manoeuvre and diastolic BP responses to isometric exercise became significantly impaired compared to controls ($p<0.05$).

Conclusions: In our PD cohort at early disease stage, neurogenic OH was not common at baseline nor after 16 months. However, we observed a progression in cardiovascular autonomic dysfunction at T1. CRTs are necessary to detect neurogenic OH and progressively evaluate cardiovascular autonomic function. Among CRTs, the Valsalva manoeuvre proved to be the most sensible test to track autonomic dysfunction in this cohort.

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C10

Ultra-high field imaging of the substantia nigra in REM sleep behavior disorder: preliminary data from a three years clinical and radiological follow-up

*Nicole Campese*¹, E. Del Prete¹, D. Frosini¹, G. Donatelli², M. Costagli³, L. Biagi⁴, M. Godani⁵, C. Pacchetti⁶, M. Terzaghi⁶, P. Cortelli⁷, D. Arnaldi⁸, E. Bonanni¹, M. Tosetti⁴, U. Bonuccelli¹, M. Cosottini², R. Ceravolo¹

¹Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

²Neuroradiology Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

³IMAGO7 Research Foundation, Pisa, Italy

⁴IRCCS, Stella Maris, Pisa, Italy

⁵Neurology Unit, Sant'Andrea Hospital, La Spezia, Italy

⁶IRCCS C. Mondino, National Neurological Institute, Pavia, Italy

⁷DIBINEM Alma Mater Studiorum, University of Bologna, Bologna, Italy; IRCCS Istituto delle Scienze Neurologiche AUSL Bologna, Bologna, Italy

⁸IRCCS Azienda Ospedaliera Universitaria San Martino, Genova, Italy

Introduction: Patients with idiopathic rapid eye movement sleep behavior disorder (RBD) have an increased risk of developing Parkinson's Disease (PD) and atypical parkinsonism [1]. Evidence of functional or structural abnormalities in the nigrostriatal pathways may be detected in these patients, thus increasing the risk of motor phenoconversion [2]. Loss of dorsolateral nigral hyperintensity (nigrosome [1]) has been reported in up to 60% of RBD patients [3] but its role in predicting clinical outcomes has not been clarified yet.

Objective: To prospectively evaluate clinical outcomes in RBD and their association with nigrosome [1] abnormalities.

Methods: Fourteen patients with polysomnography-proven RBD underwent ultra-high field (7T) susceptibility weighted imaging at baseline; seven of them repeated a 7T MRI scan after three years follow-up. MRI images were randomly presented to an expert neuroradiologist blinded to clinical diagnosis and rated according to current criteria [4]. Clinical-demographic information was collected at baseline and annually over a three years follow-up.

Results: At baseline MRI findings were rated normal in 43% of patients, potentially abnormal in 7%, abnormal in 50%. Baseline clinical-demographic features were not different between patients with normal or abnormal nigrosome [1]. After 3 years follow-up two patients developed PD (one with baseline loss of nigrosome [1], one with normal MRI findings at baseline), one patient with abnormal baseline nigrosome [1] converted to Dementia with Lewy Bodies (DLB). At radiological follow-up four patients with baseline normal findings showed preserved nigrosome [1], two with baseline abnormal findings had abnormal nigrosome [1], one patient with potentially abnormal baseline MRI finally evolved to definitely abnormal nigrosome [1].

Conclusions: Ultra-high field susceptibility-weighted imaging of the substantia nigra may help identifying patients with a higher risk of phenoconversion to Parkinson's disease and atypical parkinsonism but broader validation and longer follow-up are needed to confirm these preliminary data.

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C11

Lysosomal alterations in subjects with RBD could help predict the conversion to Parkinson's Disease

Gerardo Ongari¹, S. Cerri¹, M. Avenali^{2,3}, M. Terzaghi⁴, C. Tassorelli^{2,3}, E.M. Valente^{5,6}, F. Blandini¹

¹Laboratory of Cellular and Molecular Neurobiology, IRCCS Mondino Foundation, Pavia, Italy

²Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

³Neurorehabilitation Unit, IRCCS Mondino Foundation, Pavia, Italy

⁴Unit of Sleep Medicine and Epilepsy, IRCCS Mondino Foundation, Pavia, Italy

⁵Laboratory of Molecular Genetics and Cytogenetics, IRCCS Mondino Foundation, Pavia, Italy

⁶Department of Molecular Medicine, University of Pavia, Pavia, Italy

Introduction: Idiopathic REM sleep behavior disorders (iRBD) represent the most important prodromal marker for synucleinopathies, including Parkinson's Disease (PD) [1]. Recent studies have shown an increased incidence of RBD in subjects with lysosomal dysfunctions, such as subjects with inherited deficiency of the lysosomal enzyme glucocerebrosidase. Moreover, iRBD patients show clinical phenotypes similar to these subjects [2-8].

Objective: The objective of this study was to combine biochemical and clinical data to provide a stratification of iRBD subjects predicting the risk of converting to PD. To this aim, we investigated lysosomal dysfunctions, mainly related to glucocerebrosidase deficiency, in fibroblasts from iRBD subjects, iRBD subjects converted to PD (RBD-PD) and PD patients who developed RBD after diagnosis (PD-RBD).

Methods: We enrolled 29 subjects, subdivided in four groups: healthy subjects (n= 8), iRBD (n= 7), PD-RBD (n= 9) and RBD-PD (n= 5). The expression levels and the activity of the main glucocerebrosidase-related proteins (cathepsin D, LAMP1, LIMP2, Saposin C) were assessed by Western blotting and fluorometric assays, respectively.

Results: The study highlighted lysosomal alterations associated with the presence of RBD. Interestingly, RBD-PD showed a different alteration pattern than PD-RBD, characterized by increased levels of glucocerebrosidase, saposin C and LIMP2. In all groups, glucocerebrosidase activity was not affected. Moreover, biochemical data allowed to identify two subpopulations within RBD-PD group which differ in the time to conversion (tc) to PD. "Fast converters" subjects (tc < 3 years) showed a lower expression of all the lysosomal proteins analyzed compared to "slow converters". Lastly, it is noteworthy the levels of cathepsin D in iRBD group correlated with the severity of sleep disorders, suggesting its implication in their onset.

Conclusions: If confirmed in larger population-based studies, the alterations identified in this study pave the way for future longitudinal study on predictive markers of conversion to PD, in iRBD subjects.

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C12

Parkinson disease and the law: motor and non-motor determinants in medical courts cases

Paolo Amami, D. Ziemele, A. Albanese

Neurology Department, Humanitas Research Hospital, Rozzano, Milano, Italy

Introduction: Parkinson's disease (PD) is associated with a significant occurrence of legal issues, related to either civil or to criminal aspects. There is evidence that PD patients may be involved in a variety of lawsuits, but a comprehensive review is lacking. PD is one of the most frequent neurodegenerative disorders, affecting at least 6 million people worldwide. We reviewed the legal issues involving PD patients in Italy and United Kingdom and correlated these findings with the clinical condition of the involved PD patients.

Methods: The DeJure Italian and the Westlaw UK repositories were searched for legal cases concerning PD patients from inception to May 2019. Only cases where PD or PD symptoms were directly involved in the dispute or in the final ruling were selected. This search allowed to retrieve detailed information on the trials and served to identify the clinical conditions related to the judiciary PD cases on record. A further search was performed on PubMed and Google by combining the identified clinical conditions and PD. The motor and non-motor features relevant for trial and the final ruling were identified in each legal case.

Results: A total of 56 cases directly related to PD were found: 35 in Italy and 21 in the UK. Eight issues were involved in the reviewed cases: causes of parkinsonism, impulse control behaviours, mental status, handwriting, disability, falls, applicability of detention, and discrimination or stigma. We found that two conditions were related frequently to controversial in the trial: causes of parkinsonism and impulse control behaviours. In these two conditions, the witnesses' specialized opinions were central for the resolution of the trial. By contrast, there was adequate knowledge leading to consistent ruling on the other conditions, namely mental status, handwriting, disability, falls, applicability of detention, and discrimination or stigma.

Conclusions: PD patients may be implicated in several legal issues, far beyond cases of clinical malpractice. In some cases, PD clinical conditions represent the main bulk of lawsuits. This is particularly evident for impulse control disorders and for cases of supposedly acquired parkinsonism related to pollutants.

C13

Plasma NfL correlates with widespread extrastriatal monoaminergic deficits in early Parkinson's disease

*Stefano Masciocchi*¹, A. Pilotto^{1,2}, M. Toffali¹, S. Nocivelli¹, A. Imarisio², E. Premi¹, F. Schiano Di Cola¹, F. Conforti¹, A. Scalvini¹, S. Gipponi¹, E. Cottini¹, B. Paghera³, L. Bonanni⁴, H. Zetterberg^{5,6,7,8}, N.J. Ashton^{5,6}, A. Hye⁵, A. Padovani¹

¹Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

²FERB Onlus, Ospedale S. Isidoro, Trescore Balneario, Bergamo, Italy

³Nuclear Medicine Unit, University of Brescia, Brescia, Italy

⁴Department of Neuroscience Imaging and Clinical Sciences, University G. D'Annunzio of Chieti-Pescara, Chieti, Italy

⁵Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

⁶Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

⁷Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

⁸UK Dementia Research Institute at UCL, London, UK

⁹Wallenberg Centre for Molecular and Translational Medicine, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

¹⁰King's College London, Institute of Psychiatry, Psychology & Neuroscience, Maurice Wohl Clinical Neuroscience Institute, London, UK

¹¹NIHR Biomedical Research Centre for Mental Health & Biomedical Research Unit for Dementia at South London & Maudsley NHS Foundation, London, UK

Purpose: To investigate the relationship between striatal and extrastriatal [123I]-FP-CIT SPECT monoaminergic projections and plasma neurofilament light chain (NfL) in patients with diagnosis of Parkinson's disease (PD).

Methods: Consecutive patients with suspected PD underwent [123I]-FP-CIT SPECT imaging, clinical assessment and blood sampling. Plasma NfL levels were quantified by single molecule array. [123I]-FP-CIT SPECT binding in nigrostriatal and extrastriatal regions of interest (ROI) was calculated in each patient and in 50 controls from spatially normalized images. The relationship between NfL plasma levels and [123I]-FP-CIT was evaluated by region of interest (ROI) analyses adjusting for the effects of age of onset, sex and disease duration. A covariance analysis provided the correlates of local and long-distance regions related to higher plasma NfL levels.

Results: Out of forty patients evaluated, seven with higher NfL plasma levels ($p=0.001$) developed atypical parkinsonism and thus excluded while 28 patients with established PD at follow-up underwent imaging analyses. In PD, higher NfL plasma levels correlated with lower [123I]-FP-CIT SPECT binding in insula ($r = -0.46$, $p=0.02$), thalamus ($r = -0.41$, $p=0.04$), and cingulate ($r = -0.41$, $p=0.04$) and any nigrostriatal regions. Covariance patterns associated with insula binding showed a widespread cortical monoaminergic depletion in PD but not in controls.

Conclusions: Our data showed for the first time that plasma NfL is associated with widespread extrastriatal monoaminergic deficits in PD patients, especially in insula which is an important region associated with malignant phenotypes. This suggest a strong relationship between NfL and cortical function and pathology in PD, pointing out NfL role as early marker of motor and cognitive progression.

C14

When and how to stop subthalamic deep brain stimulation in late-stage Parkinson's disease

Margherita Fabbri^{1,2}, M. Zibetti¹, M.G. Rizzone¹, G. Giannini^{3,4}, L. Borellini⁵, A. Stefan⁶, F. Bove⁷, A. Bruno⁸, G. Calandra Buonauro^{3,4}, N. Modugno⁸, C. Piano⁷, A. Peppe⁹, G. Ardolino⁶, A. Romagnolo¹, C.A. Artusi¹, P. Berchiolla¹⁰, E. Montanaro¹, P. Cortelli^{3,4}, L.M. Romito¹¹, R. Eleopra¹¹, B. Minafra¹², C. Pacchetti¹², L. Lopiano¹

¹Department of Neuroscience Rita Levi Montalcini, University of Turin, Turin, Italy

²Instituto de Medicina Molecular, Faculdade de Medicina, University of Lisbon, Lisbon, Portugal

³IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

⁴Department of Biomedical and NeuroMotor Sciences (DIBINEM), Alma Mater Studiorum, University of Bologna, Bologna, Italy

⁵U.O. Neurofisiopatologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

⁶Department of System Medicine, UOSD Parkinson, University of Rome Tor Vergata, Rome, Italy

⁷Department of Neurology, Catholic University of Sacred Heart, Gemelli University Hospital, Rome, Italy

⁸IRCCS Neuromed, Pozzilli (IS), Italy

⁹IRCCS Santa Lucia Foundation, Rome, Italy

¹⁰Department of Clinical and Biological Sciences, University of Torino, Torino, Italy

¹¹Department of Clinical Neurosciences, Movement Disorders Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

¹²Parkinson and Movement Disorder Unit, IRCCS Mondino Foundation, Pavia, Italy

Background: Subthalamic-deep brain stimulation (STN-DBS) effects may decrease with Parkinson's disease (PD) progression. There is no indication if, when and how to consider the interruption of DBS treatment in late-stage (LS) PD.

Objective: To investigate the percentage of "poor stimulation responders" among LSPD patients for elaborating an algorithm to decide whether and when DBS interruption may be considered.

Methods: LSPD patients (Hoehn Yahr Stage 4-5 and Schwab and England Scale <50 in Med On/Stim On condition) treated with STN-DBS for at least 5 years underwent a cross-over, double-blind, randomized evaluation of acute effects of stimulation. Physicians, caregivers and patients were blinded to stimulation conditions. Poor stimulation responders (MDS-UPDRS part III change < 10% between Stim On/Med Off and Stim Off/Med Off) maintained the Stim Off/Med On condition during one month for open label assessment.

Results: Thirty-six patients were included. The acute effect of stimulation was significant (17% MDS-UPDRS part III improvement at the Stim On/Med Off vs. Stim Off/Med Off). Seven patients were classified as "poor stimulation responders" and the stimulation was switched-off, but in four cases the stimulation was switched back "On" due to worsening of parkinsonism and dysphagia with a variable time delay (up to 10 days). No serious adverse effects occurred.

Conclusions: The vast majority (92%) of LSPD patients shows a meaningful response to STN-DBS. Effects of stimulation may take days to disappear after its interruption. We present a safe and effective decisional algorithm that could guide physicians and caregivers in taking challenging therapeutic decisions in LSPD.

C15

Application of Movement Disorders Society phenotypes in a large cohort of Progressive Supranuclear Palsy patients: data from the Italian network

*Marina Picillo*¹, S. Cuoco¹, F. Abate¹, F. Bruschi², A. Cappiello¹, R. De Micco³, A. De Rosa⁴, E. Del Prete⁵, F. Di Biasio⁶, F. Elifani⁷, R. Erro¹, M. Fabbri⁸, M. Falla^{9,10}, G. Franco¹¹, D. Frosini⁵, S. Galantucci¹², G. Lazzeri¹¹, L. Magistrelli^{13,14}, M.C. Malaguti¹⁵, A.V. Milner¹³, B. Minafra², E. Olivola⁷, A. Pilotto¹⁶, C. Rascunà¹⁷, M.C. Rizzetti¹⁸, S. Satolli³, T. Schirinzi¹⁹, M.F. Tepedino¹, B. Borroni¹⁶, R. Ceravolo⁵, A. Di Fonzo¹¹, L. Lopiano⁸, R. Marchese⁶, N.B. Mercuri¹⁹, N. Modugno⁷, A. Nicoletti¹⁷, A. Padovani¹⁶, A. Stefani¹⁹, A. Tessitore³, M.A. Volontè¹², R. Zangaglia², M. Zappia¹⁷, M. Zibetti⁸, P. Barone¹

¹Center for Neurodegenerative Diseases (CEMAND), Department of Medicine, Surgery and Odontology, University of Salerno, Salerno, Italy

²Parkinson's Disease and Movement Disorders Unit, IRCCS Mondino Foundation, Pavia, Italy

³Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Napoli, Italy

⁴Department of Neurosciences and Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy

⁵Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa, Pisa, Italy

⁶IRCCS Policlinico San Martino, Genova, Italy

⁷IRCCS Neuromed, Pozzilli, Italy

⁸Department of Neuroscience Rita Levi Montalcini, University of Turin, Turin, Italy

⁹Department of Neurology, General Hospital of Bolzano, Bolzano, Italy

¹⁰CIMEc and CeRIN, University of Trento, Rovereto, Italy

¹¹IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

¹²Dipartimento Neurologico, IRCCS Ospedale San Raffaele, Milano, Italy

¹³Movement Disorders Centre, Neurology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

¹⁴PhD Program in Clinical and Experimental Medicine and Medical Humanities, University of Insubria, Varese, Italy

¹⁵UO Neurologia, Ospedale Santa Chiara Trento, Azienda Provinciale per i Servizi Sanitari Provincia Autonoma di Trento, Italy

¹⁶Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

¹⁷Department G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy

¹⁸S. Isidoro Hospital - FERB Onlus, Trescore Balneario, Bergamo, Italy

¹⁹Centro Parkinson, Dip.to Medicina dei Sistemi, Policlinico Tor Vergata, Roma, Italy

Introduction: After the release of the novel clinical diagnostic criteria for Progressive Supranuclear Palsy (PSP) [1], the Movement Disorders Society (MDS) provided guidance on phenotypic attribution [2].

Aims: Taking advantage of the data collected within the Italian Network, aims of the present study are (1) to apply the MDS algorithm for phenotypic attribution, (2) to describe motor and cognitive features according to phenotypes and (3) to analyze predictors of Quality of Life (QoL) in a large cohort of PSP patients.

Methods: One hundred and ninety PSP patients [mean age (standard deviation): 72.15 (6.71); disease duration: 4.42 (2.8)] have been enrolled in 16 Italian third level movement disorders centers. Comparison between groups was performed with parametric testing and linear regression analysis was used to evaluate predictors of QoL.

Results: According to MDS algorithm [2] 72.7% presented PSP – Richardson syndrome (PSP-RS), 16.3% predominant parkinsonism variant, 6.9% progressive gait freezing and 1.4% predominant frontal variant. PSP-RS also qualified for a second phenotype in 90% and for a third phenotype in 60%. When considering the first phenotypic attribution, PSP-RS tended to have higher motor scores compared to other phenotypes ($p=0.063$). On the other hand, no significant differences were noted in cognition as assessed with Montreal Cognitive Assessment battery. Among age, phenotype and motor scores, female sex was the only predictor of worse QoL with women scoring 12.4 (95%CI: 2 – 22.8, $p=0.019$) higher than men.

Conclusions: Current motor and cognitive assessments do not capture differences between phenotypes. As a matter of fact, each patient qualifies for multiple phenotypes. The only predictor of worse QoL is female sex.

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C16

Young onset and late onset Parkinson's disease differ in the profile of fluid biomarkers and clinical features

Tommaso Schirinzi^{1,2}, G. Di Lazzaro¹, G.M. Sancesario^{3,4}, S. Petrucci^{5,6,7}, M. Pierantozzi¹, A. Stefani¹, N.B. Mercuri^{1,3}, A. Pisani^{1,3}

¹Department of Systems Medicine, University of Roma Tor Vergata, Rome, Italy

²Department of Neurosciences, IRCCS Bambino Gesù Children's Hospital, Rome, Italy

³IRCCS Santa Lucia Foundation, Rome, Italy

⁴Department of Experimental Medicine and Surgery, University of Roma Tor Vergata, Rome, Italy

⁵Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy

⁶S. Andrea University Hospital, Rome, Italy

⁷Division of Medical Genetics, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Introduction: Young Onset Parkinson's disease (YOPD), although not precisely defined, is a relevant condition whose neurobiology is questioned if different from those of typical Late Onset PD (LOPD). Since neurodegeneration occurring at CNS level reflects in CSF and blood of patients, the assessment of fluid biomarkers allows investigating molecular mechanisms of the disease in vivo.

Objective: To explore whether the clinical-biochemical profile of PD may change depending on the age-of-onset (AO), as a possible result of a distinct neurodegenerative processes.

Methods: A panel of fluid biomarkers (CSF lactate, 42-amyloid- β peptide, total and 181-phosphorylated tau; serum uric acid) and the standard scores for motor and non-motor signs (UPDRS II-III; non-motor symptoms scale, NMSS; adjusted MMSE; Apathy Scale; levodopa equivalent daily dose, LEDD) were assessed in 76 idiopathic PD patients (genetic cases excluded; YOPD, AO \leq 50, n=44; LOPD, AO>50, n=32) and 75 sex/age-matched controls, adjusting the models for the main confounding factors (sex, disease duration, therapy). PD patients were enrolled shortly after onset, such that AO and age overlapped, thus enabling the comparison with the control group.

Results: In the whole PD group, AO directly correlated either to CSF lactate and tau proteins or to NMSS score. In controls, age was directly associated to serum urate levels. Subgroup analysis revealed that in YOPD, CSF lactate and tau proteins were lower than LOPD; moreover, MMSE and NMSS scores resulted better in YOPD than LOPD.

Conclusions: The clinical-biochemical profile of idiopathic PD may be affected by the AO, independently from the disease duration, leading to different patterns in YOPD and LOPD, whose recognition is fundamental for further pathophysiological implications and clinical applications. The neurobiological substrates of YOPD seem to differ from those of LOPD although they remain to be elucidated in future studies.

C17

Frequency-dependent modulation of bradykinesia and motor cortex excitability in Parkinson's Disease

Andrea Guerra^{1,2}, M. Bologna^{1,2}, D. Colella², M. Giangrosso², A. Cannavacciuolo², G. Paparella^{1,2}, A. Suppa^{1,2}, A. Berardelli^{1,2}

¹IRCCS Neuromed, Pozzilli (IS), Italy

²Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

Introduction: Beta (β) and gamma (γ) are the main resonant rhythms of the primary motor cortex (M1) in humans. In patients with Parkinson's Disease (PD), β and γ oscillatory activities are altered within the basal ganglia, and this abnormality contributes to the pathophysiology of motor symptoms, including bradykinesia. However, whether cortical (M1) β and γ oscillations influence bradykinesia in PD is still unclear. Transcranial alternating current stimulation (tACS) is a neurophysiological technique that entrains cortical rhythms, transiently increasing their power.

Objective: To test the effects of β - and γ -tACS on voluntary movements abnormalities and M1 excitability in PD.

Methods: Kinematic features of repetitive finger movement were recorded during β -, γ - and sham-tACS, delivered in a random order over M1. In the same stimulation conditions, we also recorded motor evoked potentials (MEPs) elicited by single and paired-pulse transcranial magnetic stimulation (short-interval intracortical inhibition – SICI, and short-latency afferent inhibition – SAI). Patients were studied OFF and ON therapy, in two different randomized sessions. A group of healthy subjects (HS) was also tested.

Results: Patients showed various movement abnormalities compared to HS. SICI was higher (reduced inhibition) in patients than in HS. In patients, β -tACS deteriorated movement amplitude and velocity, while γ -tACS slightly improved these parameters. Also, β -tACS decreased (reduced inhibition) both SICI and SAI, whereas γ -tACS decreased SICI but not SAI. The effects of tACS were independent of the medication status (OFF or ON). In PD OFF state, during β -tACS, the degree of SICI correlated with movement velocity.

Conclusions: In PD, specific bradykinesia features and intracortical excitability measures of M1 are modulated by γ - and β -tACS. Our findings support the evidence for an anti-kinetic role of cortical β oscillations in PD, and suggest a relationship between the β -induced worsening of bradykinesia and GABA-A-ergic interneuronal activity, as tested by SICI.

C18

The interplay between cognitive impairment and levodopa induced dyskinesia in Parkinson's disease. A longitudinal study from the PACOS cohort

Antonina Luca^{1*}, Roberto Monastero^{2*}, R. Baschi², C.E. Cicero¹, G. Mostile¹, M. Davi², L. Pilati², V. Restivo³, M. Zappia¹, A. Nicoletti¹

**These authors contributed equally to this work*

¹Department of Medical, Surgical Sciences and Advanced Technologies, G.F. Ingrassia, University of Catania, Catania, Italy

²Department of Biomedicine, Neuroscience and Advanced Diagnostics, University of Palermo, Palermo, Italy

³Department of Sciences for Health Promotion and Mother-Child Care, University of Palermo, Palermo, Italy

Introduction: Long-term replacement therapy with levodopa and dopamine-agonists could lead to levodopa-induced dyskinesia (LID). Cortical structures involved in motor program and inhibition such as the supplementary motor area and the inferior frontal cortex have been found to be impaired in PD patients with LID.

Aim: To evaluate possible associations between cognitive dysfunctions and LID.

Methods: PD patients from the PACOS cohort who underwent a baseline and follow-up neuropsychological evaluations were enrolled in the study. PD-MCI was diagnosed according to MDS level II criteria. PDD was diagnosed according to MDS criteria. The following five cognitive domains were evaluated: episodic memory, attention, executive function, visuo-spatial function and language. Regardless the presence of MCI, a domain was considered as "impaired" when patient scored 2 standard deviations below normality cut-off values in at least one test in the specific domain. Levodopa equivalent dose (LED), UPDRS-ME and LID were recorded at baseline and follow-up. To identify possible neuropsychological predictors associated with the probability of LID development at follow-up, Cox proportional-hazards regression model was used.

Results: One-hundred thirty-nine PD patients (87 men; mean age 65.7±9.4 years) were enrolled in the study. Eighteen (12.9%) patients were dyskinetic at baseline. Out of the 121 patients non-dyskinetic at baseline, 22 (18.1%) developed LID at follow-up. The impairment in the attention and executive domains was a strong predictors of LID development (respectively HR 4.41; 95% CI 1.49-13.07; p-value 0.007; HR 3.46; 95% CI 1.26-9.48; p value 0.02).

Conclusions: The interplay between cognitive impairment and dyskinesia could lie in the alteration of common cortical network.

Poster



P1

Gut microbiote distinctive features and microbiota-metabolome profile in Parkinson disease: focus on levodopa and LCIG

*Valentina Oppo*¹, M. Melis², S. Vascellari³, M. Fabbri⁴, M. Sarchioto⁵, D. Murgia¹, M. Zibetti⁴, L. Lopiano⁴, A. Manzin³, G. Cossu¹

¹SC Neurologia e Stroke Unit, AO Brotzu, Cagliari, Italy

²SC Neurologia, AOU Policlinico di Monserrato, Cagliari, Italy

³Dipartimento di Scienze Biomediche, Sezione di Microbiologia e Virologia, Università degli Studi di Cagliari, Cagliari, Italy

⁴Dipartimento di Neuroscienze Rita Levi Montalcini, Università di Torino, Torino, Italy

⁵Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St. George's University of London, London, UK

Background: Recent data suggest that imbalances in the composition of the intestinal microbiome could trigger and/or exacerbate the progression of PD [1]. They also suggest a modulating role on microbiome composition of some antiparkinsonian drugs [2].

Objective: The aim of this work was to study the microbiome of PD patients, studying the effect of dopaminergic drugs mainly focusing on the effect of Levodopa (LD) and its direct injection to the bowel, Levodopa Carbidopa Intrajejunal Gel (LCIG).

Methods: The composition of the microbiota in fecal extracts of 107 PD patients and 25 controls was determined. PD patients were classified in three different treatment groups: patients on oral LD (LD-Group) (n= 46), patients under LCIG (LCIG-Group) (n= 38), and patients without medicaments at the moment of recruitment (Naïve-Group) (n = 23). Microbiota was studied by 16S rRNA next-generation gene sequencing of DNA extracted from stool and a direct metabolomic analysis was conducted.

Results: After correction for confounders LD-Group showed a reduction of Bacteroides and Firmicutes phyla, while Veillonellagenus (Firmicutes) and Serratia entomophila (Proteobacteria) were increased. LCIG-Group showed an increase in the abundance in Proteobacteria, a reduction of Brevibacteriaceae and of Blautia. LCIG-Group also showed a significant higher abundance of Enterobacteriaceae family, Escherichia and Serratia genera compared to LD-Group. We identified several metabolite-players correlated to these gut microbiota alterations. The metabolic changes included SCFAs, lipids, fatty acids, polyamines, vitamin, polyphenol and amino acids.

Conclusions: Our results suggest that LD and mostly its intraduodenal injection (LCIG) might significantly influence microbiota composition with a potential pro-inflammatory effect. The LD-Group and LCIG-Group were closely associated to a decrease of anti-inflammatory metabolites and at the same time to an increase of pro-inflammatory bacterial products. Further studies with larger cohorts and high-resolution sequencing methods are required to better define the causal link between these changes and PD pathogenesis.

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P2

Risk and protective factors for Parkinson's disease in a large Italian population: a simultaneous assessment

Matteo Costanzo¹, D. Belvisi², R. Pellicciari³, G. Fabbrini¹, N. Modugno², S. Pietracupa², M. De Lucia², F. Magrinelli⁵, C. Rascunà⁶, A. Nicoletti⁶, M. Tinazzi⁵, G. Fabbrini^{1,2}, A. Berardelli^{1,2}, G. Defazio⁴

¹Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy

²Neuromed Institute, IRCCS, Pozzilli (IS), Italy

³Department of Basic Science, Neuroscience and Sense Organs, Aldo Moro University of Bari, Bari, Italy

⁴Movement Disorders Center, Department of Neurology, Institute of Neurology, University of Cagliari, Cagliari, Italy

⁵Neurology Unit, Movement Disorders Division, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

⁶Department of Medical and Surgical Sciences and Advanced Technologies G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy

Aims: The potential risk and protective factors for Parkinson's disease (PD) are still unclear [1-3]. We designed a case-control study aimed at investigating simultaneously a large number of possible risk and protective factors for PD. By using this approach, we aimed at identifying the factors that act independently on PD development and the possible interaction between factors.

Methods and Materials: We enrolled a cohort of 694 PD patients and 640 healthy controls, attending outpatient clinic of six neurological departments from September 2018 to September 2019. We administered a standardized questionnaire on demographic features, comorbidities, lifestyle, physical activity, and exposure to toxic substances and drugs possibly involved in PD development.

Results: The multivariate analysis disclosed that family history of PD, dyspepsia, exposure to pesticides, oils, metals, and general anesthesia are independent risk factors for PD. Conversely, coffee consumption, smoking, and physical activity were found to be independent protective factors for PD. Risk and protective factor did not interact between them. The k-means cluster analysis identified four groups of patients on the base of risk factors profile. In Group 1, all patients reported family history as a risk factor. In Group 2 and 3, toxic agents and dyspepsia were the most frequent observed risk factors. In Group 4 contained patients who did not report any of the investigated factors.

Conclusions: Nine factors were associated with PD development. Risk factors increase the risk score by coexisting in the same subject rather than interacting while protective factors act independently from the etiological subtype. Our study suggest that future prevention strategies aimed at reducing the coexistence of different risk factors are needed.

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P3

Chemosensory dysfunction in Parkinson's disease subtypes

*Elisa Mantovani*¹, M.P. Cecchini², A. Federico¹, R. Bacchin¹, A. Zanini², M. Tinazzi¹, S. Tamburin¹

¹Section of Neurology, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

²Section of Anatomy and Histology, Department of Neurosciences, Biomedicine and Movement Sciences University of Verona, Verona, Italy



P4

Serum NfL identified fast motor and cognitive progression in Parkinson's disease: beyond malignant phenotypes?

*Alberto Imarisio*¹, A. Pilotto^{1,2}, F. Conforti¹, A. Lupini¹, G. Gianni¹, S. Gipponi¹, E. Cottini¹, A. Scalvini¹, S. Masciocchi¹, S. Nocivelli¹, R. Grasso¹, R. Turrone¹, B. Borroni¹, M.C. Rizzetti², L. Bonanni³, M. Pizzi⁴, A. Bellucci⁴, E. Garrafa⁵, H. Zetterberg^{6,7}, A. Hye⁶, N. Ashton^{6,7}, A. Padovani¹

¹Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

²Parkinson's Disease Rehabilitation Centre, FERB ONLUS – S. Isidoro Hospital, Trescore Balneario (BG), Italy

³Department of Neuroscience Imaging and Clinical Sciences, University G. D'Annunzio of Chieti-Pescara, Chieti, Italy

⁴Division of Pharmacology, Department of Molecular and Translational Medicine, University of Brescia, Italy

⁵Division of Biochemistry, Department of Molecular and Translational Medicine, University of Brescia, Italy

⁶Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK

⁷Neurochemistry Department, University of Gothenburg, Gothenburg, Sweden

Objective: CSF and plasma neurofilament light chain (NfL) levels have been consistently proposed as reliable markers of neurodegeneration able to discriminate between Parkinson's disease (PD) and atypical parkinsonisms [1]. Increased Serum NfL might predict worse motor and cognitive progression in PD patients at single subject level.

Methods: Plasma NfL was assessed in a longitudinal study including 93 patients with Parkinson's disease and 27 patients with DLB who underwent an extensive motor and cognitive assessment and after 2 years of follow-up. The study evaluated the correlation between NfL plasma levels and motor, non-motor symptoms, cognitive and behavioral abnormalities in the two cohorts, as well as benignant/malignant phenotypes and motor/cognitive progression in PD after 2 years of follow-up.

Results: Serum NfL correlated with age and age at onset in the cohort. In DLB, NfL correlated with disease duration, hyposmia and neuropsychiatric symptoms, but not with motor function assessed by UPDRS-III. We found no significant associations between NfL and disease progression in DLB patients. In PD, higher NfL levels correlated with hyposmia ($p=0.01$), total UPDRS-II and UPDRS-III scores (0.001), gait speed (0.04) and several disability milestones, including mild cognitive impairment (0.001), symptomatic dysautonomia (0.001), loss of independency in activities of daily living ($p=0.01$) and instrumental daily living ($p=0.001$). At two years of follow-up, NfL was the best marker in multivariate regression analyses for both motor and cognitive progression beyond malignant/benignant phenotypes.

Conclusions: Elevated serum NfL levels are associated with fast progression in PD patients and could thus represent target of interventions in specific subpopulation of patients.

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P5

Difference in olfaction impairment in Parkinson's disease patients with tremor dominant subtype versus rigid-akinetic subtype

*Sabino Dagostino*¹, C. Masala², T. Ercoli¹, M.M. Mascia¹, G. Piga¹, R. Piras², P. Cimino¹, G. Defazio¹, P. Solla¹

¹Department of Neurology, Movement Disorders Center, Institute of Neurology, Azienda Ospedaliero Universitaria, University of Cagliari, Monserrato, Cagliari, Italy

²Department of Biomedical Sciences, Section of Physiology, University of Cagliari, Cagliari, Italy

Introduction: Parkinson's disease (PD) can present with different motor subtypes depending on the predominant symptoms (tremor or rigidity/bradykinesia). Slower disease progression with less severe non-motor symptoms and cognitive decline are observed in tremor-dominant (TD) patients compared to those with akinetic-rigid dominant (ARD) subtype. Olfactory disorders have been described in parkinsonian patients, although the definite correlation with different subtypes of PD is not clear.

Objective: To investigate olfactory function in PD patients with TD subtype in comparison to ARD subtype.

Methods: Sixty-Two PD patients, 20 with TD subtype and 42 with ARD subtype, were enrolled. Patients were divided into ARD and TD subgroups using tremor/rigidity ratio, calculated using UPDRS-III subscores. Olfactory function was assessed with the Sniffin' Sticks Extended Test (SSET). SSET parameters [Olfactory Threshold (OT), Discrimination (OD), Identification (OI) and Threshold-Discrimination-Identification (TDI) scores were evaluated. Patients with cognitive impairment were excluded.

Results: OT, OD and TDI scores were significantly lower in the ARD subtype than in the TD group [respectively 1.9 ± 1.4 vs 3.3 ± 2.7 ($p=0.008$); 7.0 ± 3.1 vs 8.6 ± 2.2 ($p=0.042$); 16.0 ± 6.5 vs 20.3 ± 6.1 ($p=0.017$)], while OI scores were not significantly different. On multivariate linear regression analysis the tremor/rigidity ratio was a significant predictor of OT ($p=0.01$) and TDI ($p=0.02$).

Conclusions: These findings show a more evident olfactory dysfunction in PD patients with ARD subtype. Such evidence supports the biological relevance of clinical subtypes in PD patients suggesting the idea of a different pathophysiological process between these different clinical forms.

P6

A preliminary investigation on the accuracy of the wearable systems for continuous monitoring of movement disorders

Luigi Battista¹, M. Casali², C. Coletti², P. Grassini², F.G. Radicati², F. Stocchi²

¹Biomedical Lab, Potenza, Italy

²Institute for Research and Medical Care, IRCCS San Raffaele Pisana, Rome, Italy

Introduction: The clinical assessment of Parkinson's disease (PD) symptoms is typically performed with neurological examinations and simple motor tests. However, these examinations may only consider the severity of motor symptoms during the length of the recording and may fail to capture variations in a patient's motor state, which change continuously during the day. Therefore, continuous monitoring of movement disorders in patients with PD may be a viable tool to provide additional information on motor symptoms and on response to treatment. However, the performances on accuracy, sensitivity and specificity of the continuous monitoring systems have not yet been investigated in-depth.

Objectives: The objective is to investigate on the performances provided by a system for continuous monitoring of movement disorders related to PD in terms of accuracy, sensitivity and specificity.

Methods: Data were acquired by means of a wrist-worn-device (i.e. "Parkinson's disease-watch", PD-Watch) for 72 hours and then processed in order to get information on the duration and the severity of the various possible hand tremor and dyskinesia events detected during the entire duration of monitoring period. Finally, the results provided by the wearable systems were compared to data reported in the patient symptoms diary by considering 30-minutes time intervals; during the considered comparison, each interval was identified as true positive, false positive, true negative or false negative.

Results: In this study, 5 recording sequences were performed with PD patients with tremors and dyskinesias. Preliminary results show that, as example, an accuracy on the tremor detection of about 91% and on the dyskinesia detection of about 75% was found for a monitoring sequence.

Conclusions: While results need to be extended with further clinical trials, the considered performances on the accuracy of the data provided by means of continuous monitoring may be considered as useful information in the context of motor symptoms assessment.

P7

Salivary caffeine is a marker of disease progression in Parkinson's disease

*Maria Ilenia De Bartolo*², G. Leodori², A. Fabbrini², M. Costanzo¹, D. Belvisi², A. Conte¹, S. Manetto³, A. Ciogli³, C. Villani³, A. Berardelli^{1,2}, G. Fabbrini^{1,2}

¹Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy

²IRCCS Neuromed, Pozzilli (IS), Italy

³Department of Chemistry and Technologies of Drug, Sapienza University of Rome, Rome, Italy

Introduction: Caffeine has a protective role in Parkinson's disease (PD) [1,2]. One study showed decreased caffeine blood levels in PD patients [3], even when controlled for caffeine assumption and CYP1A2 genotype, the enzyme responsible for 95% of caffeine metabolism [4]. CYP1A2 functioning (i.e. phenotype) is also influenced by environmental factors [5]. Caffeine can be accurately quantified in saliva [6].

Objective: 1) To investigate whether PD patients show decreased salivary caffeine levels. 2) To investigate CYP1A2-phenotype and caffeine absorption as possible causes of decreased caffeine levels in PD patients.

Methods: We enrolled 86 healthy subjects (HS), 38 early, and 48 moderate/advanced PD patients. Daily coffee intake, BMI, and assumption of substrate, inducers or inhibitors of CYP1A2 were recorded in all participants. Caffeine and its major metabolite paraxanthine were measured in saliva samples collected before (T0) and 4 hours after (T1) oral intake of 100mg caffeine. CYP1A2-phenotype was calculated as the paraxanthine/caffeine ratio at T1 [7]. Caffeine absorption was calculated as difference in caffeine levels between T1 and T0.

Results: Age, BMI and coffee intake were statistically similar between groups. Moderate/advanced PD patients showed lower caffeine levels ($p=0.009$), while early PD did not. Disease duration ($p=0.038$) and severity ($p=0.017$) assessed by UPDRS could both statistically significantly predict salivary caffeine levels at T0 in PD patients. PD patients and HS showed similar CYP1A2-phenotype and caffeine absorption.

Conclusions: Baseline salivary caffeine levels correlate with disease duration and severity in PD patients. This means that caffeine should be considered a marker of progression and not a marker of disease in PD. Caffeine metabolism and absorption were similar to HS in PD patients. Probably, a reduced storage could explain the reduced caffeine levels in patients with moderate/advanced PD [8,9], but further investigation are needed to confirm this hypothesis.

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P8

A gait data-driven approach to identify different clinical subtypes of Parkinson's disease: a proposal for a new classification

G. Mostile¹, G. Portaro¹, V. Dibilio^{1,2}, Roberta Terranova¹, P. Cunsolo¹, F. Contrafatto¹, G. Donzuso¹, C. Rascunà¹, C.E. Cicero¹, A. Luca¹, A. Nicoletti¹, M. Zappia¹

¹University of Catania, Department G.F. Ingrassia, Section of Neurosciences, Catania, Italy

²IRCCS Centro Neurolesi Bonino Pulejo, Messina, Italy

Background: Gait disorders are characteristics of Parkinson's Disease (PD). Spatio-temporal and kinematic parameters can be routinely quantified by gait analysis. Numerous attempts have been made to identify different clinical subtypes with poor agreement and temporal inconsistency. The principal aim of this study was to identify different clinical subtypes based on cluster analysis of gait parameters applied to a cohort of PD patients.

Methods: We retrospectively analyzed data of PD patients who underwent gait analysis. They all performed ten trials walking at their self-selected speed along a six-m walkway during their "on" pharmacological state if treated. A non-hierarchical cluster analysis using k-means method was performed using average values of forty selected spatio-temporal and kinematic parameters for the optimum solution based on the Calinski-Harabasz criterion.

Results: We enrolled thirty-nine patients. Three different subtypes were identified by cluster analysis: a first subtype (A) including the majority of enrolled subjects; a second subtype (B) characterized by pronounced instability, with prominent reduced stance phase, cadence and step length as well as enlarged step width as compared to the other groups; a third phenotype (C) with significant kinematic modifications consisting in pronounced hip flexion-extension and pelvic tilt while walking compared to A and B. No differences were detected in terms of age, disease duration and severity, treatment and cognitive profile among the three identified groups.

Conclusions: A gait data-driven approach may be adopted to practically categorize PD patients in different clinical subtypes. This could be helpful to personalize rehabilitative programs since earlier stages of disease.

P9

Frailty as clinical modulator of clinical presentation and progression in Parkinson's disease

Andrea Pilotto^{1,2}, A. Lupini¹, F. Savoldi², F. Conforti¹, G. Gianni¹, A. Imarisio¹, S. Gipponi¹, E. Cottini¹, A. Scalvini¹, S. Masciocchi¹, S. Nocivelli¹, R. Grasso¹, R. Turrone¹, M.C. Rizzetti², A. Padovani¹

¹Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

²Parkinson's Disease Rehabilitation Centre, FERB ONLUS – S. Isidoro Hospital, Trescore Balneario (BG), Italy

Introduction: Parkinson's disease (PD) is a syndrome characterised by wide variability of presentation and progression. Frailty is the most important prognostic factor in geriatric patients and might play a role as modulator in PD.

Objective: To evaluate the prevalence of frailty and correlation with motor and non motor symptoms as well as disease progression in Parkinson's disease.

Methods: Consecutive Parkinson's disease patients underwent a comprehensive motor and non motor evaluation and geriatric assessment using multidimensional prognostic index (MPI).

Results: One-hundred sixty five outpatients with PD diagnosis (mean age 68.8 y, mean disease duration 8.3 years) entered the study. Pre-Frailty assessed by MPI was presented by 38.5 % of patients and correlated with age and disease duration. When adjusting for these variables, MPI correlated with UPDRS-III, non motor symptoms assessed by UMSAR, prevalence of orthostatic hypotension, RBD and depression. At 2-years follow-up, frailty predict worse cognitive and motor progression when adjusted for disease burden.

Conclusions: Frailty is a possible important modulator of pathology and brain vulnerability in Parkinson's disease and could explain different severity in motor and non motor symptoms. Longer longitudinal studies are warranted to evaluate the impact of frailty in disease progression.

P10

Pragmatic abilities in early Parkinson's disease

Giovanna Lagravinese¹, M.A. Baraldi², S. Di Paola³, E. Pelosin^{1,4}, L. Avanzino^{4,5}, F. Domaneschi⁶

¹Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOEMI), University of Genoa, Genoa, Italy

²Department of Educational Sciences, Psychology Unit (DISFOR,) University of Genoa, Genoa, Italy ³University of Genoa, Laboratory of Language and Cognition (DAFIST), University of Genoa, Genoa, Italy

⁴IRCCS Policlinico San Martino, Genoa, Italy

⁵Department of Experimental Medicine, Section of Human Physiology (DIMES), University of Genoa, Genoa, Italy

⁶Department of Humanities (DAFIST), University of Genoa, Genoa, Italy

Background: In Parkinson's disease (PD) the impairment of executive functions has been well documented, and it typically encompasses several domains, such as planning, shifting, and inhibition. With regard to language, several studies suggested that early PD patients show an impairment at the semantic and morpho-syntactic level. Only a few studies investigated pragmatic abilities in PD, a set of abilities used for the proper utilization and interpretation of language in different communicative situations. These studies suggest that pragmatic skills might be impaired in mid-stage and advanced PD patients.

Aim: To investigate pragmatic ability in PD patients in the early stage of the disease.

Methods: 20 PD patients (HY 1-2) and 21 healthy controls (HC), matched for gender, age and education, were enrolled. Pragmatic skills were tested with the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS). Cognitive functions were assessed through a battery of neuropsychological tests (Parkinson Disease Cognitive Rating Scale (PD-CRS), Stroop test, verbal fluency, digit span).

Results: Statistical analysis showed significant between-group differences in the APACS global score ($p=0.0017$), in APACS composite scores (Production: $p=0.0083$ and Comprehension: $p=0.013$), and in Interview ($p<0.0001$) and Figurative Language 2 ($p=0.0019$) sub-scores. Within the PD group, the global functioning test (PD-CRS) positively correlated with the APACS global score ($p=0.026$), the Production composite score ($p=0.036$) and the Interview subscore ($p=0.034$). Within the HC group, only a negative correlation between Stroop test (inhibition) and all the APACS scores emerged.

Discussion: Our study shows that pragmatic abilities are already compromised in early PD patients. Furthermore, a correlation emerged between pragmatic skills and global cognitive functioning in PD patients, suggesting that already in early stages of the disease, cognitive abilities, even if not impaired, can influence linguistic, and in particular pragmatic, abilities in PD patients.

P11

The impact of a frailty on Parkinson's disease motor and non-motor symptoms: a cross-sectional study

Margherita Giangrosso¹, D. Belvisi^{1,2}, M. Costanzo¹, A. Fabbrini¹, A. Borraccino¹, M. Canevelli^{1,3}, G. Fabbrini^{1,2}

¹Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

²IRCSS Neuromed, Pozzilli (IS), Italy

³National Center for Disease Prevention and Health Promotion, National Institute of Health, Rome, Italy

Introduction: Frailty is an age-related nonspecific state of increased risk, which reflects multisystem physiological changes [1-3]. Recent studies have suggested that frailty could play a role in the clinical progression of neurodegenerative conditions.

Objective: The aim of the present study was to clarify the role of frailty in Parkinson's disease (PD), by administering the frailty index (FI) that is a useful tool to measure frailty by using a multidimensional approach.

Methods: We consecutively enrolled 150 patients affected by PD. We administered a FI questionnaire specifically designed for PD. The severity of the disease was evaluated by using Hoehn and Yahr scale. Motor symptoms and complications were evaluated by using means of the International Parkinson and Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II, III and IV. Non-motor symptoms were evaluated by means of the Non-Motor Symptoms assessment scale (NMSS) for PD, MDS-UPDRS part I and Montreal cognitive assessment (MoCA).

Results: In PD patients, FI score was significantly associated with age. On the base of the median value of FI we identified patients with high FI score and patient with low FI score. Patients with high FI score display higher H&Y, MDS-UPDRS I, MDS-UPDRS II, MDS-UPDRS III, NMSS total scores than patients with low FI score. MoCA scores were lower in patients with high FI score than in patients with low FI score. Finally, we observed a significant correlation between FI score and MDS-UPDRS I, MDS-UPDRS II, NMSS and MoCA score.

Conclusions: FI is a useful instrument to measure frailty in PD. Frailty may influence parkinsonian motor and non-motor symptoms severity, including the presence of cognitive impairment. Future longitudinal studies will clarify whether frailty is a predictor of disease progression in PD.

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P12

Correlation between quality of life and severity of Parkinson's disease by assessing an optimal cut-off point on the Parkinson's disease questionnaire (PDQ-39) as related to the Hoehn & Yahr scale

*Giovanni Galeoto*¹, A. Berardi¹, F. Colalelli¹, E. Pelosin², S. Mezzarobba³, L. Avanzino^{4,5}, M. Tofani⁶, G. Fabbrini^{1,7}

¹Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy;

²Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genoa, Genoa, Italy

³Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy

⁴Department of Experimental Medicine, Section of Human, Physiology and Centro Polifunzionale di Scienze Motorie, University of Genoa, Genoa, Italy

⁵Ospedale Policlinico San Martino, IRCSS, Genoa, Italy

⁶Neurorehabilitation Unit, Department of Neurosciences and Neurorehabilitation, Bambino Gesù Children's Hospital, Rome, Italy

⁷IRCSS Neuromed, Pozzilli (IS), Italy



P13

Technology-based therapy-response and prognostic biomarkers in Parkinson's disease

Giulia Di Lazzaro¹, M. Ricci², M. Al-Wardat¹, T. Schirinzi¹, F. Giannini², N.B. Mercuri¹, G. Saggio², A. Pisani¹

¹Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

²Department of Electronic Engineering, University of Rome Tor Vergata, Rome, Italy

Objective: To prospectively evaluate motor performances with technology-based objective measures (TOMs) in a cohort of Parkinson's disease patients in order to identify therapy response and progression biomarkers.

Materials: We enrolled 40 consecutive drug free PD patients at movement disorders clinic at Tor Vergata University Hospital. They were evaluated clinically by mean Unified Parkinson's Disease Rating Scale (UPDRS) part II and III and Non Motor Symptoms scale (NMS). Then they all underwent a kinematic assessment using a set of wearable inertial sensors, performing 7 motor tasks: rest tremor, postural tremor, rapid alternating hand movement, leg agility, heel to toe test, timed up and go test (TUG), pull test (PT).

Methods: At the time of the enrolment (T0), all patients underwent a clinical and a kinematic assessment. Then, a dopamine replacement therapy was started and after 6 months a follow-up visit was planned. At 12 months (T1), a new clinical and kinematic assessment was made. At 24 months (T2), a clinical evaluation was repeated. Kinematic features at T0 and T1 were compared with Mann-Whitney test. At T2, responder and non-responder patients were defined according to the variation in their clinical scores. Then, a Mann Whitney test was performed on the kinematic features at T0 between these two groups.

Results: 36 patients completed the study. Among all the kinematic features, at T1 at least one per task was significantly improved. Interestingly, many features from TUG test and PT ameliorated, even if they were scored as normal in UPDRS. In addition, one feature from RAHM and 6 features from TUG were significantly different between responder and non-responders at T0.

Discussion: One major unmet need in Parkinson's disease is the availability of non-invasive, early and reliable biomarkers, for diagnosis, prognosis and therapy response evaluation [1].

TOMs recently gained relevance to support clinicians in the assessment of motor function in movement disorders and in particular in Parkinson's disease (PD), although limited data are available in the early phases and no prospective studies are available [2][3].

Our study demonstrates that motor alteration in PD are measurable and that many motor features significantly improve after a dopaminergic is initiated, even in tasks clinically not affected as gait and balance. Moreover, some kinematic feature, recorded at the time of the diagnosis, discriminated responders from non-responders patients.

Conclusions: Our results demonstrate the possibility to objectively measure the efficacy of a therapeutic intervention in PD and identify candidates for early, technology-based prognostic biomarkers.

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P14

Gait alterations in idiopathic REM sleep behavioral disorders and early Parkinson's disease: a cross-sectional study with wearable motion sensors

Andrea Pilotto^{1,2}, M. Catania¹, A. Corbani¹, A. Galbiati³, C. Hansen⁴, R. Romijnders⁴, W. Maetzler⁴, M.C. Rizzetti², L. Ferini Strambi³, A. Padovani¹

¹Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

²FERB Onlus, Ospedale S. Isidoro, Trescore Balneario, Bergamo, Italy

³Sleep Disorders Center, Division of Neuroscience, Università Vita-Salute San Raffaele, Milan, Italy.

⁴Department of Neurology, Christian-Albrechts-University of Kiel, Kiel, Germany

Abstract: Subtle motor impairment and slowness of movements could be early features of the prodromal phase of Parkinson's disease (PD). Idiopathic REM sleep behavior disorders (RBD) have been included as the most specific prodromal PD symptom in MDS Prodromal Parkinson Disease Criteria.

Material and Methods: The aim of the study was investigate the differences in performances of gait and turning under supervised conditions in healthy controls (HC), idiopathic REM sleep behavior disorders (RBD) and Parkinson's disease patients (PD). Each subjects undergo a supervised assessment including timed up and go test, one minute walking in normal and dual task conditions gait using wearable sensors assessing turning and gait parameters.

Results: A population of 33 HC, 17 RBD, 26 PD drug naïve and 42 PD under treatment. PD patients (naïve and under treatment) showed differences in time execution of TUG and walking with increased stride time, double limb support variability and asymmetry index (all $p=0.001$) and lower turning speed ($p = 0.009$) compared to controls. RBD subjects showed increased swing time in TUG and dual task walking and lower angular velocity in TUG turning ($p=0.006$).

Discussion: Early movement alterations are detectable using wearables in early and prodromal phase of Parkinson's disease. The outcome of the analysis highlighted an important increase in the duration of the step in all in tasks, especially during dual task tasks. Larger multi-center studies are important in order to validate the data.

P15

Respiratory dysfunctions in advanced Parkinson's disease

Margherita Torti, M. Peraino, L. Vacca, D. Le Pera, F. Stocchi

Institute for Research and Medical Care IRCCS San Raffaele Pisana, Rome, Italy

Introduction: PD is associated to degeneration of other brainstem circuits responsible of non-motor dysfunctions, including respiratory disorders.

Objectives: Thirty subjects with advanced PD were enrolled to characterize the type of respiratory disorders and their correlation with ON-OFF state.

Materials and Methods: Tests performed were detection of oxyhemoglobin saturation values during the day and at nighttime, modified Borg scale for the perception of dyspnea at rest in the ON and OFF state and pulmonary function tests, both in ON and in the OFF state.

Results and conclusions: Impaired respiratory functions were detected in the ON phase in about 78% of cases and in 90% of subjects during the OFF phase. The restrictive syndrome is the most frequently type of dysfunction both, in ON and OFF phases (36.4% and 45% respectively). The peak expiratory flow and the maximum inspiratory pressure were less than 80% of the expected theoretical value for age, sex, weight, height and race in 68.2% of subjects in ON and in 90% of those in OFF). An increased perception of dyspnea was present in 54% of subjects in the ON state and in 80% of patients during the OFF phase.

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P16

Improved dual-task performance during turning after a single session of action observation training in Parkinson's disease patients

Elisabetta Sarasso^{1,4}, F. Agosta¹, A. Gardoni^{1,4}, A. Cristiano⁵, A. Tettamanti⁴, A. Sanna⁵, D. Trojaniello⁵, M.A. Volontè², M. Filippi^{1,2,3}

¹Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy

²Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

³Neurophysiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

⁴Laboratory of Movement Analysis, Vita-Salute San Raffaele University, Milan, Italy

⁵Center for Advanced Technology in Health and Wellbeing, IRCCS San Raffaele Scientific Institute, Milan, Italy

Background: Parkinson's disease (PD) patients with postural instability and gait disorders (PIGD) usually show reduced gait speed and postural stability performing attention-demanding tasks such as turning and dual-task. Difficulty performing dual-task is probably due to the automaticity loss and the consequent cognitive overload. Turning represents a challenge as it requests an increased cognitive load in order to modify the locomotor pattern and to increase interlimb coordination.

Objectives: To assess the effect of a single session of action observation (AO) on spatio-temporal dual-task gait parameters, particularly during the turning phase, in PD-PIGD patients.

Methods: Fourteen PD-PIGD patients were included and randomized into two groups: "AO group" and "Control group". Both groups performed a baseline evaluation including Timed Up and Go (TUG) test and TUG with cognitive dual-task (TUG-COG), which consisted in TUG while counting backwards by threes starting from 100 or 82. After the baseline acquisition, the AO group was asked to watch a video representing a high quality TUG performance while the Control group observed images of static landscapes. After the video observation, both groups performed again TUG and TUG-COG. Spatio-temporal gait parameters were acquired using a six cameras SMART-DX7000 optoelectronic system.

Results: After video observation, the AO group showed a significant improvement in execution time both in TUG and TUG-COG and in turning stride length during TUG, while Control group did not show significant changes. AO group also showed a trend toward an increased mean turning velocity during TUG-COG.

Conclusions: A single session of AO showed the possibility to improve mobility during TUG both with and without dual-task, particularly during turning. We hypothesized that AO might facilitate mobility by reducing the necessity to control movement also during dual-task. A randomized controlled trial investigating the effect of a longer AO training on dual-task gait abilities is needed to validate our hypothesis.

P17

Metabolomics in degenerative parkinsonisms: a pilot study

*Annamaria Landolfi*¹, J. Troisi², M.T. Pellicchia¹, M. Picillo¹, F. Abate¹, M.C. Russillo¹, P. Barone¹, M. Amboni¹

¹Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, Neuroscience Section, University of Salerno, Baronissi (SA), Italy

²Theoreo Srl, Montecorvino Pugliano (SA), Italy

Introduction: Metabolomics can be useful in studying multifactorial diseases like degenerative parkinsonisms [1]. Metabolomic data can also be used to train mathematical algorithms able to classify medical conditions, thus they can be of support in the differential diagnosis between Parkinson's disease and atypical parkinsonisms.

Objective: The aim of our study was to compare blood metabolomic profiles obtained from Parkinson's disease, Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA) patients and healthy controls in order to study the contribution coming from metabolomics in the diagnostic algorithm of parkinsonian syndromes.

Methods: We recruited 100 patients with a clinical diagnosis of Parkinson's disease (of whom 16 *de novo* patients), 23 patients with a clinical diagnosis of probable Progressive Supranuclear Palsy (divided into the several phenotypes), 12 patients with Multiple System Atrophy (divided into the 2 phenotypes), and 42 healthy controls. Metabolomic profiles have been obtained using gas chromatography coupled to mass spectrometry [2]. Metabolomic data were used to train 3 different classification algorithms. The outcomes coming from each of these algorithms were ensembled in order to combine the decisions and improve diagnostic performance [3].

Results: We arranged a series of dichotomic diagnostic steps (healthy subject vs. parkinsonian syndrome, Parkinson's disease vs. atypical parkinsonism, Progressive Supranuclear Palsy vs. Multiple System Atrophy, MSA-P vs. MSA-C). The Ensemble Machine Learning model related to differential diagnosis between Parkinson's disease and atypical parkinsonisms reached a good diagnostic accuracy, with an AUC of 0.986. The Partial Least Square Discriminant Analysis model selected a series of metabolites having the major role in class separation. A pathway analysis was conducted from these metabolites, in order to identify, in a probabilistic way, the reactions of the entire cellular metabolic system that may differentiate the studied conditions.

Conclusions: Metabolomic data can be useful in supporting differential diagnosis among parkinsonisms, pathogenetic studies and biomarker discovery.

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P18

Estimate of prodromal Parkinson disease probability in an Italian cohort of Parkinson disease siblings

Luca Baldelli¹, L. Sambati^{1,2}, M.G. Bacalini³, G. Calandra Buonauro^{1,2}, P. Garagnani³, P. Cortelli^{1,2}, C. Franceschi², P. Federica^{1,2}

We acknowledge and thank the PROPAG-AGEING Consortium for their support

¹Department of Biomedical and NeuroMotor Sciences (DiBiNeM), University of Bologna, Bologna, Italy

²IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

³Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy

Objective: To evaluate candidate PD biomarkers in non-affected siblings (Sibs) of PD patients supported by the calculation of prodromal PD probability (PPDP).

Background: PD originates from a complex interplay of genetics and environment [1]. Moreover, PD progressively develops over years, during which non-motor symptoms (NMS) can precede the appearance of motor dysfunction [2]. Scarce is evidence on how these non-motor markers interweave into the increased “familial” risk of PD siblings sharing both a common genetic and environmental background with PD patients.

Methods: Within the PROPAG-AGEING Phase 2 project, cohort of 100 Italian siblings of PD patients from Bologna, underwent a clinical and neurological evaluation including demographics, comorbidities, motor examination and non-motor symptoms such as RBD, hyposmia, cognitive impairment and symptoms of dysautonomia. PPDP was subsequently computed according to the updated criteria [3].

Results: Sibs (44% males) presented with a mean age of 63.64±9.64 years and were 3.24±6.63 years younger than their relatives with PD; their mean education was 11.12±4.09 years. Sibs obtained a mean corrected MoCA score of 25.39±2.98 points and a median (1st-3rd quartile) MDS-UPDRS-III of 1 (0- 2). 10 Sibs reported symptoms of constipation, 7 of thermoregulatory dysfunction and other 7 of depression; 9 Sibs were anosmic, 1 was positive for RBD at video-polysomnography. 92 Sibs were older than 50 years of age and obtained a median PPDP of 0.54% (0.27%–1.27%), with the highest being 23,0%. 79 Sibs had less than 1% probability of being prodromal PD, 10 Sibs reached a probability between 1 and 10%, just 3 greater than 10%.

Conclusions: Although sibs showed several motor and non-motor symptoms, PPDP did not reach significant values, indicating a higher risk of PD development in these cohort. These preliminary results have to be confirmed by longitudinal analyses.

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P19

Objective motor measures detected with wireless inertial sensors – SensHand and SensFoot – in parkinsonian and healthy subjects

*Simone Rossi*¹, E. Rovini², D. Esposito³, S. Salvadori⁴, A. Pecori⁴, G. Berchina⁵, J. Pasquini⁶, R. Monasterio⁷, G. Orlandi⁸, G. Calandra Buonauro^{1,9}, P. Cortelli^{1,9}, F. Cavallo², C. Maremmanni⁵

¹Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy

²The BioRobotics Institute, Scuola Superiore Sant'Anna, Pisa, Italy

³Co-Robotics Srl, Capannoli, Pisa, Italy

⁴Institute of Clinical Physiology, National Research Council, Pisa, Italy

⁵Unità Operativa di Neurologia, Ospedale Apuane di Massa, Massa, Italy

⁶Department of Neurology - Stroke Unit and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, Milan, Italy

⁷Department of Experimental Biomedicine and Clinical Neurosciences, Neurology Section, University of Palermo, Palermo, Italy

⁸Clinica Neurologica-Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

⁹IRCCS, Istituto delle Scienze Neurologiche, Bologna, Italy

Introduction: Monitoring motor disability in Parkinson's disease (PD) patients is a crucial need. The MDS-UPDRS is the most used scale to monitor motor impairment associated with PD. However, this evaluation is affected by inter-rater variability among different neurologist and intra-rater variability over time. This variability could be overcome by using technology-based objective measures of motor dysfunction [1].

Objectives: To acquire objective motor measures by using wearable inertial sensors in a group of parkinsonian and healthy subjects. We aimed to find objective measures able to discriminate between PD patients and healthy subjects.

Methods: 64 PD patients (age: 66.6; 40 males) with mild to moderate disease (mean MDS-UPDRS-III: 15.7±8.8 during ON state; mean H&Y score: 1.86±0.73) and 50 healthy subjects (age: 65.5; males: 39) performed a series of 14 tasks (8 included in the MDS-UPDRS-III; each task performed bilaterally), evaluating bradykinesia, rest and postural tremor and gait parameters. Wearable inertial devices, named SensHand and SensFoot, were used to register motion data [2-3]. For each task, several biomechanical parameters were acquired, for a total of 88 measurements. The discrimination power between PD patients and healthy subjects was assessed with effect-size (ES) computed as Cohen's d. The test-retest reliability was quantified as the intra-class correlation coefficient (ICC).

Results: 59 motor measures significantly differed between PD patients and healthy subject (ES>0.2); among these, 30 measures showed a relevant discrimination power (ES>0.8). The test-retest reliability was excellent both in PD patients (ICC = 0.85 for right limbs, 0.91 for left limbs) and healthy subjects (ICC = 0.78 for right limbs, 0.82 for left limbs).

Conclusions: Many motor parameters acquired with SensHand and SensFoot can differentiate PD patients from healthy subjects. By investigating a larger sample, we aim to find normative values for the motor parameters evaluated in this study. This could allow the realization of an objective motor rating scale for PD patients.

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P20

Neuropsychological and behavioral differences related to gender in a population of PD patients

Donatella Ottaviani^{1,2}, E. Barvas³, F. Giardina¹, B. Giometto¹, C. Papagno³

¹Unità Operativa di Neurologia, Ospedale S. Maria del Carmine, Rovereto (TN), Italy

²Ambulatorio per i Disturbi del Movimento, U.O. di Neurologia, Ospedale di Rovereto (TN), Italy

³Centro di Riabilitazione Neurocognitiva (CeRiN), Rovereto (TN); Università degli Studi di Trento, Trento, Italy

Content: Gender differences are now known to exist in many movement disorders and in PD.

The identifications of differences are important to tailor treatment, predict outcomes, and meet individual needs in men and women with PD. Knowing the sex-related characteristics can also give a better knowledge of pathogenetic mechanisms underlying the disease and give more details in order to design preclinical research and clinical studies.

Aim: The aim of our study is to look at the neuropsychological and behavioral differences related to gender in a population of PD patients and look for the correlations with motor symptoms and therapy expressed as LED.

Method and results: 80 PD patients (30 F and 50 M) underwent a complete neuropsychological and behavioural assessment. The two groups did not differ for age ($p=0.249$), education ($p=0.307$) and disease duration ($p=0.832$). Data regarding motor scores (UPDRS part III; H&Y) and LED were collected; also starting symptoms, non-motor symptoms, side of onset, and motor fluctuations were evaluated.

Results: Our preliminary results showed that in a verbal memory test men performed significantly worse than women and at the QUIP men showed less impulse controls than women ($p=0.045$). Scores on memory tests negatively correlated with H&Y in women, but not in men. In contrast, H&Y in men negatively correlated with emotion recognition. Worse motor symptoms positively correlate with LED in both sexes, but anxiety is more frequent only in men with higher LED ($p=0.016$).

Conclusions: We found that the most relevant differences between men and women with PD concerned changes in memory and in some psychiatric symptoms, such as anxiety and impulse control, which appeared to be more severe in men.

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P21

Relationship between sleep disorders and cognitive dysfunctions in Parkinson's disease: a meta-analysis

Gianpaolo Maggi, G. Santangelo

Neuropsychology and Memory Clinic, Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

Introduction: Patients with Parkinson's disease (PD) often complain very poor sleep quality due to delay in falling asleep, unexpectedly asleep during daytime, rapid eye movement sleep behavior disorder, sleep-disordered breathing and restless legs syndrome [1]. Sleep Disorders (SD) seem to be associated with cognitive impairment in PD, but some studies failed to confirm the relationship due to different methodological procedures across studies.

Objectives: The present meta-analytic study aims to determine whether sleep disorders are related to cognitive dysfunctions and to identify which cognitive domains are affected by sleep disorders.

Methods: A systematic literature search was performed on PubMed, PsycInfo (PROQUEST) and Scopus databases. Studies were included in the meta-analysis if they: 1) were published in peer-reviewed journals in English; 2) provided results about comparison on neuropsychological tests between PD patients with Sleep Disorders (PD-SD+) and those without Sleep Disorders (PD-SD-); 3) reported statistical results (i.e. mean, standard deviation). Global cognitive function, memory, executive functions, processing speed/complex attention/working memory, visuospatial abilities and language were the outcomes. We computed the effect sizes from data reported in the primary studies (e.g., means and standard deviations) using Hedges'g unbiased approach. Negative values of the Hedges'g indicated that PD-SD+ had lower scores than PD-SD- on each cognitive domain. Heterogeneity among the studies was assessed using Q and I2 statistics index.

Results: Fifty-four primary studies were included in the meta-analysis. Statistical analysis showed that PD-SD+ reported significantly poorer performance than PD-SD- on specific cognitive domains: Global Cognitive Function, Memory, Executive functions, Processing speed/attention/working memory, Visuospatial abilities and Language.

Conclusions: The findings of poorer performance across several cognitive domains in PD-SD+ when compared to PD-SD- confirmed a strong relationship between SD and cognitive dysfunctions, by increasing the risk of evolution in a faster cognitive decline. Therefore, treating sleep disorders might be considered as a possible strategy to prevent cognitive decline in PD.

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P22

A comparison of hearing and vestibular dysfunction in Parkinson's disease and Multiple System Atrophy

*Maria Claudia Russillo*¹, A. Scarpa², C. Cassandro³, C. Vitale⁴, M. Ralli⁵, A. Policastro², P. Barone¹, E. Cassandro², M.T. Pellicchia¹

¹Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, Neuroscience Section, University of Salerno, Salerno, Italy

²Department of Medicine and Surgery, University of Salerno, Salerno, Italy

³Surgical Sciences Department, University of Turin, Turin, Italy

⁴Department of Motor Sciences and Wellness, University Parthenope, Naples, Italy

⁵Department of Sense Organs, Sapienza University Rome, Rome, Italy

Introduction: Dizziness is a very common symptom in idiopathic Parkinson's disease (PD) and in multiple system atrophy (MSA) [1-3]. Hearing loss has been recently recognized as an additional non-motor feature in PD.

Objective: The aim of the present study is to evaluate hearing and vestibular function in patients affected by PD and MSA.

Methods: 15 PD patients, 16 MSA patients and 20 age-matched healthy controls were recruited. Audiovestibular examination included: pure-tone average (PTA) at 0.5,1,2,4,6 and 8 kHz, bed-side examination, video head impulse Test, and cervical vestibular-evoked myogenic potentials (cVEMPS). Kruskal-Wallis test, Mann-Whitney U test and Spearman's correlation test were used for statistical analysis.

Results: PD and MSA patients showed higher PTA thresholds than HC at high frequencies. MSA patients showed higher PTA thresholds at 125 Hz than HC (p=0.021). In PD patients we found a direct correlation between disease duration and PTA thresholds at 2000 (r=0,610, p=0.027) and 4000 (r=0,569; p=0.043). In MSA patients disease duration was directly related with PTA thresholds at 125 (r=0,659; p=0.005) and 250 Hz (r=0,526, p=0.036). Among PD patients cVEMPS were absent bilaterally in 46,7% and unilaterally in 13,3% of subjects. Among MSA patients, cVEMPs were absent bilaterally in 26,7% and unilaterally in 40% of subjects; p13 latency was significantly increased in PD patients as compared to HC (p=0.004). A significant inverse relationship was found between disease duration and cVEMPS amplitude in MSA patients (r=-0,704, p=0.016).

Conclusions: We found that high-frequency hearing impairment and cVEMPs abnormalities are frequent features of both MSA and PD pointing out audiovestibular dysfunction without self-reported audiologic or vestibular symptoms.

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P23

Interdisciplinary psychoeducation intervention in a group of parkinsonian patients and caregivers: one year experience

Giuseppe Meco^{1,2}, C.P. Papi²

¹Sapienza Università di Roma, Roma, Italy

²Obiettivo Parkinson, Centro Parkinson, Clinica Mater Misericordiae, Roma, Italy

Background: Numerous studies have been published which show the difficulties and psychosocial changes experienced by people with PD in their lives. Recent research has highlighted that family members caring for people with PD also feel an important impact on their well-being and quality of life [1,2]. The psychosocial adaptation to PD is a key mechanism for achieving better outcomes in terms of quality of life of patients with PD and their caregivers. In this study, we evaluated the effects of a psychoeducational intervention to help and motivate people with PD and their caregivers to a better psychosocial adjustment to PD.

Methods: The psychoeducational intervention group (10 PD patients and 10 caregivers) was followed once every month for 12 months. This group was conducted by neurologist and psychologist. To the control group (20 PD patients and 20 caregivers) were given a traditional therapeutic program: 1 visit with neurologist and psychologist every three months in outpatients service for 12 months. The Quality of Life Scale PDQ-39 for patients, MDS-UPDRS, GDS for depression, NPI and the Scale of Quality of Life of Caregivers SQLC for caregivers were given at baseline and after 12 months.

Results: Quality of life scales have improved in both PD patients and caregivers of the psychoeducational intervention group. In the traditional group 6/20 patients (30%) increased drugs and dyskinesias appeared or increased in 5/20 patients (25%). The depression level improved significantly in the psychoeducational intervention group in both patients and caregivers.

Conclusions: The results of this study seem to indicate the importance of psychoeducational interventions in promoting psychosocial adaptation to Parkinson's disease not only for patients but also for caregivers.

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Predictors of fatigue severity in early, *de novo* Parkinson disease patients: a one year longitudinal study

Mattia Siciliano^{1,2}, L. Trojano², R. De Micco¹, A. Giordano¹, A. Russo¹, G. Tedeschi¹, C. Chiorri³, A. Tessitore¹

¹Department of Advanced Medical and Surgical Sciences - MRI Research Center Vanvitelli-FISM, University of Campania Luigi Vanvitelli, Naples, Italy

²Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

³Department of Educational Sciences, University of Genova, Genova, Italy

Introduction: Fatigue is one of the most common and disabling nonmotor symptom in Parkinson's disease (PD). The aim of the present study was to investigate the 1-year course of fatigue in a consecutive sample of *de novo* drug-naïve patients with PD, and at systematically searching for baseline motor and nonmotor predictors associated with fatigue severity over time.

Methods: Fifty-five consecutive *de novo* PD patients (age: 64.71±7.74 years) underwent a comprehensive examination, including Parkinson Fatigue Scale, Epworth Sleepiness Scale, Parkinson's Disease Sleep Scale, Beck Depression Inventory, Parkinson's Anxiety Scale, Apathy Evaluation Scale, and an extensive neuropsychological evaluation exploring attention and working memory, executive functions, memory, visuospatial abilities and language. Bivariate regression analyses, completed by multivariate regression analysis (hierarchical method), were performed to identify baseline predictors independently related to fatigue severity at 1-year follow-up.

Results: Prevalence rate of fatigue (defined by PFS cut-off) increased from 22% at baseline to 38% at 1-year follow-up. Of the patients with fatigue at baseline, 91% continued to have fatigue at follow-up (i.e., persistent fatigue). Multivariate regression analysis identified fatigue ($p < 0.01$), daytime sleepiness ($p < 0.01$), and emotional apathy ($p < 0.01$) as the main baseline variables that significantly predicted fatigue severity at 1-year follow-up.

Conclusions: In early PD, fatigue increases and persists over time, and its severity is related to higher baseline levels of fatigue, excessive daytime sleepiness, and emotional apathy. These results warrant to monitor fatigue since the early stage of disease, and suggest that treating excessive daytime sleepiness and emotional apathy might prevent its worsening.

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P25

Relationship between impulsivity traits and awareness of motor intention in patients with Parkinson's disease: preliminary data

*Fabio Giovannelli*¹, C. Menichetti², L. Kiferle², L. Raglione², S. Brotini², P. Vanni², D. Bacci², M. Baldini², A. Borgheresi², A. Del Bene², E. Grassi², L. Guidi², L. Toscani², G. Volpi², P. Palumbo², M.P. Viggiano¹, M. Cincotta²

¹Dipartimento NEUROFARBA, Università degli Studi di Firenze, Firenze, Italy

²Area Malattie Cerebro-Vascolari e Degenerative, Dipartimento delle Specialistiche Mediche, Azienda USL Toscana Centro, Firenze, Italy

Introduction: High impulsivity levels can be found in patients with Parkinson's disease (PD). It has been hypothesized that impulsive personality traits may favour impulse control disorders (ICDs) onset during dopaminergic therapy. In healthy subjects, a relationship between the awareness of motor intention and impulsive personality traits assessed by the Barratt impulsivity scale (BIS-11) has been reported [1]. Namely, higher BIS-11 scores were associated with a shorter interval between the awareness of the intention to perform a self-initiated movement and the actual movement onset. Moreover, delayed awareness of motor intention has been observed in PD patients compared to healthy controls [2].

Objective: The aim of the present study was to evaluate the relationship between the awareness of voluntary action and impulsivity traits in PD.

Methods: Twenty-six patients with idiopathic PD (HY I–III) on dopaminergic therapy underwent an impulsivity trait assessment by the BIS-11 and a task based on the Libet's clock. Namely, they were requested to perform a self-initiated movement and to report the time they first feel their intention to move (W-judgement) or the time of the actual movement (M-judgement).

Results: Patients were split into two groups according to the median BIS-11 score. In patients with higher BIS-11 scores the mean difference between the W-judgement and the actual movement was significantly lower than in patients with lower BIS-11 score. No difference emerged in the M-judgement.

Conclusions: Data suggest that also in PD patients the impulsive personality trait is related to a 'delayed' awareness of motor intention and therefore to a shorter interval to allow a conscious 'veto' of the impending action. Characterization of the temporal profile of awareness of motor intention could prove useful in identifying PD patients at risk of developing ICDs during dopaminergic treatment.

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P26

Developing an innovative telenursing service for people with Parkinson's disease

Francesca Mancini^{1,2}, T. Carta², J. Cordasco², S. Thomas³, B.R. Bloem⁴

¹IRCCS Istituto Auxologico Italiano, Milan, Italy

²CareApt, Bresso, Italy

³Commissioning Excellence, Wilmington Healthcare, London, UK

⁴Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen Medical Centre, Nijmegen, The Netherlands

Introduction: Parkinson's disease (PD) is characterized by a wide variety of motor and non-motor symptoms, often poorly recognized and treated, which cause significant burden on quality of life of patients and their caregivers [1].

Objective: To increase continuity of care and self-efficacy in the management of symptoms of people with PD by a specialised telenursing service operating through an integrated care platform.

Methods: Combining the experience of international movement disorders specialists, nurses, patients and caregivers, key unmet needs have been mapped and digital care models have been reviewed [1-3].

Results: A novel integrated care service (ParkinsonCare) has been designed to provide patients and caregivers with regular symptoms monitoring and daily expert support provided by a Parkinson's Disease Nurse Specialists (PDNS), leveraging upon a collaborative medicine platform enabling real life data sharing and timely coordination of medical interventions. Each patient is managed by a dedicated PDNS that, supported by a suite of clinical validated scales, completes a registration document containing the demographic, social, family and clinical information, identifies health priorities and main self-management gaps, elaborates an individualized care plan and regularly follows up its outcomes. The PDNS helps the patient to prepare the planned neurological visits and liaise with the patient's care team whenever it's necessary. To properly characterize patients reported symptoms, the PDNS relies upon a suite of interactive algorithms, based on state of the art clinical practice and validated scales.

Conclusions: This innovative telenursing model is suitable to be integrated into current health care systems to improve quality of life by increasing continuity and coordination of care. The systematic real life data gathering allows better disease understanding as well as individualized clinical decision making, potentially preventing complications and consequent healthcare consumptions. Studies are needed to demonstrate clinical efficacy and impact on healthcare costs.

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P27

Non-motor symptoms and young onset Parkinsons's disease

Roberta Zangaglia, B. Minafra, L. Chiodi, M. Todisco, F. Valentino, C. Pacchetti

Parkinson and Disorders Movements Unit, IRCCS Mondino Foundation, Pavia, Italy



RITIRATO

P28

Correlation between quality of life, cognition, motor and non-motor symptoms in patients with Parkinson's disease L-dopa naïve: a prospective study

*Ottavia Baldi*¹, G. Lagravinese¹, E. Pelosin^{1,2}, R. Marchese², F. Di Biasio², C. Ogliastro¹, G. Abbruzzese¹, L. Avanzino^{2,3}

¹Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), Genoa, Italy

²IRCCS Policlinico San Martino, Genoa, Italy

³Department of Experimental Medicine, Section of Human Physiology, University of Genoa, Genoa, Italy

Introduction: It is well known that the overall burden of non-motor symptoms (NMSs) in parkinsonian fluctuating and non-fluctuating patients is a more significant contributor to the quality of life (QoL) than motor symptoms [1, 2]. Some studies have also shown that there is an effect of dopaminergic medication on NMSs in late-stage Parkinson's Disease (PD) [3].

Objectives: The aim of the present study is to assess which are the best predictors of QoL in early-stage PD patients who still do not assume L-dopa and whether L-dopa therapy would impact QoL by acting on motor and non-motor symptoms.

Methods: PD patients in Hoehn and Yahr stage I-II who had never taken L-dopa are recruited for this study. Health-related QoL is measured with the 39-item PD Questionnaire (PDQ-39). Subjects complete the MDS UPDRS Parts I-IV as well as scales to assess anxiety (HAM-A), depression (HAM-D), apathy (AES), cognition (MOCA, TMT-A, TMT-B, FAB), autonomic dysfunction (Scopa-AUT). NMSs are assessed by using the modified version of the Non-Motor Symptoms Scale (NMSS). At baseline visit we used univariate analyses to select clinical predictors. In this prospective study, patients will be followed for two years with evaluations every 6 months.

Results: So far 17 PD patients (11 males, mean age $66,7 \pm 9,4$) were included in this study and performed baseline evaluation. QoL significantly correlated with NMSs ($p < 0.001$). A significant correlation was found between PDQ-39 and UPDRS I ($p < 0.001$) and UPDRS II ($p = 0.018$), but not with UPDRS III ($p = 0.22$). PDQ-39 correlated also with HAM-A ($p = 0.005$) and HAM-D ($p = 0.008$) scores. There was no significant correlation between PDQ-39 and cognitive functions (p always > 0.05).

Conclusions: NMSs are the ones that mostly affect QoL in our small cohort of early-stage PD patients. Prospective evaluations will help in understanding whether L-dopa therapy would influence QoL by acting also on NMSs.

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P29

Influence of peripheral immune system on non motor symptoms in Parkinson's disease

Luca Magistrelli^{1,2}, E. Storelli³, A.V. Milner¹, E. Contaldi^{1,4}, E. Rasini³, F. Marino³, M. Cosentino³, R. Cantello¹, C. Comi⁵

¹Movement Disorders Centre, Neurology Unit, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

²PhD Program in Clinical and Experimental Medicine and Medical Humanities, University of Insubria, Varese, Italy

³Centre of Research in Medical Pharmacology, University of Insubria, Varese, Italy

⁴PhD Program in Medical Sciences and Biotechnology, University of Piemonte Orientale, Novara, Italy

⁵Neurology Unit, Sant'Andrea Hospital, Vercelli, Italy

Background: Recent papers highlight the emerging role of peripheral immune system in the pathophysiology of Parkinson's disease (PD). How the immune system may influence motor and non motor symptoms in PD patients is not yet fully understood. The aim of this study is to describe the suitable role of peripheral immune system on non motor symptoms in PD patients.

Methods: Patients were recruited at the Movement Disorders Center of Novara. All subjects underwent a neurological assessment using specific motor (UPDRS III and H&Y) and non motor scales: Zung score (total and percentage), Epworth, BDI II, Questionnaire for Impulsive-Compulsive Disorders, the REM Sleep Behavior Disorder Screening Questionnaire, Non-Motor Symptom (NMS) assessment scale, Compass 31. Lymphocytes subpopulations (Th1, Th2, Th17) were evaluated with flow cytometry.

Results: 43 PD patients were enrolled (13 female). Mean age was 68.9±8.4. Mean Zung, BDI-II and Epworth total score were respectively 34.8±7.04; 11.08±9.7 and 5.17±4.07. QUIP-RS total score was 13.6±14.9, with the highest sub-score in hobby with a total of 4.11±5.58. Total score NMS score was 31.5±21.7. A significant positive correlation was detected between NMS urinary sub-score and Th2 total number (p=0.04; r2=0.12) and between NMS cardiovascular sub-score and Th1 total number (p=0.004; r2=0.23). Mean RBD score was 4.8±2.9; a positive correlation was found for RBD total score and Th2 total number (p=0.003; r2=0.24).

Conclusions: In this study we point out a possible role of peripheral immune system in the development of non motor symptoms in a cohort of PD patients.

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Asymmetrical cochlear dysfunction as a lateralized non-motor feature in Parkinson's disease

*Rocco Cerroni*¹, A. Vizziano^{2,3}, E. Garasto¹, M. Conti¹, R. Sisto⁴, A. Moleti², N.B. Mercuri¹,
A. Stefani¹, M. Pierantozzi¹

¹Parkinson Centre, Department of System Medicine, University of Rome Tor Vergata, Rome, Italy

²Department of Physics, University of Rome Tor Vergata, Rome, Italy

³Department of Clinical Sciences and Translational Medicine, University of Rome Tor Vergata, Rome, Italy

⁴INAIL Research, Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, Monteporzio Catone (Rome), Italy



P31

Autonomic dysfunction in idiopathic Parkinson's Disease, GBA-PD and Multiple System Atrophy

Giulia Lazzeri¹, A. Carandina², E. Monfrini¹, M. Percetti¹, A. Centola², L. Verdi², M. Vizziello¹, F. Arienti¹, I. Trezzi¹, G. Franco¹, N. Bresolin¹, N. Montano², E. Tobaldini², A. Di Fonzo¹

¹IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy.

²Department of Internal Medicine, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

Introduction: Autonomic dysfunction is a well-known feature of α -synucleinopathies. Pathogenic and clinical differences between Parkinson's disease (PD) and Multiple System Atrophy (MSA) have been extensively described in the literature. Conversely, less is known about the impact of glucocerebrosidase (GBA) gene, associated with a more severe disease course in PD [1], on dysautonomic symptoms.

Objective: The aim of the study is to assess the differences of cardiovascular autonomic dysfunction in PD patients, with and without GBA mutations, compared to MSA patients.

Methods: Autonomic cardiac control at rest and during orthostatic challenge in 9 idiopathic PD, 6 GBA-PD and 4 MSA patients was evaluated. ECG and respiration were recorded in supine position for 10 minutes and during active standing for another 10 minutes. Segments of 250 ± 50 beats were selected for the analysis of Heart Rate Variability using two approaches, linear spectral analysis and non-linear symbolic analysis.

Results: Concerning demographic characteristics, the sub-groups did not differ significantly in age nor disease duration. At rest, autonomic parameters were similar in the 3 groups.

iPD patients showed a significant increase of heart rate and sympathetic modulation, expressed by 0V%, in response to orthostatic stress. Differently, MSA and GBA-PD patients did not show any significant modification of autonomic parameters during standing. In details, orthostatic challenge caused an higher increase of 0V%, marker of sympathetic modulation, in iPD patients compared to MSA and GBA-PD cases (120% vs 53% and 33%).

Conclusions: The study suggests that GBA-PD patients show a more severe cardiovascular autonomic dysfunction compared to IPD, similarly to MSA patients.

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P32

Changing the side of Pisa syndrome: a case of dramatic improvement with botulinum toxin

*Francesco Marchet*¹, C.A. Artusi¹, U. Dimanico², G. Massazza², L. Lopiano¹

¹Department of Neuroscience Rita Levi Montalcini, University of Torino, Torino, Italy

²Physical Medicine and Rehabilitation Unit, Department of Orthopedics, Traumatology and Rehabilitation, University of Torino, Torino, Italy

Introduction: Pisa syndrome (PS) is a disabling postural abnormality with a prevalence of 9% in Parkinson's disease (PD). Few studies suggest the efficacy of Botulinum toxin (BoNT) for treating PS, but data are still controversial and target muscles still need to be clarified.

Case report: A 76-year-old man developed PS 2 years after PD diagnosis. Twenty-four months after PS onset the extent of the left trunk flexion was 16.5°, the fulcrum at the T12 spinous process, and the back pain 4/10 at the visual-analogue scale (VAS). Orthostatic spine X-ray and dorsal-lumbar spine MRI excluded structural spine deformities and vertebral rotation. Using an ultrasound and electromyography guidance, we injected 50 units of OnabotulinumtoxinA within the left longissimus-thoracis and 50 units within the left iliocostalis-lumborum muscle at T12 level. Five days later, the patient noticed initial changes complaining of accentuated back pain. The following day he reported a complete relieving of the lateral trunk flexion. We examined the patient 10 days after BoNT injection (T1): the back pain was disappeared and the lateral trunk flexion was on the opposite side than before treatment (8° right lateral flexion). One month after BoNT injection (T2), the opposite trunk flexion had disappeared, and the patient showed an extremely improved PS, with a left lateral trunk flexion of 6.5° and no associated back pain (VAS: 0/10).

Discussion: Injecting BoNT in specific paraspinal muscles at the fulcrum level could result in a tremendous efficacy in PS, both on trunk flexion and pain. While highlighting the need for appropriate RCTs to clarify best doses and targets of BoNT in PS, this case suggests that PS is a treatable condition, even in its chronic phase and with low doses of BoNT.

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Non-motor burden in Isolated REM Sleep Behaviour disorder: systematic evaluation in a prospective cohort

Luca Baldelli¹, L. Sambati^{1,2}, G. Calandra Buonauro^{1,2}, P. Cortelli^{1,2}, F. Provini^{1,2}

¹Department of Biomedical and NeuroMotor Sciences (DiBiNeM), University of Bologna, Bologna, Italy

²IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

Introduction: Consistent evidence demonstrated how isolated REM sleep behaviour disorder (iRBD) can be the prodromal stage of an overt α -synucleinopathy [1]. The presence of cognitive and autonomic impairment increases the risk of conversion [2-3], but a comprehensive and detailed evaluation is rarely available.

Methods: We consecutively enrolled a cohort of iRBD patients and a cohort of matched controls (CTRs). Each subject underwent a battery of standardized autonomic tests (cardiovascular reflexes tests), questionnaires evaluating symptoms of dysautonomia such as the Scale for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT), a neuropsychological evaluation and an odour identification test.

Results: The study included 32 iRBD (mean age 67.94 ± 7.03 years, 7 females) and 29 CTRs (68.03 ± 9.25 years, 5 females). The difference in years of education was not significant between the two groups ($p=0.261$). At autonomic tests 18 iRBD and 1 CTR showed a pathologic Valsalva Manoeuvre ($p<0.001$), of them 9 iRBD patients and a different CTR ($p=0.009$) showed orthostatic hypotension (OH) at the 3rd minute of 65° tilting. Patients with OH had a longer iRBD duration: 11.74 ± 7.07 vs. 6.36 ± 4.02 years; $p=0.039$. SCOPA-AUT score was significantly increased in iRBD (11.84 ± 8.70 vs. 7.50 ± 7.81 ; $p=0.007$), especially within cardiovascular domain ($p=0.004$). iRBD in respect to 1 CTR fulfilled the criteria for mild cognitive impairment ($p=0.018$), with higher frequency of abnormal results in visuo-executive tasks ($p=0.026$ and 0.049). iRBD obtained a score of 6.11 ± 2.67 at odor identification test, lower than CTRs with 8.71 ± 2.72 ($p=0.001$).

Conclusions: iRBD shows a heavier non-motor burden, with dysautonomia usually developed over the years. The higher prevalence of dysautonomia and cognitive impairment an already present neurodegenerative process.

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P34

Expected and unexpected acute effects on motility and balance in *de novo* Parkinson's disease patients due to a standard dose of L-dopa. Subclinical instrumental evidences

Giovanni Mostile*, A. Nicoletti*, G. Portaro, R. Terranova, P. Cunsolo, F. Contrafatto, G. Donzuso, C. Rascunà, C.E. Cicero, A. Luca, M. Zappia

**These authors contibuted equally to this work*

Department G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy

Background: Gait impairments are a hallmark of Parkinson's disease (PD). Although patients benefit from L-dopa therapy, its acute effect on gait is poorly understood. This study investigates the acute effects of L-dopa on balance and motility in patients with *de novo* Parkinson's disease (PD) using an instrumental approach.

Methods: We studied twenty subjects newly diagnosed as clinically probable PD. All patients underwent a standardized acute L-dopa challenge test. Gait assessment was carried out both at baseline and at pharmacologic peak. For each section, subjects performed the Timed Up and Go (TUG) test wearing an inertial sensor. Conventional kinematic parameters processed by the system together with parameters from non-linear multifractal analysis of raw motion data were obtained.

Results: A common trend of improvement on medication was observed for most sensorial parameters. A subgroup of fourteen patients was identified based on short-duration response magnitude with a greater clinically detectable motor response. In these patients, L-dopa effect results in unexpected accelerations during postural changes, possibly reflecting instability. Multifractal analysis of motion signals revealed an opposite behavior as expected by the normalization effect of the drug in the rotational tasks.

Discussion: Balance and motility processes may respond differently to L-dopa in PD, also in an early stage of disease. Patients with a greater acute motor response may present worse postural control when on medication. L-dopa may sub-clinically worsen rotational tasks, requiring an instrumental monitoring for treatment optimization.

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Relationship between midbrain MRI assessments and severity of disease in progressive supranuclear palsy

*Filomena Abate*¹, M.F. Tepedino¹, R. Erro¹, S. Ponticorvo², G. Volpe⁴, D. Frosini⁵, E. Del Prete⁵, P. Cecchi⁶, M. Cosottini⁶, R. Ceravolo⁵, F. Esposito^{2,3}, M.T. Pellecchia¹, R. Manara², P. Barone¹, M. Picillo¹

¹Center for Neurodegenerative Diseases (CEMAND), Department of Medicine, Surgery and Dentistry, Neuroscience Section, University of Salerno, Salerno, Italy

²Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, University of Salerno, Baronissi, Salerno, Italy

³Department of Diagnostic Imaging, University Hospital A.O.U. OO.RR. San Giovanni di Dio e Ruggi D'Aragona, Scuola Medica Salernitana, Salerno, Italy

⁴Neurology, University Hospital A.O.U. OO.RR. San Giovanni di Dio e Ruggi D'Aragona, Scuola Medica Salernitana, Salerno, Italy

⁵Dipartimento di Medicina Clinica e Sperimentale Università di Pisa, Italy

⁶Dipartimento di Ricerca Traslationale e delle Nuove Tecnologie in Medicina e Chirurgia, Università di Pisa, Pisa, Italy

Introduction: Although different studies have explored the role of neuroimaging biomarkers in the progressive supranuclear palsy (PSP) diagnostic process, little is known about the relation between neuroimaging indexes and the patients' clinical profiles.

Objective: Aim of this study is to explore the relation between the known MRI biomarkers and the clinical outcomes in a large cohort of PSP patients, diagnosed according to MDS criteria [1].

Methods: Seventy-eight patients with PSP were included in this analysis [thirty-nine with PSP-Richardson's syndrome (PSP-RS); thirty-nine patients with other variants (vPSP)]. For all of them the available MRI indexes were calculated; as for the clinical outcomes we decided to use the scores obtained at the PSP Rating Scale (PSPRS) and at the Natural History and Neuroprotection in Parkinson Plus Syndromes-Parkinson Plus Scale (NNIPPS-PPS).

Results: Of all the MRI biomarkers, only the length of midbrain tegmentum (l-teg) [2] was significantly associated with the PSPRS scores, while none of them was in relation with the NNIPPS-PPS scores. Moreover, the l-teg was able to predict the presence of supranuclear gaze palsy, the last being also significantly associated with PSP-RS compared to vPSP subtypes. MR Parkinsonism index 2.0 (MRPI 2.0) [3] was associated with gait difficulties as measured on item 26 of PSPRS. None of the available neuroimaging biomarkers was able to predict the postural instability as measured on item 27 of PSPRS.

Conclusions: Our data suggest that most MRI biomarkers lack a significant association with the clinical profiles of PSP patients. Further studies are warranted to better define the relation between neuroimaging and clinical features, as well as whether these results could be better explained by the possibility that MRI indexes fail to include important brain areas associated with the PSP symptoms or by the inability of the currently used scales to assess the effective clinical picture of these patients.

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P36

Sex-specific whole-brain network topologic organization in drug naïve Parkinson's disease patients

*Sara Satolli*¹, R. De Micco¹, F. Agosta², S. Basaia², M. Siciliano¹, F.P. Bonifacio¹, G. Tedeschi¹, A. Tessitore¹, M. Filippi²

¹Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Napoli, Italy

²Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: Male sex is a prominent risk factor for developing Parkinson's disease (PD). Conversely, as the disease progresses female PD patients seem to be at higher risk to develop treatment-related motor complications. Compelling evidence suggests that a gender-specific pattern and functioning within the nigro-striatal dopaminergic pathway may underlie these differences.

Objectives: To investigate the potential sex-difference effect on the whole-brain network topologic organization in a large cohort of drug-naïve PD patients using resting-state functional MRI (rs-fMRI) and its correlation with baseline and longitudinal clinical features.

Methods: 147 drug-naïve PD patients (85/62 male/female) were consecutively enrolled. Motor, non-motor and neuropsychological assessments as well as rs-fMRI were performed at baseline. 38 age- and sex-matched controls (20/18 male/female) were also enrolled in the study. Graph analysis and connectomics were used to assess global and local topological network properties and regional functional connectivity (FC) in female PD patients compared to males. Multivariate linear and logistic regressions investigated whether functional imaging data at baseline were predictors of clinical outcome over a 1-year period.

Results: At baseline, female PD patients showed a preserved global functional brain architecture compared to controls. Male PD patients showed altered functional topological properties within the basal ganglia network compared to female PD patients. No FC differences were detected between male and female controls. Functional connectivity changes within the basal ganglia at baseline showed to be correlated with both motor and cognitive impairment at follow-up.

Conclusions: Our findings revealed the presence of a disease-related, sex-specific functional architecture within the basal ganglia in a large cohort of early PD patients. We hypothesize that these findings may be related to the presence of different gender-specific nigrostriatal dopaminergic pathways and might be potentially used to predict disease progression over time.

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Effects of aging on striatal [123I]-FP-CIT binding and clinical features in *de novo* Parkinson's disease

Sara Giannoni¹, G. Palermo¹, D. Frosini¹, T. Depalo², D. Volterrani², U. Bonuccelli¹, R. Ceravolo¹

¹Unit of Neurology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

²Regional Center of Nuclear Medicine, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Introduction: There is a growing recognition that Parkinson's disease (PD) has phenotypic heterogeneity in its clinical manifestations. The basis for this heterogeneity is unknown, but both age and pattern of striatal dopamine depletion at onset seem to play an important role [1-3]. However, evidence supporting an influence of age on PD phenotype and pattern of dysfunction in striatal dopaminergic system at its onset is conflicting.

Objective: To investigate age-related differences in dopamine transporter (DAT) availability in *de novo* PD patients by [123I]-FP-CIT SPECT and to examine whether the pattern of striatal dopamine depletion could provide prognostic information on the clinical profiles of early-stage PD.

Methods: We retrospectively studied 105 patients with early PD who underwent [123I]-FP-CIT SPECT and detailed neuropsychometric tests at baseline. Mean caudate and putamen SBR and caudate/putamen ratio were obtained for each patient to assess the spatial patterns of striatal dopamine depletion. Linear regression analyses were used to investigate the relationship between such baseline SPECT measures and age of PD onset as well as possible independent associations with clinical features at baseline.

Results: Older age at onset was associated with a more severe motor phenotype, worse cognitive scores and a greater dopaminergic dysfunction on [123I]-FP-CIT SPECT. Moreover, patients with older age at onset exhibited more severely decreased DAT availability in the caudate than subjects in the young-onset group ($p=0.013$). After adjusting for age, we found a significant inverse correlation of putaminal DAT binding with UPDRS motor score ($p=0.027$) and a positive correlation of caudate uptake with MMSE and Rey Complex Figure scores ($p<0.001$).

Conclusions: Our findings confirm an uneven age effects of [123I]-FP-CIT binding in the striatal subregions of *de novo* PD patients suggesting an age-related decline in caudate dopaminergic dysfunction which might represent a critical determinant of the increased risk of cognitive deterioration in old onset PD.

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Neuroanatomical findings in idiopathic REM sleep behavior disorder (iRBD) and Parkinson's disease: a VBM study

Giulia Donzuso¹, R. Squillaci¹, L. Giuliano¹, C.E. Cicero¹, A. Luca¹, G. Mostile¹, S. Palmucci², M. Zappia¹, A. Nicoletti¹

¹Department G.F. Ingrassia, Section Neuroscience, University of Catania, Catania, Italy

²Radiodiagnostic and Radiotherapy Unit, University Hospital Policlinico Vittorio Emanuele, Catania, Italy

Objectives: Idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD) is a parasomnia characterized by the loss of physiological atonia with abnormal behavior during REM sleep. RBD could be the prodromal manifestation of neurodegenerative diseases, such as Parkinson's disease (PD). Neuroimaging studies showed the presence of structural and functional abnormalities involving cortical and subcortical regions in RBD [1].

Materials and methods: Patients with iRBD, diagnosed based on thorough clinical interviews and VPSG, were recruited. Patients with PD according to the UK Brain Bank criteria were recruited from the PaCoS cohort, and evaluated with the RBD Single-Question Screen and then divided into PD with RBD (PD-RBD+) and PD without RBD (PD-RBD-). A group of healthy controls (HC) were also recruited. Each subject underwent a 3D T1-weighted brain MRI.

Results: Sixteen patients with iRBD were enrolled, 13 PD-RBD, 17 PD patients and 30 age- and sex-matched HC. VBM analysis revealed a pattern of grey matter atrophy (GM) with a gradient from HC to PD-RBD, involving left and right middle temporal gyrus and right cerebellum. An inverse pattern, showing GM increase, was found in right caudate body, left midbrain and left middle frontal gyrus ($p < 0.05$ FWE).

Discussion: We found the reduction of GM density in temporal areas and cerebellum with a decreasing pattern of atrophy from PD-RBD to HC, and the presence of increased GM volume in basal ganglia structures, together with the involvement of midbrain, with an inverse pattern, from PD-RBD to HC. Previous findings showed the involvement of cortical and subcortical structures [2]. Thus, these regions seemed to be involved in REM sleep mechanisms, but also exhibited an overlap with early stage of PD.

Conclusions: This pattern of GM abnormalities could suggest the presence of a neurobiological link connecting RBD to α -synucleinopathies and could be used as a predicting biomarker of PD [3].

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Combined use of morphometric indexes and quantitative susceptibility mapping for differential diagnosis of degenerative parkinsonisms

Sonia Mazzucchi¹, E. Del Prete¹, M. Costagli^{2,3}, D. Frosini⁴, D. Paoli¹, G. Donatelli^{2,5}, P. Cecchi⁵, G. Migaleddu⁶, U. Bonuccelli¹, M. Cosottini⁶, R. Ceravolo¹

¹Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

²Imago7 Research Foundation, Pisa, Italy

³Laboratory of Medical Physics and Biotechnologies for Magnetic Resonance, IRCCS, Stella Maris, Pisa, Italy

⁴Neurology Unit, Department of Medical Specialties, AOUP, Pisa, Italy

⁵Neuroradiology Unit, AOUP, Pisa, Italy

⁶Neuroradiology Unit, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Introduction: MRI morphometric indexes were developed to differentiate Parkinson's disease (PD) and atypical parkinsonisms. The pons-to-midbrain ratio (P/M) and the Magnetic Resonance Parkinsonism Index (MRPI) showed high diagnostic accuracy, but early diagnosis remains challenging. Iron-sensitive MRI techniques, as Quantitative Susceptibility Mapping (QSM), have recently shown encouraging diagnostic potential.

Objectives: To use a multimodal MRI approach in patients affected by PD, Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP) to compare the diagnostic accuracy of morphometric and quantitative measurements obtained on selected regions of interest (ROIs).

Methods: 100 consecutive patients recruited at the Movement Disorders Center of Pisa with a clinical diagnosis of probable PD (38), MSA (20, 12 p-MSA and 8 c-MSA) or PSP (42, 26 PSP-Richardson's Syndrome-RS and 16 PSP non-RS phenotype). Each patient underwent clinical and radiological evaluation with 3T-MRI. The morphometric indexes P/M and MRPI were manually calculated on T1-weighted images. QSM were generated and ROIs were drawn on substantia nigra (SN), red nucleus (RN), subthalamic nucleus (STN), globus pallidus, caudate and putamen.

Results: Morphometric evaluation was possible in all patients, QSM were obtained in 88 cases. The 3-group comparison showed significant differences ($p < 0.001$) in P/M, MRPI and susceptibility values of SN, RN, STN and putamen. Morphometric indexes and magnetic susceptibility of RN showed high diagnostic accuracy in differentiating PD from PSP, especially when considering only the PSP-RS subgroup (in this scenario the accuracy of QSM and MRPI are comparable, AUC=0.959). Morphometric indexes did not show significant differences between PD and p-MSA whereas magnetic susceptibility of RN and putamen were able to differentiate the two groups ($p = 0.005$). Optimal cut-off values were determined to evaluate concordance, which ranged from good to moderate.

Conclusions: Our results confirm the potential of morphometric and quantitative methods, supporting the use of multimodal MRI in the diagnostic phase of degenerative parkinsonisms.

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Bipolar disorder and Parkinson's disease: the [123I]-FP-CIT SPECT study

*Annamaria Landolfi*¹, G. D'Agostino², L. Pace³, P. Monteleone², P. Barone¹, R. Erro¹

¹University of Salerno, Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, Neuroscience Section, Salerno, Italy

²University of Salerno, Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, Psychiatry Section, Salerno, Italy

³University of Salerno, Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, Nuclear Medicine Section, Salerno, Italy

Introduction: Recent evidence suggest that patients with Bipolar Disorder (BD) have an increased risk of Parkinson's disease (PD) [1]. However, since treatment of BD can also induce parkinsonism, it is unclear whether its appearance in BD is underlined by a neurodegenerative process.

Objective: To study the integrity of the nigrostriatal dopaminergic pathway in BD patients with concomitant extrapyramidal signs by means of single photon emission computed tomography ([123I]-FP-CIT SPECT) for dopamine transporter quantification.

Methods: Twenty consecutive BD patients with extrapyramidal signs [2] underwent a [123I]-FP-CIT SPECT and a standardized neurological examination. Clinical and [123I]-FP-CIT data were compared to 25 *de novo* PD patients.

Results: Four out of 20 BD patients (20%) had [123I]-FP-CIT scores below normative values [3]. Their clinical features and cumulative exposure to both antipsychotic drugs and lithium were similar to BD patients with normal dopamine transporter imaging. When compared to PD patients, BD patients with pathological scans had lower clinical asymmetry, higher putaminal binding ratio and putamen-to-caudate ratios than PD patients, despite similar motor symptom burden, in terms of MDS-UPDRS III scores.

Conclusions: Our preliminary data suggest that up to 20% of BD patients with parkinsonism might have an underlying dopaminergic deficit. However, these patients have different clinical and SPECT characteristics compared to PD. This supports the evidence that BD may represent a risk factor for subsequent development of neurodegenerative parkinsonism, the nature of which needs to be elucidated.

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Correlation between [123I]-FP-CIT SPECT imaging and 3T brain MRI scan in patients with normal pressure hydrocephalus

*Antonino Bruno*¹, C. Del Gamba¹, D. Frosini¹, D. Volterrani², G. Migaleddu³, N. Benedetto⁴, P. Perrini⁴, C. Pacchetti⁵, M. Cosottini³, U. Bonuccelli¹, R. Ceravolo¹

¹Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy

²Department of Translational Research and of New Surgical and Medical Technologies, Nuclear Medicine Unit, University of Pisa, Pisa, Italy

³Department of Translational Research and of New Surgical and Medical Technologies, Neuroradiology Unit, University of Pisa, Pisa, Italy

⁴Department of Neurosurgery, University of Pisa, Pisa, Italy

⁵Parkinson's Disease and Movement Disorders Unit, IRCCS Mondino Foundation, Pavia, Italy

Introduction: Idiopathic normal pressure hydrocephalus (iNPH) is a neurologic disorder requiring the combination of clinical (gait, urinary and/or cognitive disturbances) and radiological criteria (Evan's index > 0.3, in addition to supportive features) to be suspected and supported by the sustained amelioration in response to cerebrospinal fluid drainage [1]. Diagnosis of iNPH is challenging because of its varying presentation and the overlapping with other neurodegenerative disorders [2].

To discriminate iNPH and NPH associated to neurodegenerative disorders [123I]-FP-CIT SPECT imaging is thought to be helpful. Furthermore 3T MRI with SWAN sequences has a high diagnostic accuracy in detecting idiopathic parkinsonisms through the visualization of the loss of the 3-layer organization of the substantia nigra (SN) [3].

Objective: To evaluate the correlation between [123I]-FP-CIT SPECT imaging and 3T brain MRI scan in patients with NPH.

Methods: Ten patients with clinical and radiological criteria for iNPH (74,4 ± 16 years; 20% women) were recruited. All patients underwent [123I]-FP-CIT SPECT and 3T brain MRI scan.

Results: 4 patients showed normal visual and semi-quantitative [123I]-FP-CIT SPECT while 6 patients had abnormal [123I]-FP-CIT SPECT. All the patients with normal DAT SPECT displayed bilateral preservation of the 3-layered organization of the SN at 3T brain MRI. Among the patients with abnormal DAT SPECT, 4 displayed loss of the 3-layer organization of the SN while 2 displayed preserved intermediate hyperintense part of SN. Among these 2 patients, 1 underwent VPS with sustained improvement in both gait and urinary function; the other didn't undergo VPS but showed very slow progression of gait and urinary disturbances at 24 months follow-up.

Conclusions: Our results may suggest that abnormal DAT imaging in patients with NPH may not always reflect an underlying neurodegenerative parkinsonism and that the nigrosome preservation at 3T brain MRI despite the DAT abnormality might improve the diagnostic accuracy.

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Parietal perfusion alterations in early Parkinson's disease

Mario Meloni¹, L. Pelizzari¹, S. Di Tella¹, F. Rossetto¹, M.M. Laganà¹, A. Pirastru¹, R. Nemni^{1,2}, F. Baglio¹

¹IRCCS, Fondazione Don Carlo Gnocchi, Milan, Italy

²Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Introduction: Cognitive deficits have been identified as an important non-motor manifestation of Parkinson's disease (PD). Alterations in the neural circuits including frontal and parietal cortical regions (fpCRs) are thought to be associated with PD cognitive deficits.

Objective: To investigate cerebral blood flow (CBF) and gray matter (GM) volume within the fpCRs in people with PD (pwPD) without dementia, and to assess their association with cognitive performance.

Methods: Twenty-seven pwPD without dementia (mean age=67.4 years, 20 males, median Hoehn and Yahr scale=1.5) and twenty-six age- and sex-matched healthy controls (HC) were scanned with arterial spin labeling (ASL) and T1-weighted magnetic resonance imaging (MRI) to investigate CBF and GM volume respectively. The cognitive performance was assessed with MoCA, Trail Making Test (TMT, part A, B, B-A), phonemic fluency and semantic fluency tests. CBF differences between pwPD and HC were tested in fpCRs with a voxel-wise approach. Voxel-based morphometry was used to compare fpCRs GM volume of PD and HC. Additional voxel-wise analysis were performed within regions showing either perfusion or GM volume alterations: correlation with neuropsychological test scores and subgroup comparison after median split on each test score.

Results: Significant hypoperfusion were found in the left inferior parietal lobule (IPL, $p=0.035$) and in the bilateral superior parietal lobule (SPL, left hemisphere: $p= 0.037$; right hemisphere: $p= 0.049$) of pwPD when compared to HC. No significant GM atrophy was observed. Local hypoperfusion didn't correlate with any neuropsychological test scores. However, significantly lower CBF was observed in the left SPL and IPL of the pwPD subgroup who performed poorer at TMT part A.

Conclusions: Perfusion alterations may occur in parietal regions of PD patients without dementia, and may be associated with lower visuomotor skills. Parietal CBF may be considered as a suitable early biomarker for longitudinal studies investigating cognitive decline in PD.

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Brain functional plasticity of the limbic circuit in Parkinson's disease patients with freezing of gait

Noemi Piramide^{1,5}, F. Agosta^{1,5}, E. Sarasso^{1,4,5}, E. Canu¹, M.A. Volontè², M. Filippi^{1,2,3,5}

¹Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy

²Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

³Neurophysiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

⁴Laboratory of Movement Analysis, Vita-Salute San Raffaele University, Milan, Italy

⁵Vita-Salute San Raffaele University, Milan, Italy

Background: Emotional processing is known to be involved in Parkinson's disease patients with Freezing of Gait (PD-FoG), but no studies have explored empathy experience in these patients.

Objective: To assess brain functional MRI (fMRI) activity during an “empathy” task in PD-FoG patients relative to healthy controls (HC).

Methods: Twenty-four PD-FoG patients were recruited and performed clinical and neuropsychological evaluations and fMRI. Eighteen age- and sex-matched HC were also included and underwent the neuropsychological assessment and the fMRI scan. PD-FoG patients and HC performed two fMRI tasks: i) the “empathy task” consisted of watching a patient who experienced FoG during a walking task usually evoking FoG; ii) the “control task” consisted of watching a healthy subject performing similar walking tasks (e.g., turning or walking through narrow spaces) without experiencing FoG. HC were emotively educated to the FoG phenomenon before undergoing the fMRI scan.

Results: PD-FoG patients had cognitive deficits relative to HC, particularly in attention/working memory and executive functions. During the empathy task, PD-FoG patients showed reduced activity of the sensorimotor part of the mirror neuron system (MNS) relative to HC. When comparing the empathy task with the control task activity, PD-FoG revealed increased recruitment of the right anterior prefrontal cortex and decreased activity of the left inferior parietal cortex during the “empathy task”, while HC showed increased recruitment of the anterior prefrontal cortex during the “empathy task” and of the MNS during the “control task”.

Conclusions: Our results suggested that when PD-FoG patients observe a subject experiencing FoG, there is increased brain activity in the limbic part of the MNS. This finding might suggest an involvement of the limbic circuit and, thus, of the emotional processes in the mechanisms underlying FoG in PD.

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Dopamine transporter imaging in progressive supranuclear palsy subtypes

*Eleonora Del Prete*¹, N. Campese¹, D. Frosini², G. Palermo¹, E. Unti², S. Mazzucchi¹, D. Volterrani³, U. Bonuccelli¹, R. Ceravolo¹

¹Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

²Neurology Unit, Department of Medical Specialties, AOUP, Pisa, Italy

³Regional Center of Nuclear Medicine, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Introduction: Recently new criteria for Progressive Supranuclear Palsy (PSP), including different phenotypes, have been proposed. A reduction in [123I]-FP-CIT dopamine transporter (DAT) uptake in single photon emission computed tomography (SPECT) has been demonstrated in PSP patients. Nowadays there is an increasing interest in identifying neuroimaging biomarkers to support differential diagnosis among different PSP phenotypes.

Aim: The aim of our study was to investigate the role of [123I]-FP-CIT SPECT in differentiating between PSP-Richardson (PSP-RS) and PSP non-RS phenotypes.

Method: Patients with diagnosis of PSP were included in the study. Patients performed [123I]-FP-CIT SPECT at disease onset; caudate and putamen binding and caudate to putamen ratio were evaluated for each side. Clinical features including motor assessment, performed by using Progressive Supranuclear Palsy Rating Scale (PSPrs), were considered.

Results: Twenty-nine PSP patients were enrolled in the study, 22 PSP-RS and 7 PSP non-RS. No significant differences were found in age, disease duration or PSPrs between groups. Any significant difference was found in caudate and putamen indices or caudate to putamen ratio for each side between PSP-RS and nonRS in SPECT-DAT imaging. SPECT –DAT imaging shows low sensitivity and specificity in differentiating PSP-RS and non-RS.

Conclusions: [123I]-FP-CIT SPECT does not show an adequate diagnostic accuracy to differentiate PSP-RS and PSP non-RS phenotypes in our samples, however such data need to be confirmed in larger samples of patients.

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Functional connectivity and cerebral perfusion in Parkinson's disease: a multimodal MRI study

Mario Meloni¹, A. Pirastru¹, M.M. Laganà¹, L. Pelizzari¹, F. Rossetto¹, S. Di Tella¹, M. Cazzoli¹, N. Bergsland^{1,2}, R. Nemni^{1,3}, F. Baglio¹

¹IRCCS, Fondazione Don Carlo Gnocchi ONLUS, Milan, Italy

²Buffalo Neuroimaging Analysis Center, Department of Neurology, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, USA

³Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

Introduction: Aberrant functional connectivity (FC) and cerebral blood flow (CBF) in Parkinson's disease (PD) has been described by previous MRI studies [1-2].

Objective: To investigate the relationship between FC and perfusion alterations in PD.

Methods: Twenty-six early PD patients (66.8±8 years, 22 males, median Hoehn & Yahr=1.5, disease duration=3 years) and 18 age/sex-matched healthy controls (HC) were enrolled. Motor and global cognitive functions were assessed according to the MDS-UPDRS Part III and Montreal Cognitive Assessment (MoCA) tests. The MRI examination was performed on a 1.5T Siemens scanner and comprised the acquisition of a resting-state functional MRI (rsfMRI) and arterial spin labeling (ASL) datasets and a T1-weighted structural image. FC differences between groups were obtained from the rsfMRI dataset. CBF and gray matter (GM) volume voxel-wise comparisons between groups were restricted to the clusters of altered FC.

Results: PD visuo-spatial performances were significantly lower ($p=0.002$) with respect to HC. Decreased FC and CBF were observed for PD within primary ($p=0.022$) and lateral ($p=0.01$) visual networks (VNs). FC alterations were also detected in the sensory-motor network (SMN, $p=0.01$). A negative trend ($p=0.06$, $r=-0.38$) between SMN z-values and UPDRS III score was found. No GM atrophy was detected concurrent to the functional alterations.

Conclusions: A significant FC decrease was observed in the SMN and in the primary and lateral VNs. The FC alterations within the VNs were also accompanied by altered CBF. This result mirrors the significantly lower visuo-spatial performances on MoCA subscales. The concurrent alteration of FC and CBF in the VNs might be indicative of a compromised neurovascular coupling mechanism in PD. FC reduction within the SMN of PD might be due instead to a dopaminergic denervation of the striatal pathways [3]. Our results suggest that FC and CBF might be proposed as early functional biomarkers as they may anticipate GM atrophy.

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Intrinsic brain functional connectivity predicts treatment-related motor complications in drug-naïve Parkinson's disease patients

*Rosa De Micco*¹, F. Di Nardo¹, M. Siciliano^{1,2}, S. Satolli¹, F.P. Bonifacio¹, G. Caiazzo¹, F. Esposito³, G. Tedeschi¹, A. Tessitore¹

¹Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Napoli, Italy

²Neuropsychology Laboratory, Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

³Department of Medicine, Surgery and Dentistry, Scuola Medica Salernitana, University of Salerno, Baronissi (SA), Italy

Introduction: Dopamine replacement therapy (DRT) is the most effective treatment for patients with Parkinson's disease (PD). However, DRT is complicated by the evolution of motor complications, (i.e. motor response fluctuations and levodopa-induced dyskinesias) which may develop progressively, with up to 80% of levodopa-treated patients showing involuntary movements after 4–6 years of treatment. Risk factors include long treatment duration, high initial dose of levodopa, young age at onset, female sex, but yet these factors alone cannot predict whether an individual patient will develop such treatment-related complications.

Objectives: Using resting-state functional MRI, we investigated intrinsic brain networks connectivity at baseline in a cohort of drug-naïve PD patients which successively developed treatment-related motor complications (PD-Fluct) over a 4-years follow-up period compared with patients who did not (PD-no-Fluct).

Methods: Baseline 3Tesla MRI images of 88 drug-naïve PD patients and 20 healthy controls (HC) were analyzed. Single-subject and group-level independent component analysis was used to investigate functional connectivity differences within the major resting state networks. Additionally, a region-of-interest analysis was performed within the basal ganglia. Sex and age were run as covariates. After the baseline assessments, all patients started DRT and were followed for an observation period lasting a maximum of 4 years. Regression analyses were used to investigate baseline predictors of motor complications development.

Results: At baseline, an increased connectivity within the default mode and the frontoparietal networks as well as within the basal ganglia were detected in PD-Fluct patients compared with PD-no-Fluct. Functional connectivity changes at baseline showed to be an independent predictor of motor complications at 4-year follow-up.

Conclusions: Our findings demonstrated that specific functional connectivity changes may characterize drug-naïve PD patients more prone to develop treatment-related complications. We hypothesize that these findings may reflect the presence of early dopaminergic pathways differences and might predict development of motor complications over time.

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Mutations in the codon 417 of TUBB2A gene are a cause of autosomal dominant complicated hereditary spastic paraplegia (HSP)

Giulia Franco, F. Arienti, E. Monfrini, G. Lazzeri, M. Vizziello, A. Di Fonzo

RCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy



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Type-3 metabotropic glutamate receptors and Parkinson's disease: preclinical studies and human genetics

*Marika Alborghetti*¹, L. Di Menna², A. Traficante², V. Bruno^{2,3}, J. Monn², F. Nicoletti^{2,3},
F.E. Pontieri¹, E. Bianchini¹, G. Spalletta⁴, M. Simmaco¹, M. Borro¹, G. Battaglia^{2,3}

¹Neuroscience, Mental Health and Sensory Organs (NESMOS), Rome, Italy

²Mol. Pathology, I.R.C.C.S. Neuromed, Pozzilli (IS), Italy

³Physiol. and Pharmacol., Univ. Sapienza, Rome, Italy

⁴I.R.C.C.S. Fondazione S. Lucia, Rome, Italy



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Genetic screening for GBA mutations in parkinsonian patients from Campania

Gianluigi Rosario Palmieri¹, G. De Michele¹, I. Ferrara¹, T. Fico¹, T. Bochinski², P. Bauer²,
G. De Michele¹, A. De Rosa^{1*}

¹Department of Neurosciences and Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy

²Centogene Ag, Rostock, Germany



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Kin-cohort analysis of GBA mutations penetrance in Parkinson's disease

*Roberta Balestrino*¹, S. Tunesi², S. Tesei³, L. Lopiano¹, A. Zecchinelli³, S. Goldwurm³

¹Department of Neuroscience Rita Levi Montalcini, University of Turin, Turin, Italy

²Unit of Medical Statistics and Epidemiology, Department of Translational Medicine, University of Eastern Piedmont, Novara, and CPO-Piedmont, Novara, Italy

³Parkinson Institute, ASST "Pini-CTO", Milano, Italy

Background: Biallelic glucocerebrosidase (GBA) mutations cause Gaucher disease (GD), while monoallelic heterozygous GBA mutations are considered the most important known genetic risk factor for Parkinson disease (PD) [1]. The estimated risk of PD in heterozygous GBA mutations-carriers is highly variable, ranging between 10 and 30%. This risk is age specific and depends on other genetic and non-genetic factors.

Objective: The aim of this study was to assess the penetrance of GBA mutations in PD in a cohort of unselected PD patients using the Kin-cohort method.

Methods: 123 PD patients with GBA mutations were previously identified in 2843 unrelated consecutive PD patients. Probands pedigrees were used in the Kin-cohort analysis [2-3]. Mutations were divided in mild (p. N370S) and severe (mainly p.L444P).

Results: Data on family history was available for 63 out of 123 PD GBA mutations-carriers; 381 first-degree relatives were analysed. The risk to develop PD was significantly different among relatives of GBA mutation-carrier compared to a non-carrier group, reaching 10% at 60, 16% at 70, and 19% at 80 years of age.

Conclusions: The estimated prevalence in this study is higher than the one estimated in GD cohorts and lower than the one estimated in familial PD cohorts. Our study was performed on unselected PD patients, avoiding the over or under estimation of penetrance that can occur in studies performed preferably on subjects with a positive family history of PD or GD [4]. It is important that neurologists and genetic counsellors consider the genetic background in its complexity in their counselling.

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P51

Brain iron accumulation in a case of rapid-onset dystonia-parkinsonism due to a *de novo* ATP1A3 mutation

Giulia Franco, F. Arienti, E. Monfrini, G. Lazzeri, M. Vizziello, A. Di Fonzo

IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy



P52

Circadian rhythm alterations in an in vitro model of induced pluripotent stem cells (iPSCs) derived from a patient affected by Spinocerebellar ataxia type 17

*Francesco Motolese*¹, A. Casamassa³, A. Vescovi³, V. Di Lazzaro¹, J. Rosati³, M. Marano^{1,2}

¹Neurology, Neurobiology and Neurophysiology Unit, University Campus Bio-Medico of Rome, Rome, Italy

²The Alberto Sordi Foundation, Università Campus Biomedico of Rome, Rome, Italy

³IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

Introduction: Spinocerebellar Ataxia 17 (SCA17) is a polyQ disorder caused by an expanded CAA/CAG repeats in the TBP gene leading to a neurodegenerative disease mimicking several conditions like parkinsonism, Alzheimer's and Huntington's disease [1]. Sleep and circadian rhythm alterations are involved in the pathogenesis of the aforementioned disorders and have never been investigated in cellular models so far [2].

Objective: To study in vitro expression of circadian rhythm genes (CLOCK, BMAL) in fibroblasts and neural cells of SCA17 patients.

Methods: Dermal fibroblast derived from two SCA 17 patients (father and son) and one healthy control (HC) were reprogrammed into human induced pluripotent stem cells (iPSCs) through virus-free and feeder-free protocol [3]. iPSCs were investigated for CLOCK and BMAL expression, for mitochondrial function and oxidative stress markers.

Results: Fibroblasts from patients and HC were successfully reprogrammed into iPSCs. These cells showed a deranged expression of circadian rhythm genes and worst energetic metabolism in accordance with the disease severity phenotype of the patient.

Conclusions: The expression of genes related to circadian rhythm is known to play a role in many neurodegenerative disorders as well as in brain aging [2]. In this study we found out that the expression of CLOCK and BMAL gene and cellular metabolism in a SCA 17 iPSCs cellular model were impaired. Although both patients shared the same number of CAG-repeats, the son had a worse clinical phenotype and his iPSCs showed a greater impairment of circadian rhythm genes expression. It can be speculated that a complex interplay exists between circadian rhythm, the length of CAA/CAG expansion in TBP gene and clinical manifestations. However, more studies on bigger sample size are warranted to confirm this hypothesis.

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P53

Autosomal dominant ataxic syndrome, abnormal ocular movements and brain iron accumulation due to SPG7 mutations

Maria Vizziello, G. Franco, F. Arienti, E. Monfrini, G. Lazzeri, A. Di Fonzo

IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Introduction: SPG7 gene mutations have been classically associated with hereditary spastic paraplegia. Recently, it has been reported that this gene is also a major cause of undiagnosed ataxia [1]. SPG7 gene encodes paraplegin, a protein that is part of the mitochondrial AAA protease, and the binding partner of AFG3L2. Both paraplegin and AFG3L2 are highly expressed in Purkinje neurons, thus explaining why SPG7 is related to ataxia.

Objective: To identify causative mutations in a young patient affected by autosomal dominant ataxia and abnormal ocular findings.

Methods: Whole exome sequencing (WES) analysis were performed using patient's DNA sample. Sanger sequencing analysis confirmed SPG7 mutation.

Results: The proband (subject II.1) is a 21-year-old woman presenting with a 12-year history of gait disturbance, ocular abnormalities (nystagmus, defective smooth pursuit, optic neuropathy) and cerebellar dysarthria. She had also been diagnosed with infantile partial epilepsy, diabetes mellitus and autonomic neuropathy causing bladder and bowel dysfunction. Brain MRI was remarkable, showing bilateral hypointensity in the globus pallidus as from paramagnetic substance accumulation, and mild atrophy of cerebellar vermis. Genetic analysis unraveled a novel heterozygous mutation in SPG7 gene. The mother (subject I.1) was affected by gait disturbance since age 20. Brain MRI was also consistent with iron accumulation and cerebellar atrophy.

Conclusions: Mutations in SPG7 gene are responsible for a wide spectrum of clinical phenotypes including spastic paraplegia, ataxia, optic neuropathy and parkinsonism. Further studies will be useful to understand whether specific mutations are associated to different clinical presentations.

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P54

Ischemic injury precipitates neuronal vulnerability in Parkinson's disease: insights from clinical observation and PINK1 mouse model study

Paola Imbriani^{1,2}, I. El Atiallah^{1,2}, V. D'Angelo¹, G. Di Lazzaro¹, S. Scalise¹, C. Salimei¹, V.L. Colona¹, N.B. Mercuri^{1,2}, P. Bonsi^{2,2}, A. Pisani^{1,2}, T. Schirinzi¹, G. Martella^{1,2}

¹Department of Systems Medicine, University of Roma Tor Vergata, Rome, Italy

²IRCCS Fondazione Santa Lucia, Rome, Italy

Introduction: Increasing evidence demonstrates the relevant association between Parkinson's disease (PD) and vascular diseases/risk factors, as well as a worse clinico-pathological progression in those patients with vascular comorbidity [1-2]. The mechanisms underlying this relationship have not been clarified yet, although their comprehension is critical in a perspective of disease-modifying treatments development or prevention.

Methods: Here we analysed retrospectively 253 PD patients, to characterize the occurrence of vascular risk factors and their correlations with clinical features. Additionally, we performed an experimental protocol of ischemic injury (glucose-oxygen deprivation, OGD) [3] on PTEN-induced kinase 1 knock-out (PINK1^{-/-}) mice, a well-established PD model, comparing them to wild-type littermates. We assessed the effects of OGD on both electrophysiological and morphological properties of striatal medium spiny neurons (MSNs), cholinergic interneurons (ChIs) and nigral dopaminergic neurons (DANs). Electrophysiological current-clamp recordings were performed on brain slices (both sagittal corticostriatal and horizontal nigral slices) with intracellular technique; histochemical analysis was carried out with Hematoxylin and Eosin (H&E) and Nissl staining.

Results: Up to 75% of PD patients exhibited vascular comorbidity. In this group, clinical severity (Hoehn and Yahr score) depended on both age and disease duration, differently from those patients without vascular risk factors. In PINK1^{-/-} mice, the OGD protocol induced electrophysiological (prolonged membrane depolarization) and morphological alterations (picnotic cells, cellular loss and swelling, thickening of nuclear chromatin) in striatal MSNs and DANs.

Conclusions: The ischemic injury precipitates neuronal vulnerability in basal ganglia of PINK1^{-/-} mice, probably through an impairment of mitochondrial metabolism and higher oxidative stress [4-5]. These experimental data justify the greater sensitivity of PD patients with vascular comorbidity to the effect of aging, providing a potential mechanistic explanation for both the association between vascular diseases and PD and their reciprocal interactions in determining the clinico-pathological burden of PD patients.

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P55

The mirror neuron system and the motor network in idiopathic cervical dystonia: an fMRI study

Anna Castagna, S. Di Tella, V. Blasi, M. Cabinio, F. Baglio

IRCCS, Fondazione Don Carlo Gnocchi ONLUS; Milano, Italy

Introduction: Idiopathic Cervical Dystonia (ICD) is a movement disorder caused by faulty sensorimotor integration and impaired motor planning involving sensorimotor cortices, basal ganglia and cerebellum network. Despite the central origin of the disease, the gold standard therapy is the botulinum neurotoxin (BoNT), acting on the neuromuscular junction. BoNT is more effective when integrated with rehabilitative interventions. These typically involve higher order cortical areas to learn strategies able to compensate the subcortical dysfunctionality. For a better planning of these interventions studies on functional and structural integrity of the motor system are needed.

Objective: To determine the morphological and functional properties of the action execution and observation system, involving both the mirror neuron system (MNS) and the cortical and subcortical motor network.

Methods: Twenty-three healthy adults (HC, mean age [SD]= 55.09 [19.83]; 16 females) and 22 subjects with ICD (mean age [SD]= 46.96 [9.19] 14 females) performed an MRI acquisition for high resolution anatomical images, and a functional MRI (fMRI) with two tasks as in [1]: 1. “Move” executing grasping movements; and 2. “Observe” watching videos of a right hand grasping objects. Structural data were analyzed with Freesurfer; 3 to measure cortical thickness and subcortical volumes. FMRI data were analyzed with SPM 12. A region of interest (ROI) analysis was performed on Move condition and Move and Observe conjunction data. Statistical analyses were performed with JASP (Version 0.11.1).

Results: Significant differences between groups were found in: 1. in the Move condition R-precentral gyrus ($p = 0.029$); L-thalamus ($p = 0.039$); and R-lentiform nucleus ($p = 0.031$); 2. in the conjunction L-inferior frontal gyrus ($p = 0.020$); 3. in structural analysis L-pallidum volume ($p = 0.042$).

Conclusions: Our results showed substantial preservation of the MNS in ICD patients with differences in the motor network. These data are relevant for the future planning of effective rehabilitation interventions.

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P56

Efficacy of Deep Brain Stimulation for dystonia: meta-analysis on the impact of genetics

*Carlo Alberto Artusi*¹, A.K. Dwivedi^{2,3}, A. Romagnolo¹, S. Bortolani¹, L. Marsili⁴, G. Imbalzano¹, A. Sturchio⁴, E.G. Keeling⁴, M. Zibetti¹, M.F. Contarino^{5,6}, A. Fasano^{7,8,9}, M. Tagliati¹⁰, M.S. Okun¹¹, A.J. Espay⁴, L. Lopiano¹, A. Merola¹²

¹Department of Neuroscience Rita Levi Montalcini, University of Torino, Torino, Italy

²Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA

³Department of Molecular and Translational Medicine, TTUHSC EL Paso, Texas, USA

⁴Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA

⁵Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

⁶Department of Neurology, Haga Teaching Hospital, The Hague, The Netherlands

⁷Morton and Gloria Shulman Movement Disorders Clinic, Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital, UHN, Division of Neurology, University of Toronto, Toronto, Ontario, Canada

⁸Krembil Research Institute, Toronto, Ontario, Canada

⁹Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, Ontario, Canada

¹⁰Department of Neurology, Cedars Sinai Medical Center, Los Angeles, California, USA

¹¹Fixel Institute for Neurological Diseases, Department of Neurology, University of Florida, Gainesville, Florida, USA

¹²Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA

Introduction: Globus pallidus pars interna deep brain stimulation (GPi-DBS) is one of the most effective treatments for chronic, medically intractable, dystonia. Carriers of DYT-TOR1A mutations are considered the best candidates for GPi-DBS. Still, no trial data analyzed whether the outcomes of these patients are comparable to those of patients with alternative genetic mutations.

Objective: To compare GPi-DBS outcomes among the most common monogenic dystonias.

Methods: Following the PRISMA and MOOSE guidelines, we searched PubMed for studies on genetically confirmed monogenic dystonia treated with GPi-DBS and measuring outcomes with the Burke-Fahn-Marsden Dystonia Rating Scale Motor Score (BFMMS) and Disability Score (BFMDS). We performed meta-analysis for each gene mutation, weighted ordinary linear regression analyses to compare BFMMS and BFMDS outcomes between DYT-TOR1A and other monogenic dystonias, adjusting for age and disease duration, and weighted linear regression analysis to estimate the effect of age, sex, and disease duration on GPi-DBS outcomes.

Results: Meta-analysis was performed on DYT-TOR1A, DYT-THAP1, and NBIA/DYT-PANK2 showing a significant improvement in BFMMS for all mutations (68% for DYT-TOR1A, 38.4 points; $p < 0.001$; 37% for DYT-THAP1 14.5 points; $p < 0.001$; 27% for NBIA/DYT-PANK2, 21.4 points; $p < 0.001$. Only DYT-TOR1A improved in BFMDS (69%, 9.7 points; $p < 0.001$). DYT-TOR1A was associated with greater motor improvement than DYT-THAP1 (-31%; $p < 0.001$), NBIA/DYT-PANK2 (-35%; $p = 0.016$), and CHOR/DYT-ADCY5 (-36%; $p < 0.001$), and greater reduction in disability than NBIA/DYT-PANK2 (-53%; $p = 0.004$), and CHOR/DYT-ADCY5 (-42%; $p = 0.003$). We found no significant differences between DYT-TOR1A and DYT/PARK-TAF1, DYT-SGCE, GNAO1, and ACTB. Worse motor outcomes were associated with longer dystonia

duration and older age at dystonia onset in DYT-TOR1A, longer dystonia duration in DYT/PARK-TAF1, and younger age at dystonia onset in DYT-SGCE.

Conclusions: This study provides evidence for different GPi-DBS outcomes depending from the underlying genetic mutations. These data serve to inform patient selection and prognostic counseling.

P57

Brain structural changes in focal dystonia – what about task specificity? A multimodal imaging study

Elisabetta Sarasso¹, F. Agosta^{1,4}, A. Tomic⁵, N. Kresojević⁵, E. Canu¹, M. Svetel⁵, V.S. Kostic⁵, M. Filippi^{1,2,3,4}

¹Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy

²Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

³Neurophysiology Unit IRCCS San Raffaele Scientific Institute, Milan, Italy

⁴Vita-Salute San Raffaele University, Milan, Italy

⁵Clinic of Neurology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Background: Brain abnormalities in the basal ganglia, thalamus, cerebellum and sensorimotor cortices were identified as common features of focal dystonia with heterogeneous phenotypic expression. However, task-specificity present in some forms of dystonia is still a poorly understood phenomenon.

Objective: This study aimed at investigating grey and white matter (WM) brain alterations in patients with task-specific (TSD) and non-task-specific dystonia (NTSD), and defining common and group-specific brain changes.

Methods: Thirty-six patients with TSD (spasmodic dysphonia and writer's cramp), 61 patients with NTSD (blepharospasm and cervical dystonia), and 83 healthy controls (HC) were included in the study. Participants underwent 3D T1-weighted and diffusion tensor MRI to study cortical thickness, basal ganglia volume, and WM tract damage.

Results: Compared to HC and NTSD, TSD patients had cortical thickening of parietal, temporal and occipital regions, increased volume of basal ganglia and amygdala, and widespread bilateral damage of subcortical WM. On the other hand, NTSD patients showed cortical thinning of frontal, parietal and temporal cortices, atrophy of thalamus bilaterally, and focal and right lateralized WM alterations. Within the TSD group, patients who received botulinum toxin (BoNT) had greater cortical thickening of parietal areas and cingulum and increased volume of left accumbens and putamen. Within the NTSD group, patients experiencing pain showed cortical thickening of frontal areas and posterior cingulate cortex and increased volume of the left accumbens.

Conclusions: TSD and NTSD patients are characterised by specific and sometimes opposite alterations of the main cortical and subcortical sensorimotor and cognitive-controlling brain structures, suggesting the possible presence of different pathophysiological and/or compensatory mechanisms underlying the complexity of these two different phenotypes of focal dystonia.

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Functional MRI connectivity of the primary motor cortex in functional dystonia patients

Noemi Piramide^{1,4}, F. Agosta^{1,4}, E. Sarasso¹, E. Canu¹, A. Tomic⁵, I. Petrovic⁵, M. Svetel⁵, A. Inuggi⁶, N.D. Miskovic⁵, V.S. Kostic⁵, M. Filippi^{1,2,3,4}

¹Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy

²Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

³Neurophysiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

⁴Vita-Salute San Raffaele University, Milan, Italy

⁵Clinic of Neurology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

⁶Unit of Robotics, Brain and Cognitive Sciences, Istituto Italiano di Tecnologia, Genoa, Italy

Background: The pathophysiological mechanisms underlying functional dystonia (FD) are poorly understood, making FD diagnosis and management a challenge for clinicians. Recent studies showed structural alterations of the sensorimotor and emotional circuits in FD.

Objective: To explore functional connectivity (FC) of the primary motor cortex in FD patients relative to healthy controls (HC), distinguishing patients into two clinical phenotypes: fixed (FixFD) and mobile FD (MobFD).

Methods: 39 FD patients (12 FixFD, 27 MobFD) and 43 controls (HC: 14 young FixFD-age-matched [yHC]; 29 old MobFD-age-matched [oHC]) underwent resting state fMRI. A seed-based FC analysis was performed using bilateral primary motor cortices (BA4) as regions of interest.

Results: Compared to HC, FD patients showed reduced FC between left BA4 and left dorsal anterior cingulate cortex, and between right BA4 and left BA4, premotor/supplementary motor area (SMA), dorsal posterior cingulate cortex, and bilateral precuneus. Relative to yHC, FixFD showed reduced FC between bilateral BA4 and bilateral precuneus. Compared to oHC, MobFD revealed reduced FC between right BA4 and left BA4, premotor/SMA, dorsal posterior cingulate cortex, bilateral primary sensory cortices and parieto-occipital areas. MobFD patients showed also increased FC of right BA4 with right associative visual cortex and bilateral ventral posterior cingulate cortices. FixFD, relative to MobFD, showed lower FC between the right BA4 and the bilateral precuneus. On the other hand, MobFD relative to FixFD revealed higher FC of the right BA4 with right associative visual area and bilateral ventral posterior cingulate cortices.

Conclusions: This study supported previous structural MRI findings suggesting an altered brain connectivity of the motor circuit in FD, with FixFD and MobFD having specific features. FixFD patients showed FC abnormalities mainly in sensorimotor areas, while MobFD present alterations in regions involved in motor preparation/planning (reduced FC) and emotional processing (increased FC).

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Cortical motor control in oromandibular dystonia: a neurophysiological pilot study

*Nicoletta Manzo*¹, F. Ginatempo², F. Deriu², A. Berardelli^{1,3}

¹IRCCS Neuromed, Pozzilli (IS), Italy

²Department of Biomedical Sciences, University of Sassari, Sassari, Italy

³Department of Human Neurosciences, Sapienza, University of Rome, Rome, Italy

Introduction: Oromandibular dystonia (OMD) is a rare form of focal dystonia that affects facial muscles in the lower part of the face, causing prominent jaw opening or closing [1]. However, in contrast to other forms of dystonia, excitability of the primary motor cortex (M1) in OMD has been poorly investigated [2] and preliminary evidence has only been obtained applying single transcranial magnetic stimulation (TMS) over hand M1 [3]. However, recent studies have shown that face and hand muscles undergo different motor control strategies [4], thus data concerning hand M1 may not be applicable to face M1.

Objectives: We first investigated the excitability, sensorimotor integration, and plasticity of face M1 in OMD. We then assessed whether possible abnormalities in OMD were specific to facial cortical circuits by investigating the same parameters in the hand M1 of the same patients. Finally, to assess whether pathophysiological mechanisms were specific to OMD, we compared OMD data with those obtained in a group of patients with focal hand dystonia (FHD).

Methods: We enrolled six OMD patients, six FHD patients, and six age- and gender-matched healthy controls. The following parameters were tested in face and hand M1 of all groups: short intracortical inhibition (SICI), intracortical facilitation (ICF), short- and long-afferent inhibition (SAI and LAI, respectively), and paired associative stimulation (PAS).

Results: Compared to healthy controls, mixed ANOVA showed that in OMD SICI was absent or strongly reduced in face M1, but not in hand M1. In contrast, in FHD patients SICI was reduced in hand M1, whereas it was normal in face M1 (all $p < 0.05$). ICF, SAI, LAI, and PAS were similar in the three groups regardless of the muscular district examined.

Conclusions: Preliminary results suggest that in OMD and FHD increased cortical excitability specifically occurs in cortical areas that are involved in clinical manifestation.

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P60

Negative symptoms in Huntington's disease

Paola Soliveri^{1,3}, D. Paridi^{2,3}, F. Del Sorbo¹, I. Tramacere⁴, C. Gellera⁵, G. Pezzoli^{1,6}, F. Girotti³

¹Parkinson Institute, ASST Gaetano Pini-CTO, Milan, Italy

²Huntington Onlus, Milan, Italy

³Parkinson and Movement Disorders Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

⁴Department of Research and Clinical Development, and Scientific Director's Office, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

⁵Genetics of Neurodegenerative and Metabolic Diseases Unit, and Motor Neuron Disease Centre, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

⁶Fondazione Grigioni per il Morbo di Parkinson, Milan, Italy

Introduction: Psychiatric symptoms are prominent in Huntington's disease (HD) and include negative symptoms, among which apathy is conspicuous [1].

Objective: To investigate the nature of negative psychiatric symptoms in a cohort of HD patients at early and intermediate disease stage, and explore symptoms in relation to motor, mood, and cognitive disturbances.

Methods: Seventy symptomatic, genetically-confirmed adult HD patients, presenting at our outpatient clinic at Besta Institute, and giving informed consent, were administered: motor part of the Unified HD Rating Scale, Total Functional Capacity (TFC), and instruments to assess cognition, anxiety, depression, and positive and negative psychiatric symptoms (SAPS and SANS).

Results: Patients were divided into two groups according to disease severity: 35 at stage 1 and 35 at stages 2-3. The groups had similar age, education and CAG repeat. Depression, anxiety and positive symptoms scores did not differ between the groups; while illness duration, motor impairment, TFC, cognitive performance, and negative symptoms were significantly worse in stage 2-3 patients. In stage 1 patients, SANS was inversely associated with cognitive performance (MMSE and verbal fluency test) and directly associated with SAPS. In stage 2-3 patients, SANS was inversely associated with speed of cognitive processing (visual search test).

Conclusions: Negative psychiatric symptoms are conspicuous in HD but more prominent in patients at disease stages 2-3. However, their causes may differ in the two groups: while compromised cognition contributes to negative symptoms at all disease stages [2], in early stage patients erroneous interpretation of reality, as suggested by the association we found between negative and positive psychiatric symptoms, may contribute to negative symptoms, consistent with reports of theory of mind impairment in HD patients [3].

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P61

First epidemiologic study of Huntington disease in Sardinia

*Antonella Muroi*¹, M.R. Murru², M. Sechi³, T. Ercoli³, A.R. Bentivoglio⁴, M. Petracca⁴, C.L. Scaglione⁵, P. Soliveri⁶, S. Cuccu², E. Cocco^{2,3}, F. Marrosu³, M. Pedron⁷, M. Murgia³, M. Deriu⁸, L. Ulgheri⁹, C. Zuccato¹⁰, G. Defazio^{1,3}

¹Institute of Neurology, AOU Cagliari, Cagliari, Italy

²Multiple Sclerosis Centre, Binaghi Hospital, ASSL Cagliari, ATS Sardegna, Cagliari, Italy

³Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

⁴Institute of Neurology, Università Cattolica del Sacro Cuore, Rome, Italy

⁵IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

⁶Fondazione IRCCS Istituto Neurologico Carlo Besta, Unit of Neurology I - Parkinson and Movement Disorders Unit, Milan, Italy

⁷Medical Services Management, AOU Cagliari, Cagliari, Italy

⁸Neurology Service, Nostra Signora della Mercede Hospital, S. Gavino Monreale, Italy

⁹S.S.D. di Genetica e Biologia dello Sviluppo, AOU Sassari, Sassari, Italy

¹⁰Department of Biosciences, University of Milan, Milan, Italy; Istituto Nazionale di Genetica Molecolare "Romeo ed Enrica Invernizzi," Milan, Italy

Introduction: The frequency of Huntington disease may vary considerably, with higher estimates in non-Asian populations [1]. In Italy, two recent studies performed in the province of Ferrara and in a restricted area of Molise county provided very different prevalence estimates, varying from 4.2x10⁵ to 10.8x10⁵ [2,3].

Objective: Here we present a study performed in the Southern part of Sardinia, a large Italian Mediterranean island that is considered as a genetic isolate.

Methods: Study area included the two neighboring counties of South Sardinia and Cagliari that hosted 353830 and 431955 inhabitants respectively on December 31st 2017 (prevalence date). Case-patients were ascertained through multiple sources in Sardinia and Italy.

Results: We identified 54 individuals with Huntington disease, of whom 47 were alive on prevalence date. The resulting prevalence rate was 5.98x10⁵ in the overall study area, however with marked variations between South Sardinia and Cagliari (9.6x10⁵ vs. 3.0x10⁵, p=0.02). The overall crude average annual incidence 2011 to 2018 was 0.38x10⁵/year. Incidence was higher in South Sardinia than in Cagliari (0.76x10⁵/year vs. 0.17x10⁵/year, p=0.02). In the two administrative study areas, we found similar CAG repeat length in normal alleles (17.5 + 2.1 vs. 17.7 + 2.2, p=0.5).

Conclusions: The overall prevalence and incidence of Huntington disease in Sardinia is close to the correspondent estimates in Caucasians. Our findings also highlighted the possibility of local microgeographic variations in the epidemiology of HD.

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P62

Lumboperitoneal shunt in idiopathic normal pressure hydrocephalus: a prospective controlled study

Massimiliano Todisco¹, M. Picascia², P. Pisano³, R. Zangaglia¹, B. Minafra¹, F. Valentino¹, P. Vitali⁴, E. Rognone⁴, A. Pichiecchio⁴, R. Ceravolo⁵, N. Vanacore⁶, A. Fasano^{7,8,9}, C. Pacchetti¹

¹Parkinson's Disease and Movement Disorders Unit, IRCCS Mondino Foundation, Pavia, Italy

²Alzheimer's Disease Assessment Unit/Laboratory of Neuropsychology, IRCCS Mondino Foundation, Pavia, Italy

³Neurosurgery Unit, IRCCS San Matteo Foundation, Pavia, Italy

⁴Neuroradiology Unit, IRCCS Mondino Foundation, Pavia, Italy

⁵Unit of Neurology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

⁶National Centre for Disease Prevention and Health Promotion, National Institute of Health, Rome, Italy

⁷Morton and Gloria Shulman Movement Disorders Centre and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada

⁸Krembil Research Institute, Toronto, Ontario, Canada

⁹Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, Ontario, Canada



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Sporadic chorea in adults: a single-centre retrospective study

*Roberta Bovenzi*¹, N.B. Mercuri^{1,2}, A. Stefani¹, M. Pierantozzi¹, T. Schirinzi¹

¹Department of System Medicine, University of Rome Tor Vergata, Rome, Italy

²IRCCS Fondazione Santa Lucia, European Centre for Brain Research, Rome, Italy

Introduction: Chorea is a rare movement disorder due to several causes, including genetic, pharmacologic, metabolic, and structural ones. Its clinical management, especially the diagnostic work-up, is often challenging and extensive [1].

Objective: To analyze retrospectively the main features of adults with sporadic chorea hospitalized in the Neurology Unit of Policlinico Tor Vergata (Rome), in order to highlight useful cues for clinical management.

Methods: Electronic charts from 2012 to 2020 were reviewed. We identified 22 patients suffering from chorea, choreoathetosis and ballism. 6 were excluded because of genetic etiology (Huntington Disease); from the 16 sporadic patients remaining, data were collected and analyzed.

Results: Patients had mean age of 66,68 years (15-87), 75% were female. 37,5% had acute onset, 50% presenting with hemichorea and 50% with hemichoreo-ballism. Associated comorbidities were hypertension (43,75%), mood disorders (25%) and diabetes mellitus (18.75%). All patients received neuroimaging tests and the most frequent finding was vascular encephalopathy (81.25%); an acute ischaemic stroke was found in 31.5% of cases. Routine blood tests were performed in all patients, showing severe hyperglycemia (599 mg/dl) in just one case. Autoantibody screen was performed in 31.5% of patients, resulting positive in one who was diagnosed with antiphospholipid antibodies syndrome. Testing for acanthocytes was performed in 25% of patients with negative results. Vascular etiology was diagnosed in 56,5% of cases and antiplatelet therapy was set. Other causes of sporadic chorea were iatrogenic, infectious, psychogenic. Concurrent normotensive hydrocephalus and tic disorder were also diagnosed. A symptomatic therapy with haloperidol was administered in 37,5% of patients.

Conclusions: This study described the main clinical features of adult patients with sporadic chorea hospitalized in a single centre, showing that vascular etiology was the most common and that females were more frequently affected. Although preliminary, these data can be useful in the clinical management of this rare condition.

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P64

The TITAN study: design and preliminary findings

Roberto Erro, on behalf of the TITAN Study Group

Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, University of Salerno, Salerno, Italy

Introduction: Tremor is deemed as the most common movement disorders. Nonetheless, research efforts have largely failed in delineating its pathophysiological mechanisms. Recently, the classification of tremor and its nosology has been completely revised. A collaborative effort was therefore put forward to collect a large number of tremor patients. The ITALian Tremor Network, T(ITA)N, is a multicenter data collection system that will prospectively assess the phenomenology and natural history of tremor syndromes.

Methods: The TITAN study has been proposed by the Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana”, University of Salerno and by the Fondazione LIMPE per il Parkinson ONLUS. Patients with different tremor syndromes (with the exception of tremor in the context of diagnosed parkinsonian syndromes) were enrolled by movement disorder centers in Italy. All patients underwent a standardized protocol gathering demographic and clinical data including the TETRAS scale, the SARA scale and the QUEST instrument.

Results: Twelve movement disorder centers have so far joined the TITAN and 330 patients were enrolled by December 2019, 31st. According to the novel MDS tremor classification, patients were diagnosed as follows: 131 (43.67%) with Essential Tremor (ET); 118 (39.33%) with ET plus (ET+); 31 (10.33%) with dystonic tremor (DT); 12 (4%) in whom diagnostic work-up disclosed a parkinsonian syndrome; and 38 (11.51%) with other forms of tremor. Comparisons between different tremor syndromes are detailed in table 1.

Conclusions: The preliminary data of the TITAN study show that former clinical features deemed to be characteristic of ET might not be present if novel criteria are used, which reflects a clear shift in the definition of ET. Analysis of baseline information of the TITAN study may be useful to delineate the clinical features of recently redefined tremor syndromes and might serve as an open platform to generate future research studies.

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Asymmetric motor and higher cortical signs in PSP Richardson's variant

Maria Francesca Tepedino, F. Abate, R. Erro, G. Volpe, S. Cuoco, A. Cappiello, M.T. Pellicchia, P. Barone, M. Picillo

Department of Medicine, Surgery and Dentistry, Neuroscience Section, Center for Neurodegenerative Diseases (CEMAND), University of Salerno, Salerno, Italy

Introduction: Progressive supranuclear palsy (PSP) is a rare, progressive neurodegenerative disease. Richardson's syndrome (PSP-RS) is the most frequent form of disease. Traditionally, clinical signs in PSP-RS are considered symmetric. Therefore, the PSP rating scale (PSP-rs)[1] does not include any information on lateralization.

Objective: Aim of this study is to report the prevalence of asymmetric motor and higher cortical signs in PSP-RS.

Methods: All patients were diagnosed with Movement Disorders Society criteria [2] and were videotaped and administered the Natural History and Neuroprotection in Parkinson Plus Syndromes [3] (NNIPPS-PPS). The following signs were retrospectively noted for each side: bradykinesia, rigidity, rest/postural/action tremor, dystonia, myoclonus (motor signs); limb apraxia and alien limb (higher cortical signs).

Results: Thirty-six PSP-RS [95% with diagnosis of probability; 2 47.2% men; median (IQR) age: 71(10); disease duration: 3(3)] were enrolled. More than 50% presented asymmetric bradykinesia in both upper (UL) and lower limbs (LL). Similarly, about 60% had asymmetric rigidity in UL and 47% in LL. Up to 25% presented asymmetric dystonia in UL and 13.8% in LL. As for myoclonus, UL stimulus-sensitive myoclonus was asymmetric in nearly 20% of patients. Any type of tremor was asymmetric in a small proportions of patients (<8%). As for higher cortical features, limb apraxia was asymmetric in 38.8% and alien limb in 11.1%.

Conclusions: Here we demonstrated both motor (bradykinesia, rigidity, dystonia and apraxia) and higher cortical features (apraxia and alien limb) are frequently asymmetric in PSP-RS. Such asymmetry can not be detected with the PSP-rs which is based on the assumption that clinical signs are symmetric in PSP-RS. Future assessments of disease severity in PSP should be able to detect asymmetry in both motor and higher cortical signs.

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P66

Effects of cerebellar intermittent theta burst stimulation (iTBS) on motor symptoms in Multiple System Atrophy (MSA)

*Angela Sanna*¹, P. Tacconi², A. Paribello³, M. Puligheddu¹, P. Solla², G. Defazio¹

¹Department of Medical Science and Public Health, Section of Neurology, University of Cagliari, Cagliari, Italy

²Azienda Ospedaliero Universitaria, University of Cagliari, Cagliari, Italy

³ATS, SC Riabilitazione Sanitaria e Socio-Sanitaria Territoriale ASSL Cagliari, Cagliari, Italy

Background: MSA is a neurodegenerative disorder characterized by parkinsonism, cerebellar ataxia, autonomic dysfunction and pyramidal signs. The pathophysiology of MSA is still unclear and no disease-modifying treatment is now available. Therefore, management of the disease remains purely symptomatic. Repetitive magnetic stimulation (rTMS) is a non-invasive technique which has been shown to be potentially helpful in several neurological diseases, due to its capability to modulate cortical excitability and to induce long-lasting effects on neuroplasticity [1-3].

Objective: The aim of the study was to investigate the efficacy of a patterned paradigm of rTMS, intermittent theta burst stimulation (iTBS) [4], applied to cerebellum, in improving clinical signs of MSA.

Methods: A double blind sham controlled cross-over study was performed in 7 patients affected by MSA, displaying predominantly cerebellar (MSA-C) or parkinsonian (MSA-P) features. Patients were randomized to receive 15 sessions of real and sham iTBS separated by 45 days. Clinical evaluation was made by Unified Multiple System Atrophy Rating Scale (UMSARS) [5] at the beginning and at the end of each trial; patients were video-recorded and a blinded evaluator generated UMSARS scores.

Results and discussion: UMSARS score was reduced after 15 session of real iTBS. These preliminary results suggest that cerebellar iTBS may improve clinical signs of MSA and underline the potential therapeutic role of non-invasive brain stimulation in the treatment of neurodegenerative disorders.

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P67

A 57 year old man with abdominal involuntary movements

Nico Golfrè Andreasi, A.E. Elia, A. Novelli, G. Devigili, L.M. Romito, R. Eleopra

I.R.C.C.S. Fondazione Istituto Neurologico Carlo Besta, UOC Neurologia 1 – Malattia di Parkinson e Disturbi del Movimento, Milano, Italy

Introduction: Since 2017 the patient experienced difficulty in writing and involuntary contraction of abdominal muscles associated with mild flexion-extension movements of the head. In his past medical history he had epatitis type A in young age and he has a mild bilateral carotid stenosis. He had no family history of neurologic diseases.

Methods and Results: Neurologic examination showed irregular contraction in abdominal muscles, present when the patient was lying down, sitting or standing. While sitting, mild flexion-extension movement of the head was also noticeable. The remaining neurologic examination was unremarkable. He underwent a comprehensive laboratory assessment, including serum and urinary copper, ceruloplasmin and acantocytes, which were normal. Brain MRI showed bilateral pallidal hypointensity and the CT scan confirmed the presence of calcifications. The EEG and [123I]-FP-CIT SPECT were unremarkable. Electromyography of head and abdomen muscles showed features of dystonia: co-contraction of left and right splenius while turning the head rightwards and irregular bursts (100-300 msec) in rectus abdomen, sometimes asynchronous, unchanged during distractory manoeuvres. Next generation sequencing (NGS) analysis showed the presence of a Variant of Unknown Significance (VUS) in heterozygosity in GNAL gene. To study the potential pathogenetic role of this variant, we visited his two healthy brother and collected their blood sample. At the neurological evaluation, no overt sign of dystonia was present in the two brothers, and the objective examination was completely normal. None of them was carrier of the variant of GNAL we found in the proband. There were no other family members available, since patient's parents were deceased and he has never had children.

Conclusions: The segregation of this variant in GNAL gene only in the proband reinforce its possible pathogenetic role. He has been since then treated with EMG-guided botulinum toxin A injections in rectus abdomen with satisfactory relief.

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A case of cerebellar ataxia with neuropathy and vestibular areflexia syndrome

*Federica Terenzi*¹, C. Ferrari¹, R. Pecci², E. Volpi¹, S. Bagnoli¹, B. Nacmias¹, S. Ramat³, A. Novelli¹, S. Sorbi^{1,4}

¹Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

²Otoneurology Clinic, Careggi University Hospital, Florence, Italy

³Neurology Unit, Careggi University Hospital, Florence, Italy

⁴IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

Introduction: CANVAS is a slowly progressive neurological disorder characterized by the combination of bilateral vestibular areflexia, cerebellar ataxia and somatosensory impairment [1-2]. Diagnosis is insidious, due to the fact that symptoms don't arise simultaneously, especially neuropathy which may develop on later stages of the disease [3].

Case Report: A 57 years old man started complaining about gait and speech disturbances associated with erectile dysfunction. He was admitted to a Neurology Unit at another hospital where an ataxic gait was revealed; a brain MRI was normal, and an EMG of the lower limbs showed a sensory motor axonal neuropathy. Lumbar puncture, blood tests, with autoantibodies and onconeural antibodies didn't show any abnormalities. During the following years, the patient worsened and, three years after the appearance of signs and symptoms he was admitted to the Center for Rare Neurological Diseases at the Neurology Department, Careggi University Hospital, Florence. At neurological examination the patient had dysarthria, an ataxic gait, horizontal bilateral gaze-evoked nystagmus and pin-prick and vibratory sensations were diminished in the lower limbs. He underwent a new MRI of the brain that showed mild atrophy of the vermis and nerve conduction studies (NCS) revealed absent sensory nerve action potentials in the upper and lower limbs bilaterally with a reduction in conduction velocities. The patient was then referred to the audiovestibular evaluation that showed an abnormal visually enhanced vestibulo-ocular reflex (VVOR). Genetic testing for SCA1,2,3,6,7,8,12,17, dentatorubral-pallidoluyian atrophy and Fragile X-associated tremor/ataxia syndrome were negative.

Conclusions: CANVAS represents a challenge in clinical practice. In patients with late onset sporadic cerebellar ataxia of unknown origin an assessment of vestibular function, nerve conduction study and electromyography should be performed in order to look for CANVAS cases.

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P69

Advanced voice analysis in patients with essential tremor

Francesco Asci¹, A. Suppa^{1,2}, G. Costantini³, G. Saggio³, P. Di Leo³, Z. Zarezadeh⁴, G. Ferrazzano^{1,2}, G. Ruoppolo⁵, A. Berardelli^{1,2}

¹Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

²IRCCS Neuromed Institute, Pozzilli (IS), Italy

³Department of Electronic Engineering, University of Rome Tor Vergata, Rome, Italy

⁴Department of History, Humanities and Society, University of Rome Tor Vergata, Rome, Italy

⁵Department of Sense Organs, Otorhinolaryngology Section, Sapienza University of Rome, Italy

Introduction: Essential Tremor (ET) is defined as an isolated tremor syndrome characterized by bilateral upper-limb action tremor, with a duration of at least 3 years, with or without tremor in other locations, including voice, in the absence of other neurologic signs [1]. Due to the lack of an objective voice evaluation, the recognition of a subclinical voice impairment in patients with ET may be challenging.

Objectives: To clarify whether advanced voice analysis based on machine learning algorithms can help clinicians to recognize voice impairment in patients with ET.

Methods: We investigated 56 ET patients (22 men; mean age±SD 71.54±9.34 years, range 56-85), and 74 age and gender-matched healthy subjects (20 men; mean age±SD 60.97±12.38 years, range 33-85). We recorded the sustained emission of a vowel by means of a high-definition audio recorder. Voice samples underwent processes of features extraction, selection and classification by means of specific machine learning algorithms, according to previously described methods [2-3].

Results: Machine learning algorithms discriminated voice samples collected in healthy subjects and in patients with ET with high sensitivity (94.7%), specificity (96.4%), positive predictive value (96.4%), negative predictive value (94.6%), accuracy (95.5%), area under curve (0.990).

Conclusions: Advanced voice analysis performed by means of machine-learning algorithms might improve the recognition of subclinical voice impairment in patients affected by ET [2-3].

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P70

Kinematic assessment of bradykinesia in essential tremor compared to Parkinson's disease: a cluster analysis

Donato Colella¹, M. Bologna^{1,2}, G. Paparella², A. Cannavacciuolo¹, L. Angelini¹,
D. Alunni-Fegatelli¹, A. Guerra², A. Berardelli^{1,2}

¹Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

²IRCCS Neuromed Institute, Pozzilli (IS), Italy

Introduction: Essential tremor (ET) is a movement disorder primarily characterized by postural tremor of the upper limb. Although still under-investigated, bradykinesia may be part of the phenotypic spectrum of ET.

Objective: To evaluate the bradykinesia features in ET by clinical examination and kinematic analysis of repetitive finger movements. We compared data collected in ET patients with those recorded in Parkinson's disease patients and healthy controls.

Methods: Overall, 258 subjects participated in the study (90 ET patients, 84 Parkinson's disease patients, and 84 healthy controls). Repetitive finger tapping was kinematically recorded using a motion analysis system. Movement velocity, amplitude and decrement (sequence effect) were measured. We first compared the three groups by one-way analysis of variance. We also performed a cluster analysis to better address the data variability observed in ET patients. Possible relationships between kinematic and clinical data were assessed in ET.

Results: ET patients were slower than healthy controls. Movement slowness in ET did not correlate with tremor severity. We also found that movement slowness in ET was not associated with sequence effect, which instead is a common feature in Parkinson's disease. Cluster analysis showed that a proportion of ET patients may have movement abnormalities as those showed in Parkinson's disease.

Conclusions: Movement slowness without sequence effect is a common feature in ET patients. The present findings are relevant when interpreted in the context of the new tremor classification system and in the pursuit of reaching a more accurate bradykinesia definition.

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Progressive ataxia and palatal tremor in adult-onset Alexander disease: a case report

*Federico Paolini Paoletti*¹, P. Prontera², C. Calvello¹, L. Gentili¹, M. Filidei¹, G. Cappelletti¹, S. Simoni¹, P. Nigro¹, L. Parnetti¹, N. Tambasco¹

¹Section of Neurology, Department of Medicine, University of Perugia, Perugia, Italy

²Medical Genetics Unit, University of Perugia, Italy

Introduction: Alexander disease (AxD) is a rare genetic, dominantly inherited disorder caused by mutations in the GFAP gene encoding for glial fibrillary acid protein. It is a leukodystrophy with progressive neurologic signs that can occur as infantile, juvenile or adult form [1].

Objective: To describe a new case of adult-onset Alexander disease.

Methods: A 35-year-old man of Albanian origin presented with a 5-year history of postural instability and gait difficulties. In the last year he developed also cognitive impairment, dysphagia and dysarthria. He was affected by type I Brugada syndrome. He was not taking any medications. His familial history was remarkable for a 7-year-old daughter with a tonic-clonic seizure at the age of 6. Neurological examination revealed palatal and laryngeal tremor which was synchronous with pendular nystagmus (oculopalatal tremor). Dysarthria and dysdiadochokinesia were present; gait was ataxic.

Results: Magnetic resonance imaging (MRI) showed a condition of diffuse atrophy involving cortex, cerebellum, brainstem and upper cervical cord. Sovratentorial FLAIR and T2 images were characterized by white matter hyperintensity involving periventricular areas predominantly. Similar signal abnormalities were evident in medulla, midbrain, inferior and superior cerebellar peduncles. No pathological contrast enhancement was found. Molecular analysis and sequencing of the GFAP gene revealed a heterozygous c.236 G>T mutation causing the aminoacidic substitution Arg79Leu.

Conclusions: Progressive ataxia and palatal tremor (PAPT) is a well-defined condition, sometimes associated with brainstem abnormalities on MRI [2]. Both sporadic and familial forms of PAP have been described. The main known etiologies for familial cases are represented by AxD, POLG mutation, SCA20 and type II GM-2 gangliosidosis [3]. In cases of adult-onset ataxia associated with palatal tremor and MRI leukodystrophy, AxD should be considered among differential diagnosis and molecular testing of GFAP gene performed.

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P72

Combined use of botulinum toxin type A and phenol blockade to treat a runner's dystonia: a case report

*Anna Chiara Landi*¹, P. Latino², M. Giovannelli²

¹Dipartimento di Neuroscienze, Salute Mentale e Organi di Senso, Sapienza Università di Roma, Rome, Italy

²UOC Neurologia, Azienda Ospedaliero-Universitaria Sant'Andrea, Roma, Rome, Italy

Background: The runner's dystonia (RD) is a task-specific, late-onset focal dystonia of the lower limb that occurs in long-distance runners limiting running and deambulation [1]. Botulinum toxin type A (BoNT-A) is the first-line therapy of focal dystonia and causes a significant reduction in muscle contractions, but the response may be unsatisfactory. Neurolysis with phenol, a chemical agent that blocks nerve conduction when injected near a nerve, is widely known treatment for spasticity. Due to its effectiveness in reducing intramuscular overactivity regardless of its origin, it could be effective in the management of focal dystonia.

Case report: Here we report a successful case of a 50-years-old long-time runner with sustained equinovarus deformity of the right ankle, right internal foot rotation and hyperextension of the big toe that limited the deambulation. A diagnosis of RD was performed. For many years he underwent periodic local injections of BoNT-A into the following muscles of the right leg: tibialis posterior, gastrocnemius, soleus and extensor hallucis longus (EHL), with progressively less therapeutic relief. Given this treatment failure, tibial nerve blockade with phenol injection was performed. After the procedure, sustained internal foot rotation was relieved and he could finally rest the foot. Due to the persistence of EHL hyperactivity, he continued periodic BoNT-A injections restricted in this muscle, and he started customized rehabilitation program with benefit.

Discussion: BoNT-A and phenol neurolysis can be used in combination to effectively manage focal muscle overactivity [2]. Good results with combined treatment have been obtained in post-stroke spasticity and in intractable paroxysmal autonomic instability with dystonia [3]. Our case shows that combined treatment with phenol neurolysis and BoNT-A injection can be an effective and safe option in the management of focal dystonia, improving the effectiveness of both. Rehabilitation treatment remains an effective therapeutic option in maintaining and improving the results obtained with pharmacological approaches.

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P73

Improvement of essential tremor after thalamic hemorrhage caused by cavernoma. A case report with three years follow up

Vincenzo Moschella, C. Roberti, M.C. Altavista

UOC di Neurologia, Ospedale S. Filippo Neri, ASL Roma 1, Rome, Italy

Background: Essential tremor is defined as a tremor that appears with action, involves, as an isolated symptom and in absence of other neurological signs, bilateral upper limbs and is present since at least 3 years [1]. Tremor is caused by a dysfunction in cerebello-thalamo-cerebral circuit [2]. Anatomical and electrophysiological studies [3-4] confirmed what clinical reports had evoked, that lesions located along this pathway could ameliorate tremor [5-9]. Surgical options can be evaluated for severe or drug resistant tremor [10-11]. Thalamic ventral intermediate nucleus (ViM) has always been the choice site for lesional or modulating treatments (thalamotomy, DBS and MRI guided high intensity focused ultrasound) [12,13]. Recently, caudal zona incerta (cZI) has been considered as an alternative site for DBS [14-15].

Methods: In November 2016, a 54-years old woman was admitted to the Emergency Department of S. Filippo Neri Hospital of Rome complaining the subacute appearance of ageusia, hypoesthesia of right hemibody, headache, nausea and diplopia. Since youth she had action and postural tremor, involving both arms, diagnosed as essential tremor. Brain MRI revealed a thirty millimetres haemorrhage in left thalamus, perilesional oedema involving mesencephalon with compression of third ventricle and cerebral aqueduct and secondary hydrocephalus. Patient were admitted and treated with antiedema therapy. Neurological condition rapidly ameliorated and patient was dismissed two weeks later. A new brain MRI, performed four months later, revealed hematoma had been caused by a cavernoma. Interestingly, immediately after stroke, tremor in right arm completely disappeared and this effect lasted unchanged for almost two years. During the last year, tremor reappeared and, especially during emotional distress, could be mildly disabling.

Conclusions: Although we cannot exclude that tremor disappearance in our patient was caused by a more widespread lesion, perhaps involving the cZI [16], our case confirms the role of thalamus, especially ViM, in the “tremor circuit”.

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P74

Follow-up in patients with primary progressive aphasia

Raffaella Di Giacopo¹, F. Zappini², E. Barvas², V. Chiarelli¹, C. Papagno²

¹Center for Cognitive and Dementia Disorders, Azienda Provinciale per i Servizi Sanitari, Trento, Italy

²Center for Neurocognitive Rehabilitation (CeRiN), Trento University, Trento, Italy

Introduction: Primary progressive aphasia (PPAs) are clinical syndromes characterized by a progressive and insidious language impairment. Semantic (svPPA) and non-fluent/agrammatic variant (nfvPPA) have been associated with frontotemporal lobar degeneration (FTLD), whereas logopenic variant (lvPPA) has been more frequently associated with Alzheimer's disease (AD). However, nfvPPA can also be the first sign of Progressive Supranuclear Palsy (PSP) [1]. Recently, the Screening for Aphasia in Neurodegeneration (SAND) has been used to better identify aphasia in PSP [2].

Objective: In light of the new therapeutic approaches available for PSP [3] we tried to identify, based on an extensive neuropsychological evaluation, a specific pattern of PPA, at risk of developing PSP.

Methods: Eight subjects presenting PPA received a follow-up of 3 months - 3 years. They underwent a neuropsychological evaluation including MoCA, SAND and BADA, ideomotor and oral apraxia, memory, attentional-executive functions.

Results: Five patients received a diagnosis of nfvPPA: of these, two developed PSP-RS phenotype, one bvFTD phenotype and two were stable at 5 months. Among lvPPA patients, two did not develop further cognitive deficits apart from worsening of language impairment at 15 months; one developed AD. All participants were diagnosed according to updated clinical criteria, supported by MRI and PET-FDG.

Conclusions: According to the literature, patients with nfvPPA developed FTD and PSP clinical phenotypes whereas patient with lvPPA developed clinical AD phenotype. An extensive neuropsychological battery allowed identifying as soon as possible subjects with nvPPA at risk to develop the motor hallmarks of PSP. We failed to identify a specific neuropsychological marker suggesting progression of nfvPPA toward PSP instead of FTD.

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P75

A case of paroxysmal hemydystonia hyperventilation triggered

*Maria Letizia Caminiti*¹, L. Ricci¹, L. di Biase^{1,2}, F. Capone¹, G. Assenza¹, M. Tombini¹, J. Lanzone¹, M. Marano¹, V. Di Lazzaro¹

¹Unit of Neurology, Neurophysiology, Neurobiology, Department of Medicine, University Campus Bio-Medico of Rome, Rome, Italy

²Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK



RITIRATO

P76

Prevalence of RBD in the province of Catania: a population-based study

Calogero Edoardo Cicero, L. Giuliano, A. Luca, G. Mostile, R. Sgroi, C. Terravecchia, V. Todaro, M. Zappia, A. Nicoletti

Department G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy

Introduction: Rem Behavior Disorder (RBD) is the strongest prodromal marker of future development of Parkinson's disease. Its exact prevalence in the general population ranges from 0.4% to 1.1% for instrumentally confirmed cases and from 4.6% to 6.7% for probable RBD (pRBD) [1-2].

Objective: Aim of our study was to assess the prevalence of pRBD in the general population of the province of Catania.

Methods: Patients aged >40 years attending the cabinets of 27 randomly selected General Practitioners of the province of Catania were screened with the RBD1Q questionnaire (stage I). Positive subjects received a standardized phone interview and the suspected cases were then invited to undergo a neurological evaluation with a sleep and a movement disorder specialist to confirm the diagnosis of pRBD (stage II). Subjects with pRBD underwent a Videopolysomnography (VPSG) to confirm the diagnosis (stage III).

Results: Participants were 1,527 (mean age 62.0±11.9 years; 876 women [57.4%]). 228 (14.9%) screened positive at the RBD1Q were 228 (14.9%). Of these, 101 (44.3%) refused to be contacted by phone (61% men; mean age 65.0±11.6). Out of the remaining 127 subjects, for 54 (42.5%) diagnosis of RBD was excluded after the telephone interview while 73 (57.5%) were considered as suspected cases and underwent the neurological examination. Of these 39 (53.4%) were diagnosed as pRBD (mean age 60.8±10.7; 18 [46.1%] women) while 34 (46.6%) had other sleep diagnoses. Prevalence of pRBD was of 2.6 % (95%CI 1.8-3.3). VPSG confirmations are ongoing.

Conclusions: Prevalence of pRBD in our population is slightly lower than those reported in previous population-based studies, probably due to the relatively low participation rate (55.7%) at stage II. However, estimating the expected number of cases among subjects positive at the RBD1Q who refused to participate, the adjusted prevalence of pRBD is 4.5%, close to rates reported in literature.

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Prognostic role of cognitive impairment in a cohort of Multiple System Atrophy patients

*Ilaria Cani*¹, L. Sambati¹, G. Giannini¹, G. Calandra Buonauro^{1,2}, P. Guaraldi¹, P. Cortelli^{1,2}

¹Department of Biomedical and NeuroMotor Sciences (DIBINEM), Alma Mater Studiorum, University of Bologna, Bologna, Italy

²IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy

Introduction: Cognitive impairment has been recently described as integral part of Multiple System Atrophy (MSA) [1]. The aim of the study is to investigate the prognostic role of cognitive impairment in our cohort of MSA patients.

Methods: We retrospectively identified patients diagnosed with MSA referred to our department and evaluated at least yearly during the disease course. Cognitive impairment was defined according to results of a comprehensive neuropsychological evaluation (NPS).

Results: Cognitive impairment was detected in 44 out of 71 patients (62%) who performed NPS. Overall survival and milestones of disease progression did not differ between patients with and without cognitive deficits. Between cognitive impaired patients, 27 had developed cognitive deficits within 5 years of disease onset (earlyCI), while 17 patients declined in cognitive performance later (lateCI). At time of NPS, no differences in demographic, clinical variables and autonomic or sleep disturbances were found between earlyCI and lateCI, with the exception of a lower disease duration in earlyCI (3,72±1,12 years vs 8,60±3,65 years, p< 0,005). EarlyCI patients presented a significant faster progression of pyramidal signs, orthostatic hypotension and urinary disturbance with a lower overall-disease duration (5,85±2,18 years vs 10,94±4,48, p< 0,005). Moreover, earlyCI patients achieved sooner all milestones of disease progression (frequent falls, urinary catheterization, severe dysphagia, wheelchair dependence, p <0,005).

Conclusions: Occurrence of cognitive impairment itself is not associated with a worse prognosis in MSA patients. Great relevance must be given at time-onset of cognitive deficits, patients who develop cognitive impairment within 5 years of onset present a more severe phenotype of disease with a faster progression.

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P78

Red blood cells alpha-synuclein heteroaggregates in the differential diagnosis of Lewy body dementias, Alzheimer's disease and healthy controls

Giovanni Palermo¹, L. Giampietri¹, S. Daniele², R. Piccarducci², G. Tognoni¹, U. Bonuccelli¹, C. Martini², F. Baldacci¹, R. Ceravolo¹

¹Unit of Neurology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

²Department of Pharmacy, University of Pisa, Pisa, Italy

Introduction: Red blood cells (RBC) account for more than 99% of α -syn concentrations in blood, representing an interesting in vivo model for studying pathophysiological mechanisms related to neurodegeneration.

Objective: To investigate the diagnostic value of RBC levels of total α -syn, A β 1-42, tau and its heteroaggregates in LBDs, AD and healthy controls (HCs).

Methods: With a "homemade" sandwich enzyme-linked immunosorbent assay (ELISA) system, RBCs levels of total α -syn, A β , tau and its heteroaggregates (α -syn/A β 1-42 and α -syn/tau) were measured in 27 subjects with LBDs (PDD, n=17; DLB, n=10), 51 subjects with AD (AD dementia, n=37, prodromal AD, n=14), and age-matched healthy controls (n=60).

Results: Compared with HCs, total tau and α -syn concentrations as well as α -syn/tau heterodimers were significantly lower in the AD group ($p = 0.011$, $p = 0.003$ and $p < 0.001$ respectively) and even further decreased in the LBDs group ($p = 0.009$, $p = 0.009$ and $p < 0.001$ respectively) whereas the heteroaggregate α -syn /A β 1-42 were only significantly lower in the AD dementia group ($p < 0.001$). RBC α -syn/tau heterodimers had the higher diagnostic accuracy for differentiating patients with LBDs vs controls (area under the receiver operating characteristic curve, 0.80). RBC total tau had a fair diagnostic accuracy (AUROC=0.73) in differentiating between the LBDs group and controls whereas AUC values indicated only poor diagnostic accuracy for RBC total α -syn.

Conclusions: RBC α -syn heteroaggregates may be useful for differentiating between neurodegenerative dementias (LBDs and AD) and HCs. In particular, RBC α -syn/tau heterodimers has demonstrated good diagnostic accuracy for differentiating LBDs from HCs but are not consistently different between LBDs and AD. Our findings also go beyond the clinical setting, supporting the notion that α -syn, A β and tau interact in vivo to promote the aggregation and accumulation of each other presumably accelerating cognitive dysfunction.

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Predictors of early and late dementia onset in Parkinson's disease

Luca Tommasini¹, G. Palermo², M. Dini², E. Del Prete², D. Frosini¹, G. Bellini², U. Bonuccelli^{1,2}, R. Ceravolo²

¹Department of Medical Specialities, Neurology Unit, AOUP, Pisa, Italy

²Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy

Introduction: Cognitive dysfunction is one of the most prevalent non-motor symptoms in PD which contributes significantly to the morbidity and mortality of the condition. However, it is still unclear whether and which cognitive symptoms may predict an early or later development of dementia in PD patients.

Objective: To identify possible baseline markers of early and late conversion to Parkinson's disease dementia (PDD).

Methods: In this retrospective study we included 92 *de novo* PD patients who were divided into two groups based on the duration of follow-up and time to dementia onset (50 with a mean follow-up of 4.3 years; 42 with a mean follow-up of 8.3 years). Baseline clinical characteristics, neuropsychological scores and [123I]-FP-CIT striatal binding of PDD converters and non-converters were compared in both follow-up groups separately. We used ROC curves to calculate the best discriminating power of each neuropsychological tests at baseline in detecting early and late PDD converters.

Results: Early development of dementia (10 of 50 PD patients) was associated with reduced educational level, PIGD phenotype, lower caudate DAT binding, diagnosis of MCI at baseline and with worse cognitive scores in RAVLT immediate recall, TMT-A, MWCST and prospective memory task. In contrast, patients with a later conversion to dementia (10 of 42 PD patients) demonstrated at baseline only a poorer performance in MWCST and Cognitive Reserve Index-leisure time. MWCST predicted dementia with an AUC >0.8 in both groups.

Conclusions: In newly diagnosed PD, the occurrence of early dementia was predicted by various demographic, clinical and imaging measures which are all known risk factors of PDD. However, the only predictors of later dementia were baseline deficits in executive functioning and a subscore of Cognitive Reserve Index suggesting a substantial contribute of other neuropathological changes as a progression of PD.

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Gender differences in cognition in early Parkinson's disease: a longitudinal, prospective study

*Arianna Cappiello*¹, S. Cuoco¹, R. Erro¹, M. Amboni^{1,2}, C. Vitale^{2,3}, G. Santangelo⁴, P. Barone¹, M.T. Pellecchia¹, M. Picillo¹

¹Center for Neurodegenerative Diseases (CEMAND), Department of Medicine, Surgery and Dentistry, Neuroscience Section, University of Salerno, Salerno, Italy

²Institute of Diagnosis and Health, IDC-Hermitage Capodimonte, Naples, Italy

³Department of Motor Sciences and Wellness, University Parthenope, Naples, Italy

⁴Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

Introduction: Evidence demonstrated the existence of gender differences in motor and non motor symptoms in Parkinson's disease (PD) [1]. Aim of the present study is (1) to report on gender differences in cognition in early, drug-naïve PD and (2) to investigate potential predictors of development of Mild Cognitive Impairment (MCI) and dementia (PDD) at 4-year follow up in relation with gender.

Methods: Forty-four early, drug-naïve PD patients underwent an extensive neuropsychological battery at diagnosis (T0) and after 4 years (T1). Patients were also asked to report on Subjective Cognitive Impairment (SCI). At T0 all patients performed a brain MRI and the Age-Related White Matter Changes (ARWMC) score was computed. Non parametric tests and chi square were used to analyze gender differences in cognitive measures and multiple binary logistic regression to investigate predictors of cognitive impairment (MCI or PDD).

Results: At T0, women had lower scores in visuo-spatial tests compared to men ($p < 0.05$). At T1 no gender differences were detected in any cognitive measures and all patients presented a worsening of visuo-spatial and executive performances ($p < 0.05$). At T0 26 % of women and 48 % of men reported SCI ($p = 0.213$). At T1 44 % of women and 67 % of men reported SCI ($p = 0.324$). At T1, 37% of women and 32% of men developed either MCI or PDD ($p = 0.793$). Logistic regression identified no predictors of development of cognitive impairment in neither gender.

Conclusions: We showed similar cognitive performances in early, drug-naïve men and women with PD during the first years of disease. Contradicting previous findings, gender did not represent a risk factor for development of cognitive impairment.

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Effects of gender on cognitive and behavioral manifestations in Multiple System Atrophy

*Sofia Cuoco*¹, M. Picillo¹, A. Cappiello², I. Carotenuto², R. Erro¹, M.C. Russillo², F. Abate², G. Volpe², M. Squillante², A. Cozzolino³, G. Cicarelli³, G. Santangelo⁴, P. Barone¹, M.T. Pellecchia¹

¹Neuroscience Section, Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, University of Salerno, Salerno, Italy

²Neurology, University Hospital A.O.U. OO.RR. San Giovanni di Dio e Ruggi D'Aragona, Scuola Medica Salernitana, Salerno, Italy

³Neurology Unit, S.G. Moscati Hospital, Avellino, Italy

⁴Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

Introduction: Gender differences have been described in several neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease. The effects of gender on cognitive and behavioral manifestations in Multiple System Atrophy and the changes of cognitive functions over time according to gender have not been investigated so far [1-2].

Methods: Fifty-five patients with a diagnosis of Multiple System Atrophy underwent a comprehensive neuropsychological and neuropsychiatric battery at baseline and 26 of them could be re-evaluated at 1 year follow-up.

Results: At baseline women with Multiple System Atrophy had poorer global cognitive state and visuo-spatial abilities, and a higher prevalence of depression and apathy than males. At follow-up, female patients deteriorated more than males on attention abilities and motor functions, and had a higher prevalence of depression than men. Executive functions and visuo-spatial abilities significantly worsened over time in both groups. Mild Cognitive Impairment single domain was significantly more frequent in females than males.

Conclusions: Cognitive and behavioral differences between genders in Multiple System Atrophy involve global cognition, planning, attention, visual-perceptive skills and depression, with female patients more compromised than males. Female patients deteriorated more than men over time as for motor functions and attention. Further longitudinal studies are deserved to confirm gender differences in progression of cognitive and behavioural features of Multiple System Atrophy.

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Does age at onset of Parkinson's disease affect the development of dementia?

*Francesca Del Sorbo*¹, P. Soliveri¹, A. Zecchinelli¹, G. Sacilotto¹, N. Meucci¹, M. Zini¹, S. Tesei¹, C. Mariani¹, G. Pezzoli^{1,2}

¹Parkinson Institute, ASST Gaetano Pini-CTO, Milan, Italy

²Fondazione Grigioni per il Morbo di Parkinson, Milan, Italy

Introduction: Dementia frequency in Parkinson disease (PD) increases with age. Older age at disease onset and disease duration are independently associated with PD dementia [1]. Cortical Lewy pathology – major correlate of dementia – usually progresses slowly but may progress rapidly in senile PD (SPD) [2].

Objective: To investigate whether progression to dementia in SPD (disease onset after 70 years) differs from that in old PD, OPD, (over 70 years but with onset at 40-70 years).

Methods: We examined the clinical records of PD patients over 70 years, seen in 2019 at the outpatient clinics of our PD Institute, dividing them into SPD and OPD according to age at PD onset, and assessing the frequency of mental decay (MMSE <26/30).

Results: Of 2072 cases over 70 years we excluded 15 because of misdiagnosis. Of the remaining 2057 cases, 908 (43.8%) were SPD and 1149 (55.4%) OPD. MMSE was administered to 87 (9.6%) SPD and 142 (12.3%) OPD (p=0.06). Forty-two SPD (48.3%) and 48 OPD (34%) (p=0.03) had age and education-adjusted MMSE score <26, suggesting mental decay. SPD and OPD patients with mental decay differed, as expected, for age at disease onset (p<0.001) and disease duration (p<0.001), but also differed for age at examination (p<0.001) with SPD older than OPD. However the two groups did not differ for years of education, MMSE and UPDRS scores, or Hoehn and Yahr stage.

Conclusions: Our data are preliminary and retrospective in nature. Nevertheless they indicate that frequency of cognitive impairment is higher in SPD than OPD, particularly since, although SPD were older than OPD, MMSE scores were adjusted for age and education. This suggests that dementia pathogenesis may differ between the two groups, although comorbidities, lifestyles, and intrinsic factors (like chronic aminergic denervation or interaction between Parkinson and Alzheimer lesions [3]) must all be taken into account when interpreting the results.

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Neuropsychological differences between Parkinson disease dementia and Dementia with Lewy bodies

Elisabetta Belli, G. Palermo, L. Tommasini, F. Baldacci, D. Frosini, U. Bonuccelli, R. Ceravolo

Department of Clinical and Experimental Medicine, Unit of Neurology, University of Pisa, Pisa, Italy

Background: Dementia with Lewy Bodies (DLB) and Parkinson's disease dementia (PDD) are two neurocognitive disorders, together known as the Lewy body dementias (LBDs), sharing many clinical, neurochemical and neuropathological features. Their distinction is based on the time of onset of cognitive and motor symptoms according to the '1-year rule'. Whether DLB and PDD are part of the same pathological spectrum or should be considered as different 'diseases' is still matter of discussion.

Objective: To explore the neuropsychological spectrum of LBDs investigating if patients with PD with a different timing from motor symptoms to the onset of dementia present distinct cognitive profiles in comparison with DLB subjects.

Materials and Methods: Neuropsychological findings at the time of the diagnosis of dementia from 71 PDD patients and 48 DLB patients were retrospectively pooled and compared. Patients with PDD were further divided into three tertile subgroups according to the time interval between the onset of parkinsonism and dementia (22 PD with early dementia, 3-4 yrs; 22 PD with dementia onset at 5-7 yrs; 27 PD with late dementia, > 8 yrs). Demographic variables, clinical features and neuropsychological performance were compared among all subgroups.

Results: There were no significant differences in age, gender and years of education between groups. Compared to PDD, DLB patients performed worse on MMSE ($p=0.016$), digit span ($p=0.037$), attentive matrices ($p=0.021$), spontaneous clock drawing ($p=0.013$), phonemic ($p=0.025$) and semantic verbal fluency ($p=0.002$), even when they are compared to PD with early dementia. To support our data, there were no significant differences in cognitive test performance between PDD subgroups.

Conclusions: Our findings provide additional insights into phenotypic diversity of DLB and PDD indicating a different cognitive profile between such disorders, even when comparing DLB with PD patients with an early onset of dementia, with DLB performing worse at the time of dementia onset on attentive and executive domains.

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Noun-verb dissociation in Parkinson's disease: the role of actionality

Margherita Grosso¹, A. Andriulo², S. Buscone², C. Caracciolo², M. Ottobri², E.N. Aiello³, C. Luzzatti¹

¹Department of Psychology, University of Milan-Bicocca, Milan, Italy

²High-Complexity Rehabilitation Unit, Casa di Cura Villa Esperia, Salice Terme (PV), Italy

³PhD in Neuroscience, University of Milano-Bicocca, Milan, Italy

Introduction: Noun-verb (N-V) dissociation was initially studied in aphasic patients, and it showed a bi-directional effect (N>V or V>N). This dissociation was also reported in Parkinson's disease (PD).

Objective: In this study, we speculated that PD patients could have greater difficulties in naming V rather than N, especially when it comes to action V.

Methods: Three groups of participants: 30 control subjects with pure PD (PD-) and 14 subjects with PD and cognitive impairment (PD+) were compared on tasks evaluating N and V lexical retrieval and the integrity of visuo-perceptual and semantic knowledge. Between groups comparisons were implemented using overdispersed generalized linear models. Logistic regression was implemented in order to investigate the effect of the degree of motor feature of lexical items (actionality) on N and V naming.

Results: N were easier to retrieve than V, however control participants performed better than PD- and PD+. In addition, PD- made fewer errors than PD+. Logistic regression analysis showed a positive effect of actionality: V with a high degree of motor feature were easier to retrieve for both control participants and PD patients.

Discussion: N-V dissociation was found in all groups: N were easier to retrieve than V. The hypothesis of a negative effect of actionality has not been confirmed. On the contrary, actionality had a facilitating effect on V retrieval for PD patients: V with high motor content were more easily retrieved than V with low actionality.

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Neuropsychological comparison between tremor-dominant Parkinson's disease and cervical dystonia

*Alfonsina D'Iorio*¹, M. Esposito^{2,3}, G. Maggi¹, M. Amboni^{4,5}, C. Vitale^{4,6}, G. Santangelo¹

¹Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

²Department of Neuroscience, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy

³Clinical Neurophysiology Unit, Cardarelli Hospital, Naples, Italy

⁴Institute of Diagnosis and Health, IDC-Hermitage Capodimonte, Naples, Italy

⁵Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy

⁶Department of Motor Sciences and Wellness, University Parthenope, Naples, Italy



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Comparative psychological profiles between functional neurological disorders, organic neurological disorders and healthy controls

*Sofia Cuoco*¹, V. Nisticò², M. Autuori³, P. Barone¹, R. Erro¹, B. Demartini²

¹Neuroscience Section, Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, University of Salerno, Salerno Italy

²Dipartimento di Scienze della Salute, University of Milan, Milano, Italy

³Neurology Unit, AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy

Introduction: Functional Neurological Disorders (FND) are characterized by motor or sensory symptoms that are inconsistent with any organic neurological disorders (OND) [1]. Although psychological factors have been implicated, the pathomechanisms of FND are poorly understood [2].

Aim: We aimed to explore the psychological profiles of FND in comparison with both OND and healthy controls (HC).

Methods: Forty-six patients with FND (M=15), 27 with OND (M=11) and 38HC (M=18) with similar age (p=0.283) and gender distribution (p=0.384), underwent the following rating scales: Toronto Alexithymia Scale (TAS-20), Beck Depression Inventory-II (BDI-II), Hamilton Depression Scale (Ham-D), Hamilton anxiety rating scale (Ham-A), Dissociative Experiences Scale (DES), Revised Experiences in Close Relationships (ECR-R), EuroQol-5Dimension (EQ-5D) and Personal Meaning organizations Questionnaire (PMQ). Symptoms severity perception was explored with a Visual Analog Scale (VAS). Non-parametric analyses were performed to explore differences between groups.

Results: FND patients were more impaired than those with OND on BDI-II, Ham-A, on the somatic-affective and cognitive components of depression (i.e., BDI-II-SA; BDI-II-C) and on the identification sub-component of the TAS-20 scale (TAS-20-I) (p<0.05). FND patients had lower education and were more impaired than HC on BDI-II, TAS-20, EQ-5D, VAS, Ham-A and Ham-D (p<0.05).

Conclusions: Our preliminary results confirm previous evidence on higher alexithymia, depression and anxiety in FND compared to HC. Novel to this study is lower education in FND than in HC, which might be a factor driving how patients interpret their symptoms, and greater presence of avoidance in FND compared to OND. The lower presence of avoidance in the latter possibly suggests that it is not reactive to the presence of clinical symptoms but could be a psychological feature of FND. Future studies are required to investigate how avoidance affects clinical variables of FND and whether it could be used as therapeutic target, influencing the clinical course of FND.

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P87

[18F] FDG-PET thalamic hypometabolism as potential diagnostic marker of DLB with respect to AD: results from a pilot study

Valentina Nicoletti¹, D. Frosini¹, G. Tognoni¹, A. Francesconi¹, U. Bonuccelli¹, D. Volterrani², R. Ceravolo¹

¹Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa, Pisa, Italy

²Dipartimento di Ricerca Traslazionale e delle Nuove Tecnologie in Medicina e Chirurgia, Università di Pisa, Pisa, Italy

Introduction: One of the clinical core features of Dementia with Lewy Bodies (DLB) is fluctuating cognition, represented by spontaneous alterations in arousal, attention and cognition [1]. This is a distinctive feature from Alzheimer's Disease (AD). Thalamus plays a central role in arousal as consciousness is thought to be generated by synchronized neural activity in thalamic neurons [2].

Methods: Eleven patients with diagnosis of possible or probable AD and 11 patients with possible or probable DLB underwent cerebral [18F] FDG-PET within 2 years from the onset of symptoms. Cognitive fluctuations were evaluated with Clinical Assessment Fluctuation (CAF) questionnaire [3]. DLB and AD metabolic patterns were tested by means of an optimized SPM approach at a group-level and then with voxel-based comparisons.

Results: All DLB patients were affected by cognitive fluctuations according to the CAF questionnaire whereas AD patients were not. The SPM voxel-based comparisons revealed significant ($p < 0,005$) hypometabolism in DLB with respect to AD patients both in cortical and subcortical areas. Actually in addition to occipital cortex and dorsolateral frontal regions bilaterally, DLB exhibited hypometabolism in midbrain bilaterally and left thalamus.

Conclusions: Our pilot study support the role of subcortical structures and thalamus particularly in fluctuating cognition, which is a topic feature of DLB patients and is not present in AD. Abnormal functional connectivity and microstructural damage within thalami have been previously reported in DLB [4, 5]. The severity of fluctuating cognition has been also related by diffusion tensor imaging and proton MR spectroscopy [6] to microstructural changes in connectivity-defined regions of thalamus projecting to frontal and occipital cortices, the same cortical regions in which we detected significant hypometabolism.

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Visuo-spatial functions in Parkinson's related Pisa Syndrome

Elisa Montanaro, C.A. Artusi, C. Rosano, F. Donetto, A. Romagnolo, M.G. Rizzone, M. Zibetti, L. Lopiano

Department of Neuroscience Rita Levi Montalcini, University of Torino, Torino, Italy

Introduction: Pisa syndrome (PS) is a disabling postural alteration with 9% prevalence in Parkinson's disease (PD). The pathogenesis of PS remains incompletely understood, but recent studies suggested an association between PS and specific cognitive deficits, pointing out the role of visuo-spatial functions.

Objective: To clarify the extent and characteristics of visuo-spatial functioning impairment in PS, we analyzed 10 PD patients with PS (PS+) by different neuropsychological tests investigating the broad spectrum of the visuo-spatial abilities, and compared the outcomes with ones of 10 matched PD patients without abnormal postures (PS-) and 10 healthy controls (HC).

Methods: Participants underwent an extensive neurological and neuropsychological assessment. Visuo-spatial abilities were investigated by following tests: Line Bisection Test (LBT), Letter Cancellation Test (LCT), Clock Drawing Test (CDT), Benton Judgment of Line Orientation Test (BJLOT) and Constructional Apraxia Test (CAT).

Results: The three groups obtained similar scores from neuropsychological screening tests (MMSE: PS+ =27.8±2.0; PS- =28.4±1.4; HC =28.7±1.3; p=0.464; FAB: PS+ =13.2±2.9; PS- =15.0±2.8; HC =15.8±1.5; p=0.141). Both PS+ and PS- groups performed worse than HC in CDT, BJLOT, and CAT (p=0.019; p=0.020; p=0.004), and not in LCT (p=0.327) and LBT right and left hand (p=0.133 p=0.379). After correction for multiple comparisons, PS+ patients performed significantly worse than PS- for BJLOT (PS+ =18.2±4.9; PS- =23.5±3.3; HC =24.0±4.9) and CAT (PS+ =11.0±2.0; PS- =12.9±1.0; HC =13.4±1.1), and showed a trend, still not significant, towards worse scores in CDT (PS+ =3.4±1.1; PS- =3.7±1.3; HC =4.7±0.5).

Conclusions: While confirming an association between PS and altered visuo-spatial functions, we found worse performances in specific visuo-spatial tests in PS patients than PD patients without postural alterations, which in turn perform worse than age-matched healthy subjects. In particular, our findings seem to suggest PS patients having lower visuo-perceptual and visuo-constructional abilities.

P89

Cognitive and psychiatric symptoms in genetically determined Parkinson's disease: a systematic review

Rosanna Piredda^{1,2}, P. Desmarais^{3,4,5,6}, M. Masellis^{3,4,5,6,7}, C. Gasca-Salas^{1,8}

¹CINAC-HM Puerta del Sur, CEU-San Pablo University, Mostoles, Madrid, Spain

²Department of Neurology IRCCS, Istituto Clinico Humanitas Rozzano, Milano, Italy

³Cognitive and Movement Disorders Clinic, Sunnybrook Health Sciences Centre, Toronto, Canada

⁴L.C. Campbell Cognitive Neurology Research Unit, Sunnybrook Health Sciences Centre, Toronto, Canada

⁵Hurvitz Brain Sciences Program, Sunnybrook Research Institute, University of Toronto, Toronto, Canada

⁶Division of Neurology, Department of Medicine, University of Toronto, Toronto, Canada

⁷Institute of Medical Science, University of Toronto, Toronto, Canada

⁸CIBERNED, Institute Carlos III, Madrid, Spain

Aim: The aim was to review the existing reports on cognitive and behavioural symptoms in monogenic forms of Parkinson's disease (PD) and to identify recurring patterns of clinical manifestations in those with specific mutations. A systematic literature search was conducted to retrieve observational studies of monogenic PD. Data pertaining to cognitive and psychiatric manifestations were extracted using standardized templates. The PRISMA guidelines were followed. Of the 1889 citations retrieved, 95 studies on PD-related gene mutations were included: 35 in SNCA, 35 in LRRK2, four in VPS35, 10 in Parkin, three in DJ1 and eight in PINK1. Nineteen studies (20%) provided adequate data from comprehensive cognitive assessment and 31 studies (32.6%) outlined psychiatric manifestations through the use of neuropsychiatric scales. Cognitive impairment was reported in all monogenic PD forms with variable rates (58.8% PINK1, 53.9% SNCA, 50% DJ1, 29.2% VPS35, 15.7% LRRK2 and 7.4% Parkin). In this regard, executive functions and attention were the domains most affected. With respect to psychiatric symptoms, depression was the most frequent symptom, occurring in 37.5% of PINK1 cases and 41.7% of VPS35 and LRRK2 cases. Co-occurrence of cognitive decline with visual hallucinations was evidenced. Widespread accumulation of Lewy bodies, distinctive of SNCA, PINK1 and DJ1 mutations, results in higher rates of cognitive impairment. Similarly, a higher degree of visual hallucinations is observed in SNCA mutations, probably owing to the more widespread accumulation. The lower rates of α -synuclein pathology in LRRK2 and Parkin may underpin the more benign disease course in these patients.

P90

Characteristic of apraxia in corticobasal degeneration and in progressive supranuclear palsy: a preliminary study

*Eleonora Del Prete*¹, L. Tommasini², K. Polsi¹, D. Frosini², S. Mazzucchi¹, G. Tognoni², U. Bonuccelli¹, R. Ceravolo¹

¹Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

²Neurology Unit, Department of Medical Specialties, AOUP, Pisa, Italy

Introduction: Corticobasal Degeneration (CBD) and Progressive Supranuclear Palsy (PSP) are closely related parkinsonisms that share many clinical features, including apraxia. In new criteria for PSP diagnosis [1], other than Richardson (PSP-RS) variant has been defined. Considering Multiple Allocations eXtinction rules (MAX) [2], a PSP-RS diagnosis is suggested even if apraxic features are present concomitant with postural instability within 3 years after symptom onset and ocular motor dysfunction.

Aim: The aim of our study was to investigate apraxia in a group of PSP-RS and CBD.

Method: PSP-RS and CBD non-demented patients, matched for age, disease duration and education were consecutively enrolled. Apraxia was investigated exploring meaningful (I-F) and meaningless (I-L) intransitive movement, pantomime and objects used. Intransitive gestures were also separately sub-scored as static vs dynamic movements and proximal vs distal movements. Motor evaluation was performed using Modified Parkinson Disease Rating scale and Progressive Supranuclear Palsy Rating Scale.

Results: Ten PSP-RS and eight CBD patients were enrolled. CBD presented worse performances than PSP-RS in pantomime and intransitive gestures in more affected side. Both PSP and CBD patients presented an impairment in most affected side for I-F (60% and 100% respectively), while for I-L gesture the impairment was 10% and 75% respectively. regarding intransitive tasks, distal worse than proximal and dynamic worse than static movement were present in both groups. Pantomime were worse than object use in both PSP and CBD groups, however only for the worse side in PSP. In both groups pantomime were more impaired than intransitive gestures. A correlation with the presence of dystonia was found in PSP group with I-F and I-L gesture.

Conclusions: Apraxia is more severe in CBD than in PSP. However apraxic features can be present also in patients with PSP-RS probable diagnosis.

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P91

Anosognosia for apathy in Parkinson's disease: discrepancies on apathy scores between patients' evaluation and caregiver's rating

*Gianpaolo Maggi*¹, A. D'Iorio¹, D. Di Meglio¹, M. Amboni², C. Vitale³, G. Santangelo¹

¹Neuropsychology and Memory Clinic, Department of Psychology, University of Campania Luigi Vanvitelli, Caserta, Italy

²Department of Medicine, Center for Neurodegenerative Diseases (CEMAND), University of Salerno, Fisciano, Italy

³Department of Motor Sciences and Wellness, University Parthenope, Napoli, Italy

Introduction: Apathy is defined as a behavioural syndrome characterized by a quantitative reduction of self-generated voluntary and goal-directed behaviours [1]. In Parkinson's disease (PD), apathy has been associated with reduced functional connectivity in frontostriatal circuits [2], and might be associated with anosognosia. Some studies revealed that PD participants' self-ratings of apathy were significantly lower than comparison their caregiver's ratings, but other studies failed to confirm an anosognosia for apathy in PD patients.

Objectives: The present study aims to investigate the possible differences in apathy evaluations according to the point of view of the patients and their caregivers.

Methods: Consecutive PD outpatients were screened. All patients underwent the Dimensional Apathy Scale and the Montreal Cognitive Assessment. Also, caregivers were asked to complete the Dimensional Apathy Scale to evaluate the patients' apathy.

Results: We enrolled 52 non-demented PD patients. The results showed that patients reported lower scores on the total score of DAS, and on two subscales: Behavioural/Cognitive Initiation and Emotional subscale than caregivers did. Correlational analysis revealed that apathy scores reported by patients were poorly associated with those reported by their caregivers.

Conclusions: Our findings indicated that PD patients and their caregivers' ratings were not associated, and, in particular, that PD patients tended to underestimate their apathetic symptoms. This result can be due to the fact that PD patients may exhibit anosognosia for apathy. This study highlights the need to evaluate non-motor symptoms of PD, such as apathy, not only by patient self-evaluation but also by caregiver-ratings.

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P92

Impaired LTP-like plasticity in Parkinson's disease can be restored by tACS in a frequency-dependent and state-independent manner

*Valentina D'Onofrio*¹, A. Guerra^{1,2}, F. Ascì¹, V. Sveva¹, M. Bologna^{1,2}, G. Fabbrini^{1,2},
A. Berardelli^{1,2}, A. Suppa^{1,2}

¹Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy

²IRCCS Neuromed Institute, Pozzilli (IS), Italy



P93

Low-frequency repetitive sensory stimulation enhances cortical inhibition and reverses abnormal temporal discrimination threshold in cervical dystonia

*Sara Scannapieco*¹, R. Erro¹, A. Latorre², K. Bhatia², A. Berardelli³, J. Rothwell², L. Rocchi²

¹Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, University of Salerno, Baronissi (SA), Italy

²Department of Clinical and Movement Neurosciences, University College London, Institute of Neurology, London, UK

³Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

Introduction: In a previous study, we have demonstrated that peripheral Repetitive Sensory Stimulation (RSS) at high frequency induces a paradoxical and detrimental response in patients with Cervical Dystonia (CD) in several inhibitory cortical mechanisms and in the somatosensory temporal discrimination threshold (STDT). We therefore aimed to explore whether low-frequency-RSS (LF-RSS) could induce a similarly inverted response in CD, at both neurophysiologic and behavioral level, as compared with healthy controls (HC).

Methods: Thirteen patients with CD and 13 age- and sex-matched HC underwent an extensive neurophysiologic battery gathering several measures of cortical sensori-motor excitability and inhibition and the STDT, before and after a 45 minute protocol of LF-RSS applied on the right index finger.

Results: Patients with CD showed a consistent inverted response, as compared to the HC, in nearly all the gathered variables. Thus, while in HC cortical inhibition was found to be decreased and STDT worsened, in CD an opposite direction of response was observed, with post-stimulation neurophysiologic measures of inhibition and STDT reversing to normal values. A significant correlation was found between measures of intracortical sensory inhibition and improvement of STDT. Interestingly, these after effects were transmitted to the motor system, where SICI strengthened after LF-RSS.

Conclusions: Together with our previous observation, the current results point at a primary dysfunction of inhibitory plasticity in the pathomechanisms of abnormal STDT. This could “prime” the cortical areas targeted by RSS and induce an inverted response in CD, suggestive of overall congruent homosynaptic plasticity response. It should be seen whether how these sensory abnormalities correlate with the development of overt motor symptoms, but our data provides the rationale for the exploration of LF-RSS as a non-invasive stimulation technique for dystonia, since we also found evidence of heterosynaptic, topographically congruent, plasticity elicited in the motor cortex.

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Reactive postural responses to axial rotations in Parkinson's disease

*Alessandro Zampogna*¹, I. Mileti², F. Martelli², M. Paoloni³, E. Palermo², A. Suppa^{1,4}

¹Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy

²Department of Mechanical and Aerospace Engineering, Sapienza University of Rome, Rome, Italy

³Department of Physical Medicine and Rehabilitation, Sapienza University of Rome, Rome, Italy

⁴IRCCS Neuromed Institute, Pozzilli (IS), Italy

Introduction: Postural instability (PI) usually occurs in advanced stages of Parkinson's disease (PD). However, even in the early stages of PD, patients have balance difficulties in situations requiring challenging postural control, such as turning [1]. Clinical assessment is rather arbitrary and poorly sensitive to detect early signs of balance disorders [2-3]. Moreover, postural control during axial rotation and the effect of dopaminergic therapy on this function have been poorly studied in PD.

Objective: Aims of this study are to examine reactive postural responses to axial rotations in patients with PD, without clinically overt PI, and to assess the effect of dopaminergic therapy on such measures.

Methods: 20 patients with PD, without clinically overt PI, and 15 age-matched Healthy Subjects (HS) underwent yaw perturbations of upright stance imposed by a mechatronic platform. We measured kinematics of axial body by Inertial Measurements Units (IMUs) on the head, trunk and pelvis. We examined motor, cognitive and emotional functions by standardized clinical scales. Patients were assessed ON and OFF dopaminergic therapy. Reactive postural responses were evaluated through the Range of Motion (ROM) of axial body displacement in Medio-Lateral (ML) and Antero-Posterior (AP) directions.

Results: All subjects completed the experimental trials without clinically overt balance disorders. However, when considering kinematics, patients showed larger ML ROM of axial body displacement than HS. AP ROM of axial body displacement was similar between the two subgroups. L-Dopa left kinematic measures unchanged. Finally, axial body displacement correlated with the degree of patients' motor impairment, emotional and balance status.

Discussion/Conclusions: Patients with PD, without clinically overt PI, present subclinical changes of balance control detectable by means of IMUs. These findings partially depend on abnormal scaling of reactive postural responses along with axial rigidity and bradykinesia. The lack of effect of L-Dopa suggests that balance disorders in PD involve neurodegeneration in non-dopaminergic pathways.

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P95

Kinematic assessment of bradykinesia in patients with amyotrophic lateral sclerosis

*Giulia Paparella*¹, M. Bologna^{1,2}, D. Colella², A. Cannavacciuolo², M. Ceccanti², A. Guerra¹, M. Inghilleri², A. Berardelli^{1,2}

¹IRCSS Neuromed, Pozzilli (IS), Italy

²Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

Introduction: Amyotrophic lateral sclerosis is primarily characterized by a progressive degeneration of motor neurons, leading to muscle weakness and motor impairment. There are some clinical reports of bradykinesia in patients with amyotrophic lateral sclerosis [1-2], but no studies have objectively assessed the movement abnormalities in these patients. Moreover, the relationship between motor neurones involvement and movement abnormalities in this condition is largely unknown.

Aims: To kinematically assess abnormalities of voluntary upper limbs movements in patients with amyotrophic lateral sclerosis compared to healthy subjects. To investigate possible relationships between altered movement kinematics and neurophysiological measures of motor neurons involvement in patients with amyotrophic lateral sclerosis.

Methods: Thirteen patients with a definite diagnosis of amyotrophic lateral sclerosis and 13 healthy subjects were enrolled in the study. Repetitive finger tapping was assessed by means of a motion analysis system. Patients with amyotrophic lateral sclerosis underwent to a motor nerve conduction study of bilateral median and ulnar nerves. The two groups were compared by one-way analysis of variance. Possible relationships between clinical, kinematic and neurophysiological data were assessed in patients with amyotrophic lateral sclerosis.

Results: Patients with amyotrophic lateral sclerosis performed less movements and they were slower than healthy controls ($P<0.01$). Patients also showed an altered movement rhythm ($P<0.05$). The relation between velocity and amplitude differed from the one observed in controls. Finally, the number of movements negatively correlated with the amplitude of the compound muscle action potential recorded from the first dorsal interosseus muscle in patients ($P=0.02$).

Conclusions: This study provides new information on the evidence of voluntary movement impairment in amyotrophic lateral sclerosis, showing movement slowness and a disruption of the normal relationship between movement amplitude and velocity in patients. In amyotrophic lateral sclerosis movement slowness likely depends on the motor neurons involvement.

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Paired-pulse flash-visual evoked potentials: evaluation of visual system excitability in Parkinson's disease

Elena Contaldi^{1,2}, A.V. Milner², B. Gori², L. Magistrelli^{1,2}, G. Strigaro², C. Comi¹, R. Cantello²

¹PhD Program in Medical Sciences and Biotechnology, Translational Medicine Department, University of Eastern Piedmont, Novara, Italy

²Clinical Neurology Department, Ospedale Maggiore della Carità, Novara, Italy

Introduction: Paired flash-visual evoked potentials represent a useful tool to explore visual system excitability [1]. Although the motor system is greatly affected in Parkinson's disease (PD), previous studies have demonstrated significant alterations also in the visual pathways [2].

Methods: We enrolled 10 PD patients (4 males, 6 females), aged 67.3 ± 5.6 years, with a mean disease duration of 6.4 ± 1.9 years and mean UPDRS part III score of 14.4 ± 3.5 . Seven patients (70%) were treated with dopamine agonists, and only two reported mild visual hallucinations (20%). Flashes were randomly delivered binocularly in single or in pairs in eye-closed condition: when in pairs, interstimulus intervals (ISIs) were 125, 62.5, 50, 33 and 16.5 ms (respectively 8, 16, 20, 30 and 60 Hz). EEG signals were registered from Oz-Pz; epochs were collected and from their grand-average a single F-VEP was obtained and divided into two epochs: the main complex and the afterdischarge complex (quantified as root mean square values or RMS). For the paired F-VEPs, the test F-VEP was obtained after subtraction of the single F-VEP from the conditioned response. Its size was then calculated as $\text{test/single F-VEP} \times 100$. 13 healthy subjects were age and sex matched to patients.

Results: As for paired F-VEPs, Spearman analysis revealed a significant inverse correlation between disease duration and the RMS values of the afterdischarge complex at 30 Hz ($r = -0.670$; $p = 0.034$) and 20 Hz ($r = -0.631$; $p = 0.05$) ISIs. Moreover, patients showed lower mean RMS values at 20 and 30 Hz ($p = 0.03$). Conversely, there were no differences in the main complex or in the single F-VEP analysis.

Conclusions: Paired F-VEPs showed higher neural inhibition within the visual system of PD patients, mainly in associative areas, as reflected by lower RMS values of the afterdischarge complex. This is the first study highlighting dysfunctional visual connectivity in PD.

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Kinematic features of bradykinesia due to structural lesions of the basal ganglia: a case report

Antonio Cannavacciuolo¹, G. Paparella¹, D. Colella¹, L. Angelini¹, A. De Biase¹, M. Bologna^{1,2},
A. Berardelli^{1,2}

¹Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

²IRCCS Neuromed Institute, Pozzilli (IS), Italy

Introduction: Bradykinesia is the cardinal symptom of Parkinson's disease and other parkinsonian syndromes. However, to date, there are no objective measurement of bradykinesia features in patients with parkinsonism due to structural lesions of the basal ganglia.

Aims: To characterize the kinematic features of bradykinesia in a male patient (83 years old) with hemi-parkinsonism (on the left side) due to a vascular lesion in the contralateral striatum.

Methods: Repetitive finger tapping was kinematically recorded using a motion analysis system. Movement velocity, amplitude, rhythm and decrement (sequence effect) were measured. We compared the data collected in the patient with the normative data previously collected in 80 healthy controls. The various parameters were considered altered if they differed more than two standard deviation (SD) from the corresponding mean value measured in healthy subjects. We also compared the kinematic features in patient OFF and ON levodopa intake.

Results: The results indicate that there was a marked reduction in the movement amplitude and altered rhythm in the patient compared to healthy controls data (both values > 2 SD from the average measured in the control subjects). In the patients, we also found a tendency toward reduced movement speed (both values > 1 SD but > 2 SD from the average measured in the control subjects). Finally, we did not observe a significant decrement (sequence effect) in the patient. The effects of levodopa on the movement parameters were negligible.

Conclusions: Bradykinesia has distinctive features, i.e. reduced amplitude without decrement, in patients with parkinsonism due to basal ganglia lesions. The present findings are relevant when interpreted in the context of the current hypothesis on of bradykinesia pathophysiology.

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Biomarkers of impulse control disorder in firing patterns of parkinsonian subthalamic nucleus

*Silvia Ramat*¹, F. Micheli^{2,3}, M. Vissani^{2,3}, G. Pecchioli¹, F. Terenzi⁴, A. Mazzoni^{2,3}

¹AOU Careggi, Dipartimento Neuromuscoloscheletrico e degli Organi di Senso, Florence, Italy

²The Biorobotics Institute, Scuola Superiore Sant'Anna, Pisa, Italy

³Department of Excellence in Robotics and AI, Scuola Superiore Sant'Anna, Pisa, Italy

⁴Università degli Studi di Firenze, Dipartimento di Neuroscienze, Psicologia, Area del Farmaco e Salute del Bambino, Firenze, Italy

Introduction: Impulse Control Disorders (ICD) are a widespread co-morbidity of Parkinson's disease (PD) severely affecting the quality of life of patients. The Subthalamic Nucleus (STN) is a pivotal element of the cortico-basal ganglia-thalamic network that encompasses both motor and cognitive functions, and is a common target for Deep Brain Stimulation (DBS) PD therapy. So far, the relation between STN activity and ICD in PD is not completely understood, hampering the development of specific therapies.

Objective: We aimed to find possible biomarkers for ICD in PD from single units activity in the STN. A specific biomarker in this region could improve the utility of recordings in this region for online and offline diagnosis and treatments.

Methods: We analyzed the firing pattern of single STN neurons, acquired from exploratory microrecordings during DBS implant surgery with an approach that was already effective in capturing temporal structure in the spike trains during STN DBS implant procedures [1], based on inter-spike interval distribution.

Results: Temporal structure of firing patterns of subthalamic neurons, is significantly different in PD patient with and without ICD. ICD PD patients, indeed, present spontaneous firing activity far from the poissonian regime, as indicated by the shape factor of the Inter-spike Interval distribution. Poissonian firing is instead the dominant regime in non-ICD PD patients. No such difference between ICD and non-ICD PD patients is detectable in the average firing rate.

Conclusions: These results corroborates the hypothesis that PD-related ICD is associated to altered patterns of firing in STN. The shape factor is then a candidate biomarker for the assessment of ICD in PD patients, paving the way for the development of specific treatments.

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Clinical and kinematic features of valproate-induced tremor compared to essential and dystonic tremor

Luca Angelini¹, A. De Biase¹, A. Cannavacciuolo¹, G. Paparella², D. Colella¹, C. Di Bonaventura¹, A.T. Giallonardo¹, M. Bologna^{1,2}, A. Berardelli^{1,2}

¹Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

²Neuromed Institute IRCCS, Pozzilli (IS), Italy

Introduction: Tremor is frequently observed in patients with epilepsy treated with valproate. However, no studies have objectively assessed the features of valproate-induced tremor (VIT) by kinematic analysis in the upper limbs and other body segments. Moreover, it is still unclear if VIT features differ from those observed in patients with essential tremor (ET) and dystonic tremor (DT).

Objective: In the present study, we aimed to investigate the main features of VIT by clinical examination and kinematic analysis. The data in patients with VIT were compared with those collected in patients with ET and DT.

Methods: We enrolled 16 patients with VIT, 17 patients with ET and 15 patients with dystonia and tremor of head and upper limbs. Tremor severity was assessed by means of the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS). Patients also underwent a kinematic recording of rest, postural and kinetic tremor of upper limbs and head, by means of a motion analysis system.

Results: The clinical evaluation overall showed higher FTMTRS scores in VIT than in ET and DT, including objective and subjective items of assessment. Kinetic, but not postural, tremor of the upper limbs was more severe in VIT and ET than in DT ($P < 0.01$). Again, concerning the upper limbs, rest tremor was more prevalent in patients with VIT than in patients with ET and DT ($P < 0.01$). Conversely, head tremor was higher in DT than in VIT and ET ($P < 0.01$). Correlation analysis showed no significant relationship between clinical data (i.e. valproate serum concentration, epilepsy duration etc.) and neurophysiological measures of tremor.

Conclusions: VIT is characterised by more severe and specific clinical and kinematic features compared to ET and DT. The results have implications for better understand tremor pathophysiology in different disease entities. Together with clinical examination, kinematic assessment of tremor may help clinicians in the diagnostic process.

P100

Safinamide is not harmful for the human retina: an electrophysiological study

*Fabio Bandini*¹, G. Di Bon¹, L. Vestito²

¹Department of Neurology, S. Paolo Hospital, Savona, Italy

² Phoniatic Unit, IRCCS San Martino IST, Genova, Italy

Background: Safinamide is a selective and reversible MAO-B inhibitor, indicated for the treatment of Parkinson's disease as an add-on therapy to L-dopa, at a dose of 50 and 100 mg once a day. Caution is suggested in the use of Safinamide due to the potential damage to the retina. Actually, the European patient information leaflet says: "Potential for retinal degeneration in patients with presence/prior history of retinal disease: Safinamide should not be administered to patients with ophthalmological history that would put them at increased risk for potential retinal effects (e.g., albino patients, family history of hereditary retinal disease, retinitis pigmentosa, any active retinopathy, or uveitis)". Surprisingly, however, the available literature misses any scientific data concerning these potential detrimental effects of Safinamide on the human retina. This prompted us to implement a neurophysiological study aimed at testing this possible drug-related retinal toxicity.

Methods: Twenty patients (11 men and 9 women, average age 62 years) with PD were consecutively recruited by the Movement Disorder Outpatient Clinic of the Department of Neurology of the S. Paolo Hospital of Savona, between June 2016 and June 2017, after signature of the informed consent. All patients had corrected visual acuity above 7/10. Patients with a history of ophthalmological diseases were excluded from the study. The average duration of the illness was 30.2 months. Safinamide was administered at an initial dose of 50 mg/day, then increased to 100 mg/day after 15 days. The *de novo* inclusion of any other drug with potential neurological or ophthalmological effect was not allowed. All subjects underwent visual acuity measurement and a neurophysiological study of visual function, which included full field ERG, multifocal ERG (mfERG), pattern ERG (PERG) and pattern VEP. The neurophysiological and clinical (UPDRS) evaluations were invariably carried out at the same time (10-10.30 a.m.) at the baseline (T0), after 30 days (T1), at the sixth month (T2) and at the twelfth month (T2).

Results: PD patients showed, as expected, a significant delay of the mean latency values of PERG and VEP, while ERG and mfERG results were within the normal limits. Over the entire study period, however, the neurophysiological measures (ERG, mfERG, PERG, PEV) did not show any significant changes. No patient experienced visual disturbances and visual acuity remained stable in all patients. From a motor point of view, the mean UPDR scores improved significantly ($p < 0.01$).

Discussion: The current results provide evidence that Safinamide is not harmful for the human retina, both for diffuse (full field ERG) and focal (mfERG, PERG) functional damage, even over a long period of time (one year). The optic nerve (VEP) was not involved as well. Due to the relatively small sample tested, however, the absence of drug-related functional retinal toxicity should be confirmed in larger cohort studies.

P101

Differential diagnosis between functional facial spasm and hemifacial spasm: role of blink reflex

Valentina Oppo^{1,2}, G. Cossu^{1,2}, J. Cabras², L. Daga², V. Fois², F. Matta², M. Edwards³, F. Morgante³

¹SC Neurologia e Stroke Unit, AO Brotzu, Cagliari, Italy

²SSD Neurofisiologia e Disturbi del Movimento, AO Brotzu, Cagliari, Italy

³Neurosciences Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK

Objective: This study aimed to determine the value of Blink Reflex (BR) as an electrophysiological tool in differentiating functional facial spasm (F-FS) from hemifacial spasm (HFS).

Background: Diagnosis of functional movement disorders (FMD) relies upon demonstrating specific positive clinical signs and is supported by electrophysiological testing for functional tremor and jerks. The diagnostic electrophysiological feature of HFS is spread of BR responses to lower facial muscles after stimulation of supraorbital nerve, resembling the R1 response. This is likely an ephaptic activation of facial nerve fibers.

Methods: BR was performed in 3 patient groups: 15 HSF; 8 clinically definite F-FS; 15 healthy controls (HC). BR was obtained by bilateral stimulation of supraorbital nerve and recording with 4 surface electrodes from orbicularis oculi (OOculi) and orbicularis oris (OOris) bilaterally. We verified how many subjects, after stimulation of supraorbital nerve of the affected side, displayed an early R1-like response in ipsilateral OOris, in addition to the physiological ipsilateral OOculi R1 response.

Results: In all (15/15) HFS, stimulation of ipsilateral supraorbital nerve, triggered activation of a consistent and constant early response in ipsilateral, or even bilateral, OOris, with a latency similar to physiological R1. This synkinetic activation of OOris was absent in all HC (0/15) and F-FS (0/8).

Conclusions: FMD involving face (F-FS) are often asymmetric, resembling HFS, from which they can be differentiated through few distinctive clinical features, like inverted Babinski-2 sign and resistance of eyelid to passive opening. Yet, none of these clinical signs have been never validated. Our study demonstrated that lack of R1-like response in lower facial muscles has a high predicting value for the differential diagnosis between F-FS and HFS. This findings support the role of electrophysiology and specifically BR as a tool for the positive diagnosis of FMD.

P102

A physical therapy programme for functional motor symptoms: a telemedicine pilot study

Benedetta Demartini^{1,2,3}, F. Bombieri⁴, D. Goeta^{1,2}, O. Gambini^{1,2,3}, L. Ricciardi^{5*}, M. Tinazzi^{4*}

¹Dipartimento di Scienze della Salute, Università degli Studi di Milano, Milano, Italy

²Unità di Psichiatria II, A.O. San Paolo, ASST Santi Paolo e Carlo, Milano, Italy

³Aldo Ravelli Research Center for Neurotechnology and Experimental Brain Therapeutics, University of Milan, Milano, Italy

⁴Dipartimento di Neuroscienze, Biomedicina e Movimento, Università di Verona, Verona, Italy

⁵Neurosciences Research Centre, Molecular and Clinical Sciences Institute, St George's University of London, UK

**These authors share senior authorship*

Introduction: For a proportion of patients with functional motor symptoms (FMS), specific physiotherapy has recently emerged as a promising treatment. Aim of the present study was to assess the efficacy of a physical therapy-based telemedicine programme in a sample of patients affected by FMS on the motor symptoms themselves and on some psychological variables such as quality of life, alexithymia, anxiety and depression.

Materials and Methods: Eighteen patients were recruited. The programme consisted of 24 sessions: three face-to-face sessions (at week 0 (T0), week 12 (T1) and week 24 (T2)) and 21 tele sessions. Each session included education, movement retraining exercises and development of a management plan. All patients underwent the following assessment at T0, T1 and T2: PMDRS, assessment of depression, anxiety, alexithymia and quality of life. Self-assessment of outcome (CGI) was recorded at T1 and T2.

Results: On the CGI improvement was reported by 66,7 % of patients at T1 and 77,8 % at T2. A significant improvement over the three time points was shown for PMDRS and for the following domains of the SF-36: general health, vitality, social functioning and mental health.

Conclusions: The use of two innovative approaches for FMS (physiotherapy and telemedicine), combined together, might have a valuable role in the treatment of this neuropsychiatric condition.

P103

Emotional state modulates gait initiation in individuals with Parkinson's disease differently from healthy subjects

Tiziana Lencioni^{1,2}, T. Bowman¹, A. Marzegan¹, A. Castagna¹, C. Cosentino², L. Avanzino^{3,4}, M. Meloni¹, M. Ferrarin¹, E. Pelosin^{2,4}

¹IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy

²Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, University of Genoa, Genoa, Italy

³Department of Experimental Medicine, Section of Human Physiology, University of Genoa, Genoa, Italy

⁴IRCCS Policlinico San Martino, Genoa, Italy

Introduction: Gait initiation combines motor and cognitive components of movement preparation (referred to as Anticipatory Postural Adjustments) and movement execution. APAs have been studied extensively in Parkinson's disease (PD), however the origin of their alterations in PD is still under debate. Recently, it has been hypothesized that limbic pathways (i.e. emotions) could play an important role in implementing this motor program [1,2].

Objective: To investigate the influence of auditory-emotional stimuli on gait initiation characteristics in people with PD.

Methods: Eight subjects with PD (72.3±8.8 yrs, Hoehn&Yahr 2-3) and ten elders (ELD, 67.7±3.3 yrs) stood on a dynamometric platform and were asked to initiate gait in response to neutral, pleasant and unpleasant auditory stimuli. The experiment took place during the "on" state (1 hour after taking their antiparkinsonian medications). APAs (imbalance/unloading phases calculated as Center of Pressure (COP) antero-posterior (AP)/medio-lateral (ML) displacement normalized to foot-length/intramalleolus-distance, respectively [3]) were calculated. Parameters were analyzed with a repeated measures ANOVA (Group: PD/ELD, Stimuli: Neutral(N)/Pleasant(P)/Unpleasant(U)). P values<0.05 were considered statistically significant, while values ranging from 0.05 to 0.1 as a strong trend.

Results: The main finding was on ML unloading phase. ANOVA revealed a significant effect of the main factors Group (p<0.001, normalized-COP trace [%] mean (95%): PD -0.39(-0.43/-0.34), ELD -0.50 (-0.54/-0.46)) and Stimuli (p=0.02). In addition, interaction effect (p=0.07, GroupXStimuli) highlighted that ELD had the same unloading phase with all stimuli, while PD modulated the ML-COP displacement according to emotional category, mostly in P condition (p=0.001 PvsN, p=0.01 PvsU, N -0.40(-0.44/-0.35), P -0.37(-0.41/-0.32), U -0.39(-0.43/-0.35)).

Conclusions: The different shortening of ML-COP displacement during the unloading phase according to the category of emotional stimuli suggests that in people with PD emotions modulate not only the high level of the motor planning (imbalance phase) as evidenced previously [1] but also the lower levels (unloading phase).

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New perspectives in Parkinson's disease rehabilitation

*Giovanni Pietro Salvi*¹, A. Quarenghi¹, E. Sigismondi¹, E. Mion², M. Simonini¹, S. Mazzoleni³

¹U.O. Riabilitazione Neuromotoria, Istituto Clinico Quarenghi, San Pellegrino Terme, Italy

²Scuola di Specializzazione in Medicina Fisica e Riabilitativa, Università di Pavia, Pavia, Italy

³Istituto di BioRobotica, Scuola Superiore Sant'Anna, Pisa, Italy



P105

Efficacy of cognitive rehabilitation in gait disturbances in Parkinson's disease: a narrative review

Edoardo Bianchini¹, M. Virgilio¹, F. Barcherini¹, M. Alborghetti¹, L. De Carolis¹, M. Giovannelli¹, F.E. Pontieri^{1,2}

¹Dipartimento NESMOS, Sapienza Università di Roma, Roma, Italy

²Fondazione Santa Lucia, IRCCS, Roma, Italy

Introduction: In recent years, interest has been growing on non-motor symptoms (NMS) of Parkinson's disease (PD) as well as on the relationships between motor and non-motor impairment in the disease. Cognitive impairment is rather common in PD, mainly with the features of executive dysfunction (ED). ED has been also associated with gait disturbances as demonstrated by the worsening of gait parameters during dual-task. Therefore there's a growing body of literature investigating the effect of cognitive training (CT) on gait disturbances in PD patients.

Objective: The aim of this review is to evaluate the evidence on the effect of CT on gait disturbances in PD patients.

Materials and Methods: Search terms included "Parkinson's disease" AND "rehabilitation OR training OR therapy" AND "gait" AND "cognitive" [Mesh Terms]. All RCTs between February 1989 and January 2020 referring to CT in PD patients with gait disturbances were included. Search strategy was performed on 4 separate databases: Pubmed, Scopus, PEDro, OTseeker. No language restriction was imposed. Two investigators independently evaluated titles and abstracts. Quality assessment was performed using the Cochrane Collaboration's tool for assessing the Risk of Bias and by extracting the PEDro scores.

Results: The database search returned 14 articles meeting the inclusion criteria and focusing on CT alone, motor-cognitive intervention, protocols implementing virtual reality and dual-task training. Given the heterogeneity in interventions and outcome measures, it was not possible to perform a meta-analysis.

Conclusions: The majority of included studies showed a small-to-medium sample size. On the basis of a qualitative analysis, it is possible to state that rehabilitation protocols including cognitive training may improve gait disturbances in PD patients. Nevertheless the heterogeneity in outcome measures and the lack of standardization in the evaluation of the impact on gait parameters is a current issue and further work is needed to address it.

P106

Effectiveness of an intensive inpatient multidisciplinary rehabilitation program in Parkinson's disease in mild-moderate to severe stages: a non-pharmacological, retrospective, observational

F.L. Saibene¹, S. Di Tella¹, M. Di Cesare¹, F. Borgnis¹, R. Nemni^{1,2}, F. Baglio¹, Mario Meloni¹

¹IRCCS Fondazione Don Carlo Gnocchi-ONLUS, Milan, Italy

²Università degli Studi di Milano, Milan, Italy

Introduction: In recent years, several studies found that the neurorehabilitation therapy is an effective treatment in addition to optimal pharmacological management in persons with Parkinson's disease (PwPD) [1-2].

Objective: The aim of this study was to explore the effects of an intensive, inpatient, multidisciplinary and person-tailored rehabilitative program in PwPD.

Methods: This is a retrospective, non-pharmacological, observational study which included 24 PwPD in Mild-Moderate to Severe stages [age (mean, SD) =76.25ys±9.42; M/F=10/14; H&Y (median; IQR) =4.00;1.75] [3]. Motor, cognitive, functional, neuropsychiatric aspects were collected in admission (T0) and in discharge (T1). Type, dose/number of sessions about pharmacological and non-pharmacological treatments were filled in a database created ad hoc. PwPD were involved in a comprehensive, tailored to individual's needs, inpatient multidisciplinary rehabilitation program combining cognitive, physical, occupational and speech therapy, 5 to 7 days per week. According to MDS-UPDRS-III cut-off PwPD were classified in Mild-Moderate (M-Ms) or Severe (Ss) stages (M-Ms≤ 59; Ss>59) [4]; in addition to the total score, 7 Factor Scores were calculated [5]. Paired Samples T-Test, Wilcoxon Test, χ^2 Test were performed to evaluate differences between T1vs.T0. Spearman's correlations (rs) were computed between Δ T1-T0 and the 7 MDS-UPDRS-III Factors at T0.

Results: 87.50% of our sample reported significant reduction of functional disability at Barthel Index (BI) (p<0.001). Significant differences were also found for the Scale of Pain (p<0.001) and for the Norton Scale (p<0.001). A significant improvement in Token Test (p=0.020), Rey's Figure-Copy (p=0.001) and Raven's Coloured Progressive Matrices (p=0.005) were observed. Δ BI was positively associated with the scores in Right (p=0.028) and Left Upper Bradykinesia scores (p=0.012) of MDS-UPDRS-III.

Conclusions: Our findings suggest that an intensive, inpatient, multidisciplinary rehabilitation program for PwPD leads to significant improvements albeit in Mild-Moderate to Severe phases of Parkinson's disease.

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Cerebellar transcranial direct current stimulation (tDCS) combined with physical rehabilitation in progressive supranuclear palsy: a double blind randomized sham controlled study

Andrea Pilotto^{1,2}, M.C. Rizzetti², A. Lombardi¹, C. Hansen³, R. Serughetti², D. Locatelli², B. Cavaletti², A. Pedrini², W. Maetzler³, B. Borroni¹, A. Padovani¹

¹Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

²FERB Onlus, Ospedale S. Isidoro, Trescore Balneario, Bergamo, Italy

³Department of Neurology, Christian-Albrechts-University of Kiel, Kiel, Germany

Introduction: There are no medical effective treatments for progressive supranuclear palsy (PSP). Physical rehabilitation (PR) has a potential but still limited effect on postural instability and motor function in PSP patients. Several studies showed a positive effect of active transcranial cerebellar anodal Direct Current Stimulation (tDCS) in patients with postural instability.

Objective: To investigate the effects of active cerebellar anodal tDCS combined with physical rehabilitation on postural instability and motor function in PSP patients.

Methods: Sixteen patients with PSP were assigned to either active cerebellar tDCS plus physical rehabilitation (PR) or sham tDCS plus PR groups. Each patient underwent two weeks of PR and daily application of tDCS for 20 minutes. Each patient was evaluated at baseline and after treatment with an extensive clinical and functional assessment including PSP rating scale (PSP-RS), Berg Balance test (BBS), timed up and go test (TUG) and Six Minutes Walking Test (6MWT).

Results: There was a significant interaction between treatment and time on PSP-RS, BBS and 6MWT. Patients on active tDCS showed significantly higher improvement on total PSP-RS ($p=0.003$), a trend for higher improvement on BBS score ($p=0.06$) and no differences in TUG or 6MWT compared to PSP patients with sham stimulation.

Conclusions: We concluded that physical rehabilitation along with active cerebellar tDCS is a useful combined approach for postural instability and motor symptoms in PSP patients.

P108

Magnetic resonance-guided focused ultrasound thalamotomy in essential tremor: two-year clinical experience from a single center

Stefano Tamburin^{1,2}, G.K. Ricciardi¹, T. Bovi¹, M. Longhi¹, G. Bulgarelli¹, R. Feroni¹, A. Nicolato¹, B. Bonetti¹, M. Tinazzi^{1,2}, E. Ciceri¹, S. Montemezzi¹

¹Verona University Hospital (Azienda Ospedaliera Universitaria Integrata Verona), Verona, Italy

²Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy



P109

Botulinum Toxin for Pisa syndrome: how and when

Carlo Alberto Artusi¹, F. Marchet¹, U. Dimanico², M. Zibetti¹, C. Zanella², G. Massazza², L. Lopiano¹

¹Department of Neuroscience Rita Levi Montalcini, University of Torino, Torino, Italy

²Physical Medicine and Rehabilitation Unit, Department of Orthopedics, Traumatology and Rehabilitation, University of Torino, Torino, Italy

Introduction: Pisa syndrome (PS) is a frequent Parkinson's disease (PD) complication defined as a $\geq 10^\circ$ lateral trunk flexion reverted by lying position or passive mobilization. Few studies proved the efficacy of Botulinum toxin (BoNT) in PS but candidates and timing for treatment are undetermined.

Objective: To compare the 1-month efficacy of BoNT between patients with PS $\geq 10^\circ$ (PS+) and patients with PS not reaching the 10° threshold (pre-PS), and evaluate the BoNT effect wearing-off after 4 months.

Methods: Ten PS+ (mean angle $18.6 \pm 7.3^\circ$) and 8 pre-PS ($5.5 \pm 3.2^\circ$) patients were prospectively assessed. Ultrasound- and electromyography-guided BoNT injections were delivered in longissimus-thoracis (50U) and iliocostalis-lumborum (50U) at the flexion side (T0). The primary endpoint was the percentage of patients improving the lateral trunk flexion angle $>20\%$ (responders) 1 month after BoNT (T1). Secondary endpoints were: improvement of PS-associated pain, as per the visual-analogue scale (VAS), and residual effect of BoNT after 4 months (T2).

Results: At T1 we found a higher, not significant, number of responders in PS+ group, with 60% PS+ responders (n=6/10) vs. 33.3% pre-PS (n=3/9) (p:0.37). The mean flexion improvement among responders was 43% in PS+ ($7.9 \pm 3.8^\circ$), and 72% in pre-PS ($1.9 \pm 0.9^\circ$). VAS score improved by 54% in PS+ (from 4.4 ± 2.8 to 2.1 ± 2) and 85% in pre-PS (from 5.5 ± 2 to 3 ± 4.6).

Eight patients received follow-up at T2 (5 PS+ and 2 pre-PS). Three of them were responders and showed a surprising further improvement at T2 (T0: 18.3 ± 10.9 , T1: 11.1 ± 7.1 , T2: 4.3 ± 4.5). Globally, at T2 the mean flexion showed a 12.4% improvement than baseline ($3.8 \pm 10.9^\circ$; T0: 17.0 ± 10.0 , T1: 17.1 ± 12.1 , T2: 13.1 ± 12.0), and pain showed a 6.9% improvement than baseline (0.8 ± 3.4 ; T0: 5.3 ± 2.5 , T1: 3.0 ± 3.7 , T2: 4.3 ± 3.5).

Conclusions: BoNT is effective for PS with a possible long-lasting efficacy. Pre-PS patients may also benefit from BoNT, especially for the associated back pain.

P110

Diplopia in Parkinson's Disease, a possible role of dopaminergic treatment

Elisabetta Belli, E. Del Prete, D. Frosini, E. Unti, U. Bonuccelli, R. Ceravolo

Department of Clinical and Experimental Medicine, Unit of Neurology, University of Pisa, Pisa, Italy

Background: Diplopia could be present in 10-30% of Parkinson's disease (PD) patients. Its pathophysiology is discussed; associations with dementia and visual hallucinations have been proposed. Diplopia is also reported as a non-common side effect of dopamine-agonist (DA).

Objective: Aim of our study was to explore the role of dopaminergic treatment in PD patients with diplopia.

Method: PD non-demented patients with diplopia were retrospectively recruited and matched with PD patients without diplopia for age and disease duration. Motor and cognitive assessment, respectively through MDS Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) and Mini Mental State Examination (MMSE), were evaluated at diplopia onset (T0) in all patients and after 1 year (T1) in a subgroup. In diplopic patients, DA was reduced or withdrawn. For each patient we evaluated Daily Levo-Dopa Dose Equivalent Total (LEDD-T) and for DA (LEDD-DA). Presence of other side effects of DA was assessed.

Results: Forty-eight PD were recruited, 24 with diplopia and 24 without (age $58,8 \pm 11,5$ vs $58,7 \pm 12,0$ years, disease duration $13,4 \pm 8,3$ vs $13,9 \pm 7,5$ years respectively), all diplopic patients and 17 of non diplopic patients were assuming DAs. LEDD-DA was significantly higher in diplopic patients than in those without diplopia ($p=0.008$); mean disease duration before diplopia onset was $10,6 \pm 7,6$ years. The two groups did not show differences in the prevalence of hallucinations, somnolence and impulsive control disorder evaluated over the years. No significant differences were found in MDS-UPDRS-III and MMSE at T0 (24 diplopic and 24 non diplopic patients) and T1 (18 diplopic and 13 non diplopic patients). At T1 twelve patients reported reduction or disappearance of diplopia.

Conclusions: Dopaminergic treatment, in particular DA, seems to have a role in the pathogenesis of diplopia in non-demented PD patients; however longer follow up is needed to validate the PD psychosis spectrum hypothesis for this symptom.

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Compliance to levodopa-carbidopa intestinal gel: a possible, underestimated gender effect?

Matteo Conti¹, R. Cerroni¹, S. Scalise¹, M. Pierantozzi¹, N.B. Mercuri^{1,2}, A. Pisani^{1,2}, A. Stefani¹

¹Parkinson Centre, Department of System Medicine, University of Rome Tor Vergata, Rome, Italy

²IRCCS Fondazione Santa Lucia, European Centre for Brain Research, Rome, Italy

Introduction: Several studies investigated causes and incidence of LCIG discontinuation, without clear evidence of sex prevalence [1-2]. In a retrospective Swedish analysis, a small but significant increased prevalence in discontinuation was found in female population [3].

Objective: To evaluate how gender influences LCIG discontinuation in our cohort of patients.

Methods: We describe our 7 years' experience about LCIG compliance, presenting our patients series, with standard follow-up protocol, consisting of quarterly visits including clinical evaluation, psychological interview and PD-specific assessment scales.

Results: Since 2013 41 patients admitted to our Parkinson's Centre have been implanted and 35 reached 36 months follow-up. Of these 35 patients seven male patients (20%) and one female patients (2.8%) discontinued LCIG therapy and two died (1M, 1F), with a global dropout rate (22.8%) similar to those reported in the literature [1-2]. Of those seven male dropouts, two discontinued treatment because of PEG-J-related problems and one due to the occurrence of severe polyneuropathy. The single female patient also discontinued LCIG-therapy because of PEG-J-related problems. The remaining four male patients discontinued the infusion although LCIG therapy's efficacy, because of dyskinesic phenomena (n=1), dopamine dysregulation syndrome (DDS) (n=2) and impulse control disorder (ICD) (n=1), not previously emerged despite standard follow up, without significant increase in LEED. Starting conditions in males and females were the same and no risk factors for interruption had previously identified.

Conclusions: The better tolerability found in our female patients might be due to psycho-behavioural characteristics defined by gender that transcend the aspect of mere sexual differentiation between men and women. LCIG compliance might be influenced by individual vulnerability to LCIG-therapy dependent on psycho-behavioural characteristics, social and cultural influences defined by gender. Our data could express a different trend in Central-South Italy with respect to other geographical areas.

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Safinamide effect on bladder disturbances in Parkinson's disease patients

*Livia Brusa*¹, M. Canesi², R. Cerroni³, C. Iani¹, E. Finazzi-Agrò⁴, A. Stefani³

¹UOC Neurologia, Ospedale S. Eugenio, Roma, Italy

²Dip. Riabilitazione, Ospedale Moriggia-Pelascini, Gravedona, Italy

³Clinica Neurologica Università di Roma Tor Vergata, Roma, Italy

⁴Clinica Urologica, Università di Roma Tor Vergata, Roma, Italy

Introduction: It is well known that urinary disturbances such as urinary urgency, increased urinary frequency or urinary incontinence are present in two thirds of parkinsonian patients as result of a detrusor overactivity. Dopamine plays a central role in central bladder control [1-2].

Aim: Aim of our study was to evaluate safinamide (known to increase the amount of dopamine availability at synaptic level) effect on lower urinary tract (LUT) behavior in a group of PD patients complaining of mild urologic disturbances.

Methods: Fifteen patients affected by PD were enrolled. All of the subjects were evaluated with IPSS questionnaire (International Prostate Symptoms Score questionnaire) and UPDRS section III executed under the usual antiparkinsonian treatment. Following the first evaluating section, subjects added on their usual dopaminergic therapy a morning dose of safinamide (50 mg) for the sequent two months and at the end of this period all were re-evaluated in a second section of evaluation (IPSS and UPDRS section III), executed in the morning.

Results: Statistical analysis showed significant improvement on both IPSS and UPDRS section III following two-months of safinamide.

Conclusions: This results support previous evidence of pathophysiological involvement of dopaminergic transmission on bladder dysfunction in PD.

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P113

Levodopa carbidopa intestinal gel as a successful therapeutic option after deep brain stimulation removal

*Alessio Novelli*¹, F. Terenzi¹, L. Talamucci², S. Ramat³

¹Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Florence, Italy

²Advanced Interventional Endoscopy Unit, Careggi University Hospital, Florence, Italy

³Neurology Unit, Careggi University Hospital, Florence, Italy



P114

Safety and efficacy of opicapone and switching from entacapone in advanced Parkinson's disease

Francesca Valentino^{1,2}, S. Regalbuto³, B. Minafra², M. Todisco², R. Zangaglia², C. Pacchetti²

¹IRCCS Fondazione Mondino, U.O. Neurologia d'Urgenza, Pavia, Italy

²IRCCS Fondazione Mondino, S.C. Malattia di Parkinson e Disordini del Movimento, Pavia, Italy

³Università di Pavia, Pavia, Italy



P115

A pilot study on the efficacy, tolerability and safety of safinamide in elderly Parkinson's disease patients

Domiziana Rinaldi¹, M. Sforza¹, E. Bianchini¹, S. Galli¹, M. Giovannelli¹, F.E. Pontieri^{1,2}

¹Dipartimento di Neuroscienze, Salute Mentale e Organi di Senso (NESMOS), Sapienza Università di Roma, Rome, Italy

²Dipartimento di Neurologia Clinica e Comportamentale, IRCCS Fondazione Santa Lucia, Rome, Italy

Introduction: Safinamide (SF) is a reversible MAO-B-inhibitor, with therapeutic indication as add-on to levodopa in fluctuating Parkinson's disease patients. The majority of subjects enrolled in registrative studies with SF were aged <70 years. Consequently, data on the efficacy, safety and tolerability of SF in elderly patients are rather poor.

Objective: The aim of the study is to evaluate the safety and tolerability of SF (50 and 100 mg / day) in elderly patients (> 75 years) with motor and non-motor fluctuations, compared to patients aged 65-75 years.

Methods: Twenty-eight PD patients aged 65-75 years, and 23 patients aged >75 were enrolled consecutively at our PD unit. Fluctuations were identified by means of a ≥ 3 score at the WOQ-19, and SF was started the day next to the visit. Daily SF dose was 50 mg (n=26) or 100 mg (n=25). We excluded patients with dementia, history of hallucinations in the past six months, disabling dyskinesia, disabling orthostatic hypotension and poor compliance.

Results: At 6-months follow-up, the majority of subjects displayed efficacy on fluctuations, with no significant difference between groups. Moreover, adverse events were rated as mild and were similarly infrequent in both groups. Eventually, there were no significant differences in terms of safety between the 50 and 100 mg daily SF doses.

Conclusions: This is the first study investigating the efficacy, safety and tolerability of SF in PD patients aged >75 years. Our results indicate that the drug maintains clinical efficacy and is safe and tolerable in elderly PD subjects.

P116

A pilot study on the shift from rasagiline to safinamide in fluctuating PD patients

*Michela Sforza*¹, D. Rinaldi¹, E. Bianchini¹, M. Alborghetti¹, M. Giovannelli¹, F.E. Pontieri^{1,2}

¹Dip. NESMOS, Sapienza Università di Roma, AOU Sant'Andrea, Roma, Italy

²Fondazione Santa Lucia, IRCCS, Roma, Italy

Introduction: Monoamino-oxidase-B inhibitors (MAO-B-i) showed efficacy as add-on to levodopa in fluctuating PD patients. All MAO-B-i potentiate dopaminergic transmission. Safinamide (SF), however, showed also anti-glutamatergic activity, particularly at the dose of 100 mg/day. This latter feature may, indeed, be useful for further controlling motor and non-motor complications of PD.

Objectives: Here we investigated the consequences of the shift from rasagiline (RS) to SF in fluctuating PD patients. To this end, we selected patients from our cohort who developed side-effects to RS or showed worsening of symptoms and development or re-occurrence of fluctuations while on add-on therapy with RS.

Materials and Methods: Twenty-seven patients were shifted from RS to SF (50 or 100 mg/day) in the last 18 months. Reasons for switching were side-effects to RS (n=2), development of fluctuations (n=8), re-occurrence of fluctuations while on therapy with RS (n=17). Fluctuations were investigated and measured by the WOQ-19, other assessments included the MDS-UPDRS-III scale and the NMS scale.

Results: Patients switched because of side-effects or development of fluctuations while on RS therapy displayed amelioration after SF. As to patients showing re-occurrence of fluctuations while on RS, 12/17 showed significant improvement after switching to SF. Overall analysis of the effects on fluctuations showed a significant benefit ($p > 0.01$) on fluctuations by the switch from RS to SF.

Conclusions: Findings from the pilot study suggest that symptoms of WO non adequately controlled by add-on with RS may benefit from switch to SF.

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The effects of opicapone on motor and non-motor fluctuations in Parkinson's disease: an open-label study

Maria Claudia Russillo, M. Picillo, M.T. Pellecchia, G. Volpe, P. Barone, R. Erro

Department of Medicine, Surgery and Dentistry Scuola Medica Salernitana, Neuroscience Section, University of Salerno, Salerno, Italy

Introduction: Opicapone is a third-generation Catechol O-methyltransferase inhibitor that has been proven to reduce OFF time and to increase ON time without troublesome dyskinesia in Parkinson's disease (PD) patients with motor fluctuations [1]. However, the effects of opicapone on non-motor fluctuations (NMF) have not been yet explored.

Objective: To assess whether opicapone might improve NMF in PD.

Methods: We recruited 28 consecutive PD patients with motor and NMF. We administered the MDS-UPDRS part II, III and IV, and the wearing-off questionnaire (WOQ-19) at baseline and after one month of treatment with 50-mg opicapone. We further gathered the number of levodopa daily doses and calculated the levodopa equivalent daily dose (LEDD). The Paired Difference Test was used to assess pre/post treatment differences.

Results: Out of the 28 patients initially enrolled, 24 completed the study, while 4 discontinued the drug due to adverse events (namely, psychomotor agitation and worsening of dyskinesias). We found an improvement of motor symptoms, as shown by the reduction of total score of MDS-UPDRS part II ($p<0.01$), part III ($p=0.01$) and part IV ($p=0.01$). A significant reduction was observed for the WOQ-19 total score ($p<0.01$). Beyond the items evaluating motor performances, this was driven by an improvement of the items assessing pain ($p=0.02$) and thermoregulation ($p=0.04$). Conversely, the items evaluating mood and concentration were not found to be significantly changed ($p>0.05$). Lastly, we found a significant reduction of LEDD ($p=0.01$), whereas the number of Levodopa daily doses was not significantly modified at follow-up.

Conclusions: We confirm the efficacy of opicapone in ameliorating motor fluctuations in PD [2-3]. Moreover, we found that opicapone further led to a significant improvement of NMF. These preliminary findings need to be confirmed in larger controlled-studies.

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P118

A careful protocol in handling PD patients enrolled for MgFUS targeting VIM

*Alessandro Stefani*¹, R. Cerroni¹, M. Conti¹, P. Sucapane², D. Cerone², C. Marini^{2,3}

¹Parkinson Centre, Department of System Medicine, University of Rome Tor Vergata, Rome, Italy

²Neurology Unit, San Salvatore Hospital, ASL 1, L'Aquila, Italy

³Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy



P119

Safinamide improves restless leg syndrome in patients with Parkinson's disease: case report

Sara Varanese, M. Cipulli, S. Viola, M.P. Buongarzone, L. Fiorelli, P. Litterio

ASL Lanciano-Vasto-Chieti, Ospedale Civile San Pio Vasto, UOC Neurologia, Vasto (CH), Italy

Introduction: Restless legs syndrome (RLS) is a condition that causes an uncontrollable urge to move legs, and less commonly arms, due uncomfortable sensations. Some studies have shown that people with Parkinson's disease (PD) are more likely to have restless legs syndrome than people without PD.

Aims: To report the effect of safinamide on RLS in three patients affected by PD.

Methods: This report involves 2 males and 1 female PD patients, who develop RLS over the course of the disease without other symptoms or signs of motor deterioration. Peripheral neuropathy, kidney failure, iron deficiency and spinal cord conditions were excluded in all the patients. Safinamide was well tolerated in all patients.

Results: Patient 1 is a 73 year-old man with a 7 years history of PD, treated with opicapone 50 mg and l-dopa 500 mg/day. When RLS started his MDS-UPDRS III was 16 and he did not present motor fluctuations. Safinamide 50 mg was started as patient developed ICD with ramipexole at PD onset. RLS completely disappeared after few days of safinamide treatment never reoccurred to date (5 months follow up). Patient 2 is a 66 year-old woman with a 2 years history of PD. At the time of onset of RLS she was treated with l-dopa 600 mg/day, ropinirole 4 mg/day and safinamide 50 mg/day, her MDS-UPDRS III was stable on 28, with wearing off at 4 hour but no other motor fluctuations. Safinamide was increased up to 100 mg/day, and by the following day patient referred amelioration of RLS which disappeared in about one week and never reoccurred in the last six months.

Patient 3 is a 84 year old man with a 3 years history of bradykinesia. He was brought to our attention after almost one year from the onset of severe RLS causing marked impairment in life quality. Safinamide 50 mg was started with improvement of RLS by the very first days of treatment, with the patients being free from symptoms for the last two months.

Conclusions: Safinamide was effective in treating RLS complicating PD in these three patients and may warrant further and more extensive investigation.

P120

Genetic heterogeneity and outcomes in PD patients treated with levodopa-carbidopa intestinal infusion

*Roberta Balestrino*¹, T. Martone¹, M. Toffoli², M. Fabbri¹, M. Zibetti¹, S. Goldwurm¹, A.H.V. Schapira², L. Lopiano¹

¹Department of Neuroscience, University of Turin, Turin, Italy

²Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK

Introduction: Parkinson disease (PD) is the most common neurodegenerative movement disorder. In the advanced phases of the disease, levodopa-carbidopa intestinal gel infusion (LCIG) represents one of the available therapeutic options for patients with fluctuating symptoms unresponsive to conventional oral treatment [1]. Current evidence suggests that genetic background may influence the natural progression of the disease and the individual responsiveness to treatments in PD. However, it is still unclear how genetic factors influence the outcome of advanced therapies [2].

Methods: Patients treated with LCIG and followed up at our institution between 2008 and 2018 underwent a cross-sectional neurological evaluation and blood sample collection. A subgroup of patients underwent neuropsychological follow-up as well. All baseline and follow-up data were extracted from the database of the Movement Disorders Center of the University of Torino.

Results: Of 56 patients analysed, 9 (15%) had at least 1 mutation in a PD gene: 5 GBA, 2 SNCA, 1 LRRK2, 1 PRKN. Demographic, neurological and neuropsychological data at baseline and follow-up did not lead to identification of significant differences between mutated and non-mutated patients.

Conclusions: To our knowledge, this is the first description of LCIG outcome in PD patients carrying genetic mutations, yet no definitive conclusions can be drawn on the impact of genotype on LCIG outcomes. Well-designed prospective studies performed on larger cohorts with longer follow-up and a wider PD related gene panel are needed.

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P121

Can directional stimulation in GPi DBS be helpful in Parkinson's disease?

*Brigida Minafra*¹, S. Regalbuto¹, R. Zangaglia¹, M. Todisco¹, F. Valentino¹, D. Servello²,
C. Pacchetti¹

¹SC Parkinson Disease and Movement Disorders Unit, Mondino Foundation IRCCS, Pavia, Italy

²Department of Neurosurgery, Istituto Galeazzi, Milano, Italy



P122

Does jejunal levodopa infusion reduce impulse control and repetitive behavior disorders in PD patients? A cross-sectional study

*Giulia Cappelletti*², S. Simoni¹, F. Paolini Paoletti^{1,2}, P. Eusebi², M. Filidei², P. Nigro¹, L. Parnetti^{2,3}, N. Tambasco^{1,2}

¹Movement Disorders Center, Neurology Department, Perugia General Hospital and University of Perugia, Perugia, Italy

²Neurology Department, Perugia General Hospital and University of Perugia, Perugia, Italy

³Section of Neurology Department, Center for Memory Disturbances, Laboratory of Clinical Neurochemistry, Perugia General Hospital and University of Perugia, Perugia, Italy

Introduction: Long-term dopaminergic replacement treatment in Parkinson's disease (PD) can be related to the development of both motor and behavioral complications, namely levodopa-induced dyskinesia (LID) and impulse control and repetitive behavior disorders (ICRB) [1].

Objective: To investigate ICRB, LID, and their relationship with dopaminergic therapies in a cohort of 117 PD patients.

Methods: LID and ICRB were assessed by means of Rush Dyskinesia Rating Scale (RDRS) and Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS), respectively. Statistical analysis was carried out.

Results: 62 patients had not LID (NLID) and all of them were on therapy only with oral drugs. Among 55 patients with LID, 37 were treated only by oral therapy (LID/OT), while 18 were on treatment with jejunal levodopa infusion (LID/JLI). Disease duration and levodopa equivalent daily dose (LEDD) were significantly higher in LID/JLI patients compared to the other two groups ($p < 0.001$). Other demographic (age, gender) and motor characteristics (UPDRS-III and H&Y scores) were comparable among the three groups. The overall prevalence of ICRB was 34% (95% CI = 26% to 43%), with punding representing the most common disorder, and the mean value (\pm SD) of QUIP-RS total score was 5.4 ± 8.5 . The prevalence of clinically significant ICRB and the QUIP-RS total score were significantly higher in LID/OT patients compared to LID/JLI ($p = 0.058$ and $p = 0.019$, respectively) and NLID ($p = 0.008$ and $p < 0.001$, respectively) groups.

Conclusions: LID patients treated only with oral drugs showed ICRB more frequently and more severely than patients LID patients treated by JLI and NLID patients. In line with previous literature [2], a potential protective effect of JLI on ICRB could be hypothesized, although further studies are needed to better elucidate this issue.

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P123

PEG-J related complications in levodopa-carbidopa intestinal gel treated patients with advanced Parkinson's disease: a long term follow up

Simone Simoni, F. Paolini Paoletti, M. Filidei, G. Cappelletti, P. Nigro, N. Tambasco

Centro per la Malattia di Parkinson e i Disturbi del Movimento, Clinica Neurologica, Università degli Studi di Perugia, Perugia, Italy



P124

Subacute cognitive decline after DBS in a patient with idiopathic delayed-onset edema

Tiziana De Santis, S. Lalli, A. Cocco, D. Calandrella, M. Di Giovanni, P. Amami, A. Albanese

Department of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Milano, Italy

Introduction: Idiopathic delayed-onset edema (IDE) is an uncommon, self-limiting complication of deep brain stimulation (DBS) procedures, defined as onset of edema along the DBS lead, occurring 72 h [AA1] after implantation, in the absence of trauma, vascular events or signs of infection.

Objective: To describe the onset and outcome of a patient with IDE who presented with subacute cognitive decline three days after subthalamic nucleus (STN) DBS.

Care observation: A 55-year-old man with a 10-year history of Parkinson's disease and generalized seizures was admitted one month after implant due to subacute onset of apathy, memory impairment and apraxia. These symptoms started three days after surgery and stimulation had not yet been started.

Cerebrospinal fluid examination revealed slightly increased protein concentration with normal cells count. There was no evidence for viral or bacterial infections. Electroencephalogram showed diffuse slowing, with bilateral theta rhythm and sporadic delta waves on the left hemisphere without epileptiform activity.

Brain magnetic resonance imaging showed bilateral edema (increased FLAIR signal and increased T2 signal intensity) and micro-hemorrhages along the DBS electrode at the level of the left thalamus and supra-adjacent white matter with no associated significant mass effect. Left side was more involved. Neuropsychological evaluation showed a decay on tests assessing executive functions (phonemic fluency, Stroop Test and Trial Making Test) and anterograde verbal memory. The scores had worsened compared to a pre-implant assessment. Brain metabolic activity was assessed with [18F]-fluorodeoxyglucose positron emission tomography.

Conclusions: IDE-related cognitive decline may indicate that a surgical microlesion has involved cortical–basal ganglioni circuits or more distant cortical regions. Functional neuroimaging may contribute to identify the anatomical boundaries affected by IDE.

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