The image features two open books, one on the left and one on the right, with their pages slightly curved. A bright light emanates from the center where the two books meet. From this light, a dense shower of white, three-dimensional letters falls downwards, filling the space between the books. The letters are of various sizes and orientations, creating a dynamic, rain-like effect. The background is a soft, light gray, and the overall composition is symmetrical and visually striking.

*Giornata
dello Specializzando
in Neurologia*

Roma, 15 maggio 2018

Sin

SOCIETÀ ITALIANA DI NEUROLOGIA



SALUTO DI BENVENUTO

La “Giornata dello specializzando” nasce da una idea del prof. Giovanni Meola, professore ordinario di Neurologia presso il Policlinico San Donato di Milano, che ha organizzato in Lombardia, a partire dal 2012, una intera giornata dedicata alla ricerca svolta dagli specializzandi di neurologia. L’idea è così interessante ed ha avuto un tale successo che la SIN ha voluto generalizzare questa iniziativa, coinvolgendo le scuole di specialità del Nord, che si incontrano il 15 maggio a Milano in un meeting coordinato dal prof. Meola, gli specializzandi del Centro, che si incontrano nella stessa data a Roma presso il Policlinico Gemelli e quelli del Sud, che hanno organizzato il loro Congresso a Napoli presso il Complesso Didattico di Sant’Andrea delle Dame. La ricerca e lo studio sono le attività che rendono così interessante il lavoro del medico, ed in specie quello del neurologo, che è sempre stata una professione con un forte indirizzo di approfondimento e di studio, con l’obiettivo di risolvere i numerosi misteri che avvolgono le malattie del sistema nervoso. Quindi il percorso della ricerca fa parte del percorso formativo dello specializzando ed è una parte non secondaria della scuola di specialità di neurologia. I giovani sono tutti interessati all’approfondimento e alla sperimentazione clinica e di base e nella giornata dello specializzando avranno la opportunità di presentare i loro studi e di discuterli con i senior e i professori della loro Università. In questa giornata gli specializzandi sono i protagonisti e avranno una occasione importante per pensare al loro futuro e agli interessi che dovranno sviluppare alla fine del loro percorso formativo. La SIN ha, fra i suoi obiettivi principali, la formazione dei neurologi e in particolare di coloro che stanno per diventare la neurologia dei prossimi anni e quindi ci adoperiamo tutti in maniera tale che la “Giornata dello specializzando” diventi un appuntamento annuale, importante per lo sviluppo costante della nostra specialità.

Prof. Gianluigi Mancardi
Presidente SIN

9 maggio 2018



INFORMAZIONI GENERALI

Sede del Convegno

Aula 617
Policlinico Agostino Gemelli
Largo A. Gemelli, 8
Roma

Segreteria Scientifica

Prof. Leandro Provinciali
Scuola di Specializzazione in Neurologia
Università degli Studi Politecnica delle Marche
Mail: l.provinciali@univpm.it

Prof. Paolo Maria Rossini
Scuola di Specializzazione in Neurologia
Università Cattolica del Sacro Cuore (Roma)
Mail: paolomaria.rossini@policlinicogemelli.it

Prof. Serenella Servidei
Istituto di Neurologia
Università Cattolica del Sacro Cuore (Roma)
Mail: Serenella.servidei@unicatt.it

Segreteria Organizzativa

Segreteria SIN
Studio CongressLAB
Via del Rastrello, 7
53100 Siena
Tel. 0577 286003
Mail: info@neuro.it

Lingua ufficiale

La lingua ufficiale del convegno è l'italiano



Comunicazioni orali e hot topics

Tutte le presentazioni si tengono in lingua italiana.

Il tempo a disposizione per ogni comunicazione è di 10 minuti (8 per la presentazione e 2 per la discussione).

Si invitano gli autori a consegnare la propria relazione al centro slide almeno 1 ora prima del loro intervento

Badge

I badge dovranno essere ritirati presso il desk di segreteria che sarà aperto 30 minuti prima dell'inizio dell'evento.

Si raccomanda ai partecipanti di indossare il proprio badge durante tutta la durata dei lavori

Attestato di partecipazione

L'attestato di partecipazione sarà rilasciato, al termine dei lavori, presso il desk di segreteria a tutti i partecipanti regolarmente presenti

Agevolazioni Soci SIN

Esclusivamente per gli associati SIN, in regola con il pagamento della quota associativa annuale, e residenti oltre 250 chilometri dalla sede dell'evento è possibile prevedere (su espressa richiesta da far pervenire alla segreteria sin info@neuro.it) il soggiorno in albergo 3 stelle in camera a due letti (assegnazione a insindacabile giudizio della segreteria) per la notte del 14 maggio, unitamente a un rimborso spese di viaggio fino alla concorrenza di max 150 €.

Per coloro che ancora non sono soci Sin, e desiderino diventarlo, le informazioni sono disponibili sul sito www.neuro.it.

Assicurazione

La partecipazione all'evento non implica alcuna responsabilità da parte della segreteria scientifica e organizzativa per qualsivoglia incidente, danni personali o materiali o furti subiti dal partecipante durante la manifestazione.

Avvisi

Si ricorda che è tassativamente vietato fumare nell'area congressuale e che tutti i partecipanti sono caldamente invitati a tenere i cellulari in modalità silenziosa all'interno delle aule dove si svolgono i lavori.



COME RAGGIUNGERE LA SEDE CONGRESSUALE

VIABILITÀ E PARCHEGGI

La vasta area che circonda il Policlinico è accessibile alle automobili dei visitatori, che possono trovarvi parcheggi, liberi o a tariffa oraria.

Parcheggi

Gli ingressi del Policlinico per accedere alle aree di parcheggio sono:

1. Largo A. Gemelli, 8 (sempre aperto H24)
2. Via Trionfale
 - dal lunedì al venerdì dalle ore 5,30 alle ore 21,30
 - sabato dalle ore 5,30 alle 14,00
 - domenica e festivi chiuso
3. Largo F. Vito, 1
 - dal lunedì al venerdì dalle ore 5,30 alle ore 21,30;
 - sabato dalle ore 5,30 alle 14,00;
 - domenica e festivi sempre chiuso (aperto dalle ore 11,00 alle ore 14,00 e dalle ore 19,00 alle ore 21,15 (per funzioni religiose Chiesa Centrale)

Ingressi Policlinico

Gli ingressi alle struttura ospedaliera sono le seguenti:

1. Portineria piano IV° è aperta dal lunedì alla domenica (compresi festivi) dalle ore 07.00 alle ore 21.00
2. Portineria piano III° (ingresso dipendenti) è sempre aperto H24

Navetta

E' in funzione un servizio di **trasporto gratuito (bus navetta)** dalle ore 7.40 alle ore 17.35, dal lunedì al venerdì. Il percorso prevede fermate - tutte segnalate da appositi cartelli di colore giallo - nell'area che comprende la Facoltà, il Policlinico, gli Istituti Biologici, la Residenza Sanitaria Protetta e i vari parcheggi; i passaggi sono previsti ogni 30 minuti circa.

Servizio Taxi

Durante il giorno è possibile usufruire dei **taxi del servizio urbano** che posteggiano davanti alla portineria di accesso al Policlinico, in largo A. Gemelli, 8.



TRENO

Dalla stazione Termini prendere la metropolitana fino a Valle Aurelia, poi il treno della linea FM3 Roma-Viterbo e scendere alla fermata “Gemelli”.

METROPOLITANA

Linea A. Fermate: Valle Aurelia - Cornelia o Battistini. In superficie è necessario prendere le seguenti linee di autobus, che hanno fermate all’ingresso del Policlinico:

AUTOBUS

- linea 994 (percorso: Valle Aurelia - Pineta Sacchetti, Ospedale San Filippo Neri);
- linea 446 (Circonvallazione Cornelia - Pineta Sacchetti - Cortina d’Ampezzo - Ponte Milvio - Piazza Mancini);
- linea 146 (Battistini - Pineta Sacchetti - Policlinico Gemelli).

AUTOSTRADA

Chi proviene da Sud (Napoli), dopo essersi immesso nel Grande Raccordo Anulare, può prendere:

- l’uscita 1 - Via Aurelia (direzione Piazza Imerio - Via della Pineta Sacchetti)
- l’uscita 2 - Via Boccea (direzione Via di Torvecchia - Via della Pineta Sacchetti).

Chi proviene da Nord (Firenze) può prendere l’uscita 3 - Via Cassia (direzione Via Trionfale - Via della Pineta Sacchetti) del Grande Raccordo Anulare.

AEROPORTO

- Aeroporto di Fiumicino, fermata “Fiumicino”
- Prendere la linea FR1 “Settebagni” per 5 fermate
- Scendere alla fermata Trastevere
- Prendere la linea FR3B “Cesano” per 5 fermate
- Scendere alla fermata Gemelli



PROGRAMMA SCIENTIFICO

- 9.30 Registrazione dei partecipanti
- 10.00 Introduzione e presentazione del progetto
P.M. Rossini, *Roma*
- 10.20 **Lettura Magistrale**
Vulnerabilità selettiva dei gangli della base all'insulto ischemico e tossico
P. Calabresi, *Perugia*
- 11.00 Pausa Caffè
- 11.15 **Comunicazioni orali**
Moderatori: P. Calabresi, Perugia - P.M. Rossini, Roma
- 11.15 **Progressive axonal polyneuropathy in a mitochondrial disorder: an uncommon association with familial amyloid neuropathy**
F. Barbato, M. Luigetti, G. Primiano, G. Bisogni, C. Cuccagna, G. Bisogni, D. Bernardo, C. Sancricca, R. Carrozzo, L. Obici, S. Servidei, *Roma, Pavia*
- 11.25 **Multifocal motor neuropathy uncommonly occurring after acute motor axonal neuropathy: two stages of the same disease?**
S. Bocci, F. Ginanneschi, G. Capoccitti, L. Franci, L. Africa, F. Giannini, *Siena*
- 11.35 **A very late-onset case of lipid storage myopathy: the need for muscle biopsy**
D. Genovese, G. Primiano, S. Servidei, *Roma*
- 11.45 **Mitochondrial disorder hiding Myasthenia Gravis and autoimmune dysthyroidism: Chinese boxes of rare and autoimmune diseases**
J. Marotta, D. Genovese, G. Primiano, G. Colacicco, S. Servidei, *Roma*
- 11.55 **Evaluation of multifrequency bioimpedance analysis (BIA) as a potential out-come measure for muscle involvement in myotonic dystrophy type 1 (DM1): a small pilot study**
A. Perna, E. Rinninella, M. Cintoni, M. Ricci, T. Nicoletti, S. Rossi, G. Miggiano, A. Gasbarrini, M. Mele, G. Silvestri, *Roma*
- 12.05 **POEMS syndrome: an uncommon cause of bilateral papilloedema and reduced visual acuity**
A. Romano, M. Sabatelli, G. Bisogni, A. Di Paolantonio, P. M. Rossini, M. Luigetti, *Roma*

- 12.15 **Autoimmune sensory and cerebellar ataxia: neurological manifestation in benign autoimmune lymphoproliferative syndrome (ALPS)**
V. Guglielmino, A. Perna, G. Silvestri, *Roma*
- 12.25 **Paraneoplastic Stiff-Person Syndrome with positive amphiphysin antibodies: a case report**
M. Mainardi, A. Antonini, *Padova*
- 12.35 **Microglial activation and the nitric oxide/cGMP/PKG pathway underlie enhanced neuronal vulnerability to mitochondrial dysfunction in experimental multiple sclerosis**
A. Mancini, M. Tantucci, P. Mazzocchetti, A. de Iure, V. Durante, L. Macchioni, C. Giampà, A. Alvino, L. Gaetani, C. Costa, A. Tozzi, P. Calabresi, M. Di Filippo, *Perugia, Roma*
- 12.45 **A case of reversible encephalopathy due to Cerebral Amyloid Angiopathy Related Inflammation (CAA-RI)**
T.F. Nicoletti, E. Lozupone, V. Guglielmi, S. Gaudino, A. Evoli, *Roma*
- 12.55 **Wolfram Syndrome: clinical and genetic features of a new adult case**
G. Peppoloni, I. Di Donato, A. Mignarri, F. M. Santorelli, M.T. Dotti, *Siena, Pisa*
- 13.05 **Eye tracking and saccades analysis in the clinical practice**
D. Zaino, A. Rufa, *Siena*
- 13.15 Pausa pranzo
- 14.00 **Comunicazioni orali**
Moderatori: S. Servidei, *Roma* - G. Siciliano, *Pisa*
- 14.00 **Wake-Up Right-Sided Hemiparesis and Dysarthria in a Heavy Snorer**
V. Brunetti, M.A.D. Ferilli, C. Vollono, A. Di Franco, G. Della Marca, *Roma*
- 14.10 **PRES after post traumatic spine injury: a case report and a literature review**
A. Di Paolantonio, F. Pilato, V. Cassano, B. Condró, *Roma*
- 14.20 **TMS evaluation in mild cognitive impaired patients according to new criteria for AD: a 36 months follow up study.**
F. Di Lorenzo, C. Motta, V. Ponzo, S. Bonni, C. Caltagirone, A. Martorana, G. Koch, *Roma*
- 14.30 **Progressive Nonfluent Aphasia: a new mutation in exon 10 of MAPT**
P. Libertini, L. Giampietri, F. Baldacci, V. Nicoletti, F. Sean Giorgi, C. Pagni, S. Cintoli, J. Bonaccorsi, C. Radicchi, I. Ghicopulos, B. Nacmias, S. Bagnoli, U. Bonuccelli, G. Tognoni, *Pisa, Firenze*

14.40 **A possible novel pathogenetic mutation of presenilin-1 for Alzheimer Disease**
L. Giampietri, P. Libertini, B. Nacmias, F. Baldacci, S. Bagnoli, V. Nicoletti, F. Sean Giorgi,
U. Bonuccelli, G. Tognoni, *Pisa, Firenze*

14.50 **The dual role of premorbid intelligence in Subjective Cognitive Decline and Mild Cognitive Impairment. A 7-years Follow-Up study.**
S. Mazzeo, V. Bessi, S. Padiglioni, C. Piccini, B. Nacmias, L. Bracco, S. Sorbi, *Firenze*

15.00 **Hot Topic sessione 1**

Encefaliti virali: escludendo la forma erpetica, la diagnosi cambia la terapia in fase acuta?

15.00 *Pros*
L. Africa, *Siena*

15.10 *Cons*
F. Iodice, *Roma*

15.20 *Discussione*

L'imaging dell'amiloide è utile per la diagnosi della malattia di Alzheimer?

15.25 *Pros*
S. Mazzeo, *Firenze*

15.35 *Cons*
P. Libertini, *Siena*

15.45 *Discussione*

Stroke ischemico: l'estensione della trombolisi endovascolare alle 24 ore

15.50 *Pros*
M.C. Acciarri, *Ancona*

16.00 *Cons*
R. Ornello, *L'Aquila*

16.10 *Discussione*



16.15 Coffee break

16.30 **Hot Topic sessione 2**

Quale terapia per il trattamento di prima linea della CIDP: Steroidi o IGeV?

16.30 *Steroidi*

F. Barbato, *Roma*

16.40 *IgEV*

F. Dono, *Chieti*

16.50 Discussione

L'utilizzo precoce della levodopa

16.55 *Pros*

M. Romoli, *Perugia*

17.05 *Cons*

G. Paparella, *Roma*

17.15 Discussione

Peggioramento delle neuroimmagini nella SM: utili per cambiare terapia?

17.20 *Pros*

C. Gabri Nicoletti, *Roma*

17.30 *Cons*

E. Falato, *Roma*

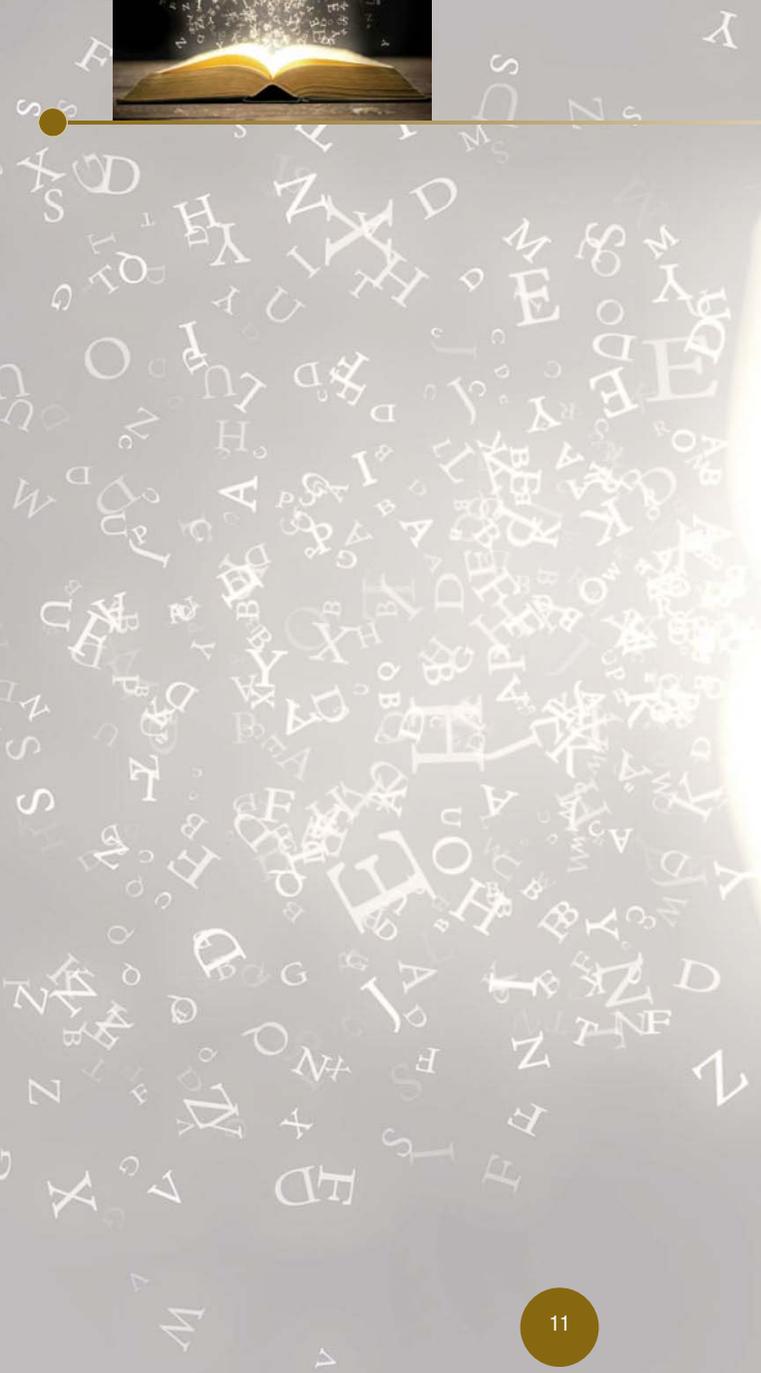
17.40 Discussione

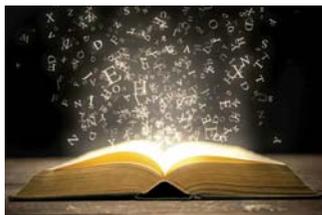
17.45 **Conclusioni and take home message**

S. Servidei, *Roma*



BOOK OF ABSTRACTS





THE DUAL ROLE OF PREMORBID INTELLIGENCE IN SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT. A 7-YEARS FOLLOW-UP STUDY

Salvatore Mazzeo¹, V. Bessi¹, S. Padiglioni¹, C. Piccini², B. Nacmias¹, L. Bracco¹, S. Sorbi¹

¹ Department of Neuroscience, Psychology, Drug Research and Child Health - University of Florence - Florence

² Neurology Unit - Local Sanitary Unit 10 - Florence

Background: The Cognitive Reserve (CR) model predicts that greater premorbid intelligence allows the brain to cope with a greater amount of cerebral damage. However, when this reserve is overcome, a faster decline is evident. Therefore the investigation of CR in population at risk for Alzheimer's Disease (AD) is of great interest. AIMS: To evaluate the contribution of premorbid intelligence as an index of CR on the progression from Subjective Cognitive Decline (SCD) to Mild Cognitive Impairment (MCI) and from MCI to AD.

Materials and Methods: As part of a longitudinal clinical-neuropsychological-genetic survey on SCD and MCI, 211 patients referred to our hospital between 1990 and 2015 were included. All patients underwent extensive neuropsychological evaluation and Apolipoprotein E genotyping. In order to estimate the premorbid intelligence, all cases were assessed by the TIB (Test di Intelligenza Breve). Each patient underwent at least two years of clinical-neuropsychological follow-up. RESULTS: TIB was positively correlated with age at baseline both in SCD ($\chi^2=0.257$, $p=0.04$) and in MCI ($\chi^2=0.283$, $p=0.01$). During the follow-up, 32 out of 126 SCD converted to MCI (SCD-c) in 6.21 ± 3.00 years on average and 94 remained stable (SCD-s) with a mean follow-up time of 5.70 ± 2.68 years. Performing a Cox-regression analysis considering age at baseline, schooling, MMSE and TIB as covariates and age at conversion as time, TIB resulted as a protective factor ($p=0.015$, $HR=0.944$). A Kaplan-Meier analysis on SCD-c, ranked into three percentiles according to TIB score, showed that age at conversion to MCI were statistically significantly lower in "low" (69.50 ± 4.51 years) and "intermediate" (70.36 ± 4.08 years) respect to "high" TIB (76.925 ± 3.84 years). 12 out of 32 SCD-c and 33 out of 85 MCI converted to AD in 3.16 ± 2.19 years on average (45 MCI-c in total). 20 SCD-c and 52 MCI subjects who did not progressed to AD were considered as MCI-s (mean follow-up time: 5.71 ± 3.02 years). Performing the regression analysis on this group considering follow-up time as time, TIB showed a statistically significant effect on progression to AD only in ApoE ϵ 4+ subjects ($p=0.043$). In this group, high TIB represented a risk factor for progression to AD ($HR=1.165$).



Discussion: In line with the CR model, our results show delayed SCD and MCI onset and slower progression from SCD to MCI in subjects with high premorbid intelligence. On the contrary, when an objective cognitive impairment appeared, premorbid intelligence played as a risk factor for faster progression to AD in ApoE ϵ 4 carriers.

References: Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 1994, 271, 1004–1010.

Colombo L, Sartori G, Brivio C. Stima del quoziente intellettuale tramite l'applicazione del TIB (Test Breve di Intelligenza). *G. Ital. Psicol.* 2002, 616-638.

Bracco L, Piccini C, Baccini M, Bessi V, Biancucci F, Nacmias B, Bagnoli S, Sorbi S. Pattern and progression of cognitive decline in Alzheimer's disease: role of premorbid intelligence and ApoE genotype. *Dement Geriatr Cogn Disord.* 2007;24(6):483-91.



PARANEOPLASTIC STIFF-PERSON SYNDROME WITH POSITIVE AMPHIPHYSIN ANTIBODIES: A CASE REPORT

Michele Mainardi, A. Antonini

Department of Neurology - University of Padova - Padova

Abstract: A 54-year old woman was admitted to the emergency room of the Padua University Hospital for acute generalised seizure (head trauma, sphincter release, tongue biting). In the previous 4 months she had been investigated for a left breast nodule of the superior-external quadrant (at biopsy: left-sided infiltrating ductal carcinoma with positivity for the sentinel lymph node) and for progressive difficulty in walking. Gait problems had been attributed initially to peripheral neuropathy and subsequently to possible central pathology. However, she had normal nerve conduction and EMG as well as no specific signal abnormalities on brain and spine MRI. When she was transferred to our neurology ward she could not remember the circumstances leading to the seizure. EEG was normal. Neurological examination showed left stiff-leg gait, marked postural instability, left leg increased tone, absence of deep tendon reflexes, left extension plantar cutaneous reflex. Patient could not walk alone and had to use a wheelchair. Following oncology consult, she had a whole-body and brain PET-CT showing increased uptake in the left breast nodule and in two axillary lymph nodes with no other metabolic changes. In the CSF, there were increased cells (28 WBC/ μ L), elevated proteins with blood-brain barrier damage without oligoclonal bands [Albumin 0.642 g/l; IgG 0.0910 g/L, barrier damage 15.140], no cellular abnormalities on cytological examination. Given clinical manifestations suggestive of Stiff-Person Syndrome (SPS), we searched for anti-neuronal antibodies (AMPA-R GAD, GABA-BR, NMDA-R, voltage potassium channel, CASPR2, amphiphysin). We found positivity of amphiphysin antibodies, consistent with paraneoplastic SPS (1),(2). We started therapy with GABAergic drugs, steroids and hormone (baclofen 12.5 mg + 25 mg, prednisone 50 mg, gabapentin 600 mg t.i.d, diazepam 25/50 drops, anastrozole 5 mg) (3). She improved markedly with relief of muscle stiffness. After discharge, she underwent left mammary surgery but clinical manifestations did not change and she is still treated.

Conclusion: These findings expand current knowledge on clinical manifestations secondary to amphiphysin antibodies including generalised seizures and confirm the non-reversibility of the condition even after neoplasm removal.



References: Murinson BB, Guarnaccia JB. Stiff-person syndrome with amphiphysin antibodies: Distinctive features of a rare disease. *Neurology*. 2008;71(24):1955-1958.

Balint B, Vincent A, Meinck H-M, Irani SR, Bhatia KP. Movement disorders with neuronal antibodies: syndromic approach, genetic parallels and pathophysiology. *Brain*. 2018;141(1):13-36.

Bhatti AB, Gazali ZA. Recent Advances and Review on Treatment of Stiff Person Syndrome in Adults and Pediatric Patients. Muacevic A, Adler JR, eds. *Cureus*. 2015;7(12):e427.



MICROGLIAL ACTIVATION AND THE NITRIC OXIDE/CGMP/PKG PATHWAY UNDERLIE ENHANCED NEURONAL VULNERABILITY TO MITOCHONDRIAL DYSFUNCTION IN EXPERIMENTAL MULTIPLE SCLEROSIS

Andrea Mancini¹, M. Tantucci¹, P. Mazzocchetti¹, A. de Iure¹, V. Durante¹, L. Macchioni², C. Giampà³, A. Alvino³, L. Gaetani¹, C. Costa¹, A. Tozzi², P. Calabresi¹, M. Di Filippo¹

¹ Clinica Neurologica - Università degli Studi di Perugia - Perugia

² Sezione di Fisiologia e Biochimica - Università degli Studi di Perugia - Perugia

³ Istituto di Anatomia Umana e Biologia Cellulare - Università Cattolica del Sacro Cuore - Roma

Background and aims: A close link between inflammation and neurodegeneration has been demonstrated during multiple sclerosis (MS), leading to the hypothesis that immune mechanisms may control and even promote neuronal degeneration and irreversible disease progression. In this scenario, it has recently been proposed a potential pathogenic role for mitochondrial dysfunction¹. The main aim of our project was to investigate, with electrophysiological recordings, if the neuro-inflammatory process associated with experimental autoimmune encephalomyelitis (EAE) may increase neuronal vulnerability to mitochondrial impairment, and the possible pathways of this effect.

Materials and methods: EAE was induced in Biozzi ABH mice by the injection of syngeneic spinal cord homogenate. Extracellular field potential recordings (fEPSPs) were performed in the striatum during the acute relapsing phase of the disease. In vitro exposure to sodium azide was used for pharmacological inhibition of mitochondrial complex IV.

Results: We showed that during the acute relapsing phase of EAE, neuronal susceptibility to mitochondrial complex IV inhibition is markedly enhanced, with a proportional 65.7% increase in the final absolute reduction of fEPSPs amplitude with respect to control conditions ($p < .001$, $n=14$). We then investigated which pathogenic mechanism might link the inflammation to the enhanced toxicity of sodium-azide. Interestingly, we found that the inhibition of NO synthesis and of its intracellular pathways (involving soluble guanylyl cyclase, sGC, and protein kinase G, PKG) markedly counteracted the enhancing effect of inflammation on sodium-azide neuronal toxicity. Moreover, the in vivo treatment of EAE mice with minocycline, a compound able to inhibit microglial activation, was able to reduce neuronal susceptibility to mitochondrial complex IV inhibition.

Discussion and conclusion: The obtained results suggest that mitochondrial complex



IV exerts an important role in maintaining neuronal energetic homeostasis during EAE. The pathological processes associated with experimental MS, and in particular the activation of microglia and of the NO pathway, lead to an increased neuronal vulnerability to mitochondrial complex IV inhibition, representing promising pharmacological targets.

References: Mahad D, Ziabreva I, Lassmann H, Turnbull D. Mitochondrial defects in acute multiple sclerosis lesions. *Brain*. 2008 Jul;131(Pt 7):1722-35.



A POSSIBLE NOVEL PATHOGENETIC MUTATION OF PRESENILIN-1 FOR ALZHEIMER DISEASE

Linda Giampietri¹, P. Libertini¹, B. Nacmias², F. Baldacci¹, S. Bagnoli², V. Nicoletti¹, F Sean Giorgi¹, U. Bonuccelli¹, G. Tognoni¹

¹ Department of Clinical and Experimental Medicine - University of Pisa - Pisa

² Department of Neuroscience, Psychology, Drug Research and Child Health - University of Florence - Florence

Introduction: Even though monogenic forms of Alzheimer Disease (AD) account for less than 1% of cases, their study greatly contributed to comprehension of the pathophysiological mechanisms of the idiopathic ones.

Case description: We describe a probable novel pathogenetic mutation of presenilin-1 associated to dementia in a family with four subjects affected (three out of four were younger than 60 at onset). The index patient is a 53-years-old man with one-year history of depression and memory complaints. Psychometric evaluation revealed prominent verbal and visuo-spatial memory impairment, brain MRI was normal, and 18-FDG brain PET showed bilateral precuneus and mesial temporal cortex hypometabolism. Afterwards, he was diagnosed with Mild Cognitive Impairment due to AD supported by a compatible Cerebrospinal Fluid (CSF) AD core biomarker profile. Genetic analysis identified a missense mutation in exon 4 of PSEN1 (Thr99Asn) that has never been described so far and it is likely to be pathogenetic. The probable pathogenicity of this PSEN1 mutation is supported by the facts that the variant is not reported in the 1000 genomes, single nucleotide polymorphism database (Exome Variant Server and Exome Aggregation Consortium). Moreover, computer analyses with different programs (PolyPhen-2, Mutation Tester, SIFT, I-Mutant2.0) predicted the disease-causing nature of the p.Thr99Asn change and suggested that the aminoacid substitution is not tolerated. None of the three other affected family members is still alive nor has ever performed genetic analysis.

Conclusions: We reported a case of familial early onset AD probably due to an undescribed mutation of presenilin-1.

References: Cacace, Rita, Kristel Slegers, and Christine Van Broeckhoven. "Molecular genetics of early-onset Alzheimer's disease revisited." *Alzheimer's & dementia: the journal of the Alzheimer's Association* 12.6 (2016): 733-748.

Zhang, Shuting, et al. "Biological function of Presenilin and its role in AD pathogenesis." *Translational neurodegeneration* 2.1 (2013): 15.

PROGRESSIVE NONFLUENT APHASIA: A NEW MUTATION IN EXON 10 OF MAPT

Paolo Libertini¹, L. Giampietri¹, F. Baldacci¹, V. Nicoletti¹, F. Sean Giorgi¹, C. Pagni¹, S. Cintoli¹, J. Bonaccorsi¹, C. Radicchi¹, I. Ghicopulos¹, B. Nacmias², S. Bagnoli², U. Bonuccelli¹, G. Tognoni¹

¹ Department of Clinical and Experimental Medicine - University of Pisa - Pisa

² Department of Neuroscience, Psychology, Drug Research and Child Health NEUROFARBA - University of Florence - Florence

Introduction: Most neurodegenerative diseases (NDs) are characterized by intracellular aggregates of insoluble proteins. Among these, the microtubule associated protein tau (MAPT) forms brain neurofibrillary deposits in a large variety of NDs classified within the tauopathies spectrum.

Case description: The proband, a 68-years-old male, was admitted to the Alzheimer Center of our neurology unit, and underwent a complete diagnostic workup, including detailed past medical history, general and neurological examination, extensive psychometric evaluation, brain CT scan, brain 18F-FDG PET, 18F-flutemetamol amyloid PET and genetic analysis for progranulin, Fused in Sarcoma, c9orf72, TDP-43, transactive response DNA binding protein 43, and MAPT mutations. He came to our attention with 1-year history of progressive language impairment characterized by word-finding pauses, and dysgraphia. The psychometric evaluation revealed a severe dysgraphia and executive dysfunction. The brain 18F-FDG PET and 18F-flutemetamol amyloid PET proved normal. Hence, we suggest a diagnosis Nonfluent/agrammatic variant Primary Progressive Aphasia (nvPPA) (according to Gorno-Tempini classification). Genetic analysis identified a new missense mutation in exon 10 of MAPT (1915 G<A responsible for Gly304Ser). The computer analyses with Polyphen-2, ClustalW, SIFT e Mutation Taster supported the probable pathogenicity of this mutation.

Conclusions: We described a case report of a clinical phenotype of nvPPA associated with a novel mutation of tau protein.

References: Gorno-Tempini, Maria Luisa, et al. Mesulam, M-Marsel, et al.



UNIVERSITÀ CATTOLICA DEL SACRO CUORE - ROMA

PROGRESSIVE AXONAL POLYNEUROPATHY IN A MITOCHONDRIAL DISORDER: AN UNCOMMON ASSOCIATION WITH FAMILIAL AMYLOID NEUROPATHY

Francesco Barbato¹, M. Luigetti², G. Primiano³, G. Bisogni², C. Cuccagna², G. Bisogni⁴, D. Bernardo⁴, C. Sancricca², R. Carrozzo⁵, L. Obici⁶, S. Servidei²

¹ Neurologia - Università Cattolica del Sacro Cuore - Roma

² UOC Neurology - Fondazione Policlinico Universitario Agostino Gemelli - Roma

³ UOC Neurophysiopathology - Fondazione Policlinico Universitario Agostino Gemelli - Roma

⁴ Centro Clinico NEMO adulti - Fondazione Policlinico Universitario Agostino Gemelli - Roma

⁵ Unit of Neuromuscular and Neurodegenerative Disorders - Bambino Gesù Children's Research Hospital - Roma

⁶ Amyloidosis Research and Treatment Center - Foundation IRCCS Policlinico San Matteo - Pavia

Abstract: Mitochondrial diseases are inherited disorders of oxidative phosphorylation that present with a multitude of clinical features in different combinations and with various inheritance patterns. The occurrence and characteristics of peripheral nerve involvement vary considerably amongst various syndromes and genetic background. Transthyretin (TTR) amyloidosis is a rare, life-threatening, progressively debilitating, autosomal dominant condition characterized by extracellular deposition of TTR-derived amyloid fibrils in peripheral and autonomic nervous system, heart, and other organs, leading to tissue damage and organ failure. Characteristic of polyneuropathy in TTR-amyloidosis may vary according to geographic area.

Case Report: We report a 67 year-old man that came to our observation for a three years history of numbness and tingling in lower limb associated with walking difficulties and exercise intolerance. Extensive clinical, neurophysiological, pathological and genetic assessment was carried out.

Neurological examination revealed bilateral ptosis, foot-drop gait, bilateral strength impairment of tibialis anterior and extensor longus hallucis, hypoesthesia with stocking distribution, and reduced tendon reflexes in lower limbs. Nerve conduction studies confirmed an axonal polyneuropathy. Lactic acid production was abnormally increased after exercise. Muscle biopsy showed the presence of mitochondrial abnormalities. Long range PCR confirmed the presence of accumulation of multiple mitochondrial DNA deletions. After one year patient neuropathy dramatically worsened. Further investigations were planned including sural nerve biopsy that showed amyloid deposition. Sequence analysis of TTR gene confirmed the presence of p.Phe64Leu mutation.



Discussion and Conclusion: Occurrence of two rare neurological diseases is a rare condition but often reported in neurology. Even in genetic era clinical approach should orient our diagnostic process. TTR-related amyloidosis is often misdiagnosed in favour of other more common or treatable conditions. In our patients with mitochondrial disorder evolution of polyneuropathy was atypical for this setting and suggestive for other conditions, namely amyloid neuropathy. A progressive axonal polyneuropathy should be always screened for amyloid also in patients with other rare or multisystemic diseases.

WAKE-UP RIGHT-SIDED HEMIPARESIS AND DYSARTHRIA IN A HEAVY SNORER

Valerio Brunetti, M.A.D. Ferilli, C. Vollono, A. Di Franco, G. Della Marca

Neurologia - Università Cattolica del Sacro Cuore - Roma

Case presentation: A 57-year-old man was referred to the ED for wake-up right-sided hemiparesis, hypoesthesia, and dysarthria (NIHSS score 7). The patient was obese and a heavy snorer; he reported two previous episodes of thrombophlebitis of the lower limbs. The family medical history was suggestive for thrombophilia. Three days after admission, the patient had syncope associated with severe bradycardia, dyspnea, and severe hemoglobin desaturation, suggestive of a pulmonary embolism.

Diagnostic studies: CT brain imaging revealed ischemic stroke in the left temporal and insular lobes. Urgent pulmonary CT angiography revealed subtotal occlusion of both pulmonary arteries.

Venous Doppler ultrasonography of the lower limbs showed bilateral DVT extending to the common femoral veins. Transcranial Doppler ultrasonography showed microembolic signals at rest, which markedly increased after a Valsalva maneuver.

The presence of a patent foramen ovale (PFO) was further confirmed by transesophageal echocardiography.

Polysomnography on day 15 showed snoring and prolonged apnea consistent with severe OSA.

Screening for thrombophilia showed a deficit of antithrombin III. Analysis of the antithrombin III gene showed a heterozygous mutation in exon 4, which converts tryptophan in a stop codon at position 307.

Discussion: PFO has a high prevalence in cryptogenic stroke, especially in younger patients. Moreover, patients with PFO and previous cryptogenic ischemic stroke are at risk for recurrence of cerebrovascular events. The most widely accepted mechanism of PFO-related stroke being considered is the paradoxical embolism. A massive right to left shunt across a PFO is normally prevented by the higher pressures in the left-sided heart chamber. OSA is one of the conditions in which pressure can rise in the right-sided chambers. In fact, during obstructive apneas, patients breathe against resistance, thus performing Müller and Valsalva maneuvers. The suspicion of paradoxical embolism also implies a venous source. Inheritance of ATIII deficiency is in an autosomal dominant fashion with variable penetrance.

Conclusion: In conclusion, the combination of these three risk factors concurred in the etiopathogenesis of ischemic stroke in the patient: ATIII deficiency was responsible for DVT; during sleep, prolonged sleep apnea induced a massive right to left shunt across the PFO, and this in turn resulted in paradoxical embolism and stroke. This pathogenic mechanism suggested a peculiar therapeutic strategy, consisting of a combination of anticoagulation treatment, nocturnal positive-pressure ventilation, and closure of the PFO.

PRES AFTER POST TRAUMATIC SPINE INJURY: A CASE REPORT AND A LITERATURE REVIEW

Andrea Di Paolantonio, F. Pilato, V. Cassano, B. Condó

Neurology - Catholic University of Rome - Rome

Abstract: Posterior reversible encephalopathy syndrome (PRES) is caused by vasogenic edema in brain. Delivery or hypertensive peaks usually precede the symptoms. Clinic is characterised by headache, systemic hypertension, seizures, visual and conscience disturbance. MIR study showing brain edema is mandatory for diagnosis. Prognosis is good. We describe the case of a woman with a post-traumatic spine lesion. During her delivery she had a PRES that resolved few days later. We reviewed literature to deepen clinical characteristics of post-traumatic spine damage PRES. We noticed higher prevalence of headache in comparison to “classic” PRES.

Background: At the age of 21 our patient had a C5-C6 spine damage after a road accident. Six years later, a week after her delivery, she complained of headache, aphasia,



hemianopsia, arterial hypertension and generalized motor seizures. Brain imaging showed multiple areas of vasogenic edema in temporo-parieto-occipital lobes and cerebellar hemispheres. After the diagnosis of PRES, she started levetiracetam and intravenous antihypertensive drugs. After four days all her symptoms disappeared.

Materials and methods: We searched in pubmed all cases of post spine trauma PRES. We founded 9 episodes occurred at 7 patients. We compared presence of seizure, visual or other focal deficits, hypertension, conscience impairment, sequelae or death between spine damage PRES and “classic” PRES.

Results: We founded higher prevalence of headache in spine damage group (70% vs 26-53%), probably due to the strong prevalence of arterial hypertension (80% vs 61-80%).

Discussion and conclusion: Two major hypothesis were formulated for PRES pathogenesis. The “vascular” one originates from the association between PRES and systemic hypertension, the latter being common in post spine injury autonomic dysfunction. Very high values of PA could overwhelm blood brain pressure autoregulation, resulting in edema. The “toxic” one is due to endothelial dysregulation provoked by drugs or eclampsia. In our case we imagined a double-shot hypothesis to explicate pathogenesis: on a previous autonomic instability due to her progress spine trauma (vascular hypothesis), delivery worked as new shot (toxic hypothesis) and provoked PRES. Post traumatic spine damage should be considered a risk factor for PRES. Clinic and prognostic features aren't different from classical PRES. A major attention should be given to patients carrying post traumatic spine lesions during deliveries, because could be at risk of PRES for a combination of two risk factors.

A VERY LATE-ONSET CASE OF LIPID STORAGE MYOPATHY: THE NEED FOR MUSCLE BIOPSY

Danilo Genovese, G. Primiano, S. Servidei

Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy

Background: Lipid storage myopathies (LSMs) are a heterogeneous group of metabolic disorders characterized by a multitude of clinical features in different combinations, with isolated myopathy or multisystem involvement, and with various age of onset and rates of clinical progression, and overall clinical severity. There are four types of genetically

diagnosable LSMs: primary carnitine deficiency (PCD), multiple acyl-coenzyme A dehydrogenase deficiency (MADD), neutral lipid storage disease with ichthyosis, and neutral lipid storage disease with myopathy.

Case presentation: A 70-year-old male, with no family history of neuromuscular diseases, presented with an eight-months history of progressive muscular weakness, more evident in lower limbs with difficult walking, and exercise intolerance. He also experienced difficulty in swallowing.

Serum CK was elevated up to 1000 UI/L and EMG showed myopathic abnormalities. Evaluated in another center, a diagnosis of inflammatory myopathy was made and treatment with oral steroids was started (prednisone 75mg per day), without improvement of the muscle weakness. Because of the worsening of symptoms was recently referred to our Centre.

Neurological examination showed severe axial and proximal muscle weakness with strength of 1-2 in the lower limbs and 2-3 in the upper limbs according to MRC scale. He was bedridden, dyspnoeic and dysphagic for both liquids and solids with need of tube feeding. Surprisingly, muscle MRI was almost normal. Muscle biopsy revealed instead a severe vacuolar myopathy with numerous small round vacuoles stained with oil-red-O and the presence of ragged-blue COX depleted fibers in the absence of inflammatory infiltrates, suggesting a lipid storage myopathy. Organic acid profiles in urine showed an increase in ethylmalonate, adipic acid and 4-OH-phenylacetate. A decrease of plasma free carnitine was associated with a slight increase of medium- and longchain acylcarnitines. Genetic analysis are ongoing.

Oral supplementation with CoQ10 (450 mg/day) and riboflavin (300 mg/day) led to improvement in a few days with the resolution of dysphagia and dyspnea and improvement of the muscle weakness. After 10 days of treatment he is able to walk for a few steps with assistance.

Conclusions: LSM is a rare, heterogeneous group of metabolic diseases characterized by impaired fatty acids oxidation, often misdiagnosed in adult patients as inflammatory myopathies. Making an accurate diagnosis is mandatory as they are treatable disorders, probably underestimated because of mimicking different pathologies. In this perspective, this report strongly supports the need to perform muscle biopsy as central diagnostic tool in the work-out of adult onset myopathies to set a prompt and adequate treatment that may result in some patients in a complete recovery.

AUTOIMMUNE SENSORY AND CEREBELLAR ATAXIA: NEUROLOGICAL MANIFESTATION IN BENIGN AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME (ALPS)

Valeria Guglielmino, A. Perna, G. Silvestri

Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy

Abstract: We describe a patient manifesting relapsing, predominant, cerebellar ataxia as neurological manifestation of benign autoimmune lymphoproliferative syndrome (ALPS). Neurological symptoms responded to immunomodulatory treatment.

Background: Autoimmune lymphoproliferative syndrome (ALPS) is a rare inherited syndrome due to impaired Fas-Fas ligand apoptotic pathway, characterized by nonmalignant, noninfectious lymphadenopathy and/or splenomegaly, and various, including neurological, autoimmune pathologies.

Aims: Cerebellar ataxia was seldom reported in ALPS. Here we describe a case of a woman manifesting this symptom as a main clinical manifestation of such a rare disease.

Materials and methods: a 49 year-old woman, with history of ulcerative colitis, about one year ago developed a severe dermatitis eczema, treated with omalizumab without benefit. Shortly after, she manifested gait and speech impairment: she had been evaluated in other medical centers by extensive diagnostic tests including neuroimaging studies resulted negative, CSF examination showing increased protein and cell content and positive oligoclonal bands, total body CT scan showing diffuse lymphadenopathy. Blood tests showed severe B12 hypervitaminosis . Haematological disorders were ruled out; systemic, onconeural and cerebellar autoantibodies were negative. Treatment with i.v steroids had benefit both on cutaneous and neurological manifestations.

Few months later, she came to our observation because of the relapsing of ataxia. Diagnostic assessment included: brain and spinal cord MRI, total body CT, EMG studies, evoked potentials, extensive biochemical, haematological and autoimmune tests on blood and CSF.

Results: Neurological evaluation showed trunk and limb ataxia with positive Romberg sign, reduced O.T. reflexes and right Babinski sign. EMG studies documented a motor neuropathy in the lower limbs; brain MRI showed a T2- weighted and FLAIR hyperintense lesion in the right frontal white matter; TC total body displayed a mild splenomegaly. Blood tests revealed high glucose levels, indicative of a condition of Type 1 diabetes,

hypereosinophilia, hypergammaglobulinemia, and very high vitamin B12 levels. Search for peripheral “double negative T cells” resulted elevated (1.7% of the CD3+ subset), supporting the diagnosis of ALPS. Elevated anti-GAD65 and anti islet-cells antibodies were also detected. She was treated by a course of high doses i.v Ig with clinical benefit, testified by improvement of SARA and ICARS scores and EMG findings. Search for mutations in FAS, FASL, CASP-8, and CASP10 genes, associated to ALPS, is in progress.

Discussion and conclusions: ALPS is a rare, primary immune disease often misdiagnosed. Detection of very high levels of serum vitamin B12 is a key feature to suspect this condition.

MITOCHONDRIAL DISORDER HIDING MYASTHENIA GRAVIS AND AUTOIMMUNE DYSTHYROIDISM: CHINESE BOXES OF RARE AND AUTOIMMUNE DISEASES

Jessica Marotta, D. Genovese, G. Primiano, G. Colacicco, S. Servidei

Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy

Background: Mitochondrial disorder and Myasthenia gravis, two rare pathological conditions, may present with similar clinical symptoms as palpebral ptosis, ophthalmoparesis and muscle fatigue, sometimes with difficulties in the differential diagnosis. In the literature there are very few reports describing the rare association of the two diseases.

Case report: A 72year-old woman came to our observation because of one year history of progressive bilateral ptosis and diplopia. At the time of neurological examination the patient had bilateral ptosis, ophthalmoplegia with no diplopia, mild weakness of cervical and proximal limbs muscles more evident at lower limbs. Muscle biopsy showed the typical hallmarks of mitochondrial pathology with numerous ragged-red COX depleted fibers.

However, due to excessive muscle fatigue with some fluctuations she was tested with low-frequency repetitive nerve stimulation of the right facial nerve and left axillar nerve that demonstrated a decline in amplitude of the compound muscle action potential of -58.6% and -20.3% respectively. Moreover, a high titer of anti-acetylcholine receptor antibodies was detected in serum and i.m. injection of neostigmine methylsulfate resulted in rapid improvement of ptosis (figure 2) and of limb muscles, but not of the

ophthalmoplegia. Based on electrophysiological, immunological, and pharmacological tests a diagnosis of myasthenia gravis was then made.

Furthermore, the treatment with acetylcholinesterase inhibitors unmasked a clear exophthalmos and lid retraction. MRI showed enlargement of the extraocular muscles without fatty degeneration and a bright signal from the inferior and medial recti muscles at the Fat-suppressed and gadolinium-enhanced. Thyroid function test suggested a condition of an chronic autoimmune thyreopathy associated with TSH receptor antibodies.

Conclusions: Co-occurrence of rare and autoimmune diseases is uncommon and when it happens is not only by chance but also for sharing common mechanisms and pathogenic background. Interestingly, mitochondrial diseases, myasthenia gravis and autoimmune thyreopathies have as a common target the extraocular muscles and as common symptom the easy fatigability. This report shows how the comprehensive and accurate phenotyping is essential to reach a correct diagnosis, mostly in rare diseases characterized by a large overlaps of clinical manifestations.

A CASE OF REVERSIBLE ENCEPHALOPATHY DUE TO CEREBRAL AMYLOID ANGIOPATHY RELATED INFLAMMATION (CAA-RI)

Tommaso Filippo Nicoletti¹, E. Lozupone², V. Guglielmi², S. Gaudino², A. Evoli¹

¹ Neurology, Catholic University of the Sacred Heart, Rome, Italy

² Radiology, Catholic University of the Sacred Heart, Rome, Italy

Abstract: Here we present a patient with rapidly progressive cognitive decline, followed by focal neurological signs due to extensive asymmetrical bihemispheric lesions corresponding to areas of vasogenic edema. According to the recently revised clinical and neuroradiologic criteria, we diagnosed the disease as Cerebral Amyloid Angiopathy Related Inflammation (CAA-RI) and treated the patient with high dose steroids with good clinical response.

Background: Cerebral Amyloid Angiopathy Related Inflammation (CAA-RI) is a rare subtype of CAA.

Aims: To report the clinical and radiological findings of CAA-ri and to discuss diagnostic difficulties and clinical management.

Case report: A 71-year-old woman, with a history of well-controlled artery hypertension, presented with rapidly progressive cognitive decline and difficulty walking in the previous week. Neurologic examination showed left hemiparesis, hemi inattention and prosopagnosia. CSF examination showed elevated protein level (345 mg/dl, 20-40), no cells and normal glucose. Brain MRI revealed diffuse asymmetric (dx>sx) hyperintense signal alterations on T2-weighted images with subcortical distribution of both cerebral hemispheres, corresponding to vasogenic edema. No diffusion restriction on DWI sequences was documented. T1 post-contrast images showed a diffuse leptomeningeal enhancement. SWI sequences showed multiple cortical and subcortical hemosiderin deposits with supra- and subtentorial localization. Neuropsychological assessment revealed impaired attentive functions, difficulties in all visuo-spatial items, consistent with signs of left spatial hemi-neglect. According to the recent clinical and neuroradiologic criteria (1), we diagnosed Cerebral Amyloid Angiopathy Related Inflammation (CAA-RI). Clinical status significantly improved after pulse steroid therapy.

Conclusions: CAA-related inflammation is a rare condition. Early recognition of the disease is crucial to proper and prompt treatment. The differential diagnosis encompasses low-grade glioma, progressive multifocal leukoencephalopathy and posterior reversible encephalopathy syndrome. We confirm the validity of existing diagnostic criteria (1) with special reference to neuroradiological investigation, in order to avoid more invasive procedures and provide adequate treatment.

Figures: Brain CT and MR imaging in a 71-year-old woman with probable CAA-ri. Initial CT (a) shows an expansive hypodense subcortical lesion involving the right frontal and parietal lobes that corresponds to an area of high signal intensity on T2-weighted FLAIR image (b), ascribable to vasogenic edema. Contrast-enhanced T1 weighted image (c) shows slight leptomeningeal enhancement of the altered area. Susceptibility-weighted imaging (d) demonstrates multiple cortical–subcortical microbleeds in both brain hemispheres.

References: (1) Validation of Clinicoradiological Criteria for the Diagnosis of Cerebral Amyloid Angiopathy Related Inflammation, Auriel et al., JAMA Neurology 2015.

EVALUATION OF MULTIFREQUENCY BIOIMPEDANCE ANALYSIS (BIA) AS A POTENTIAL OUT-COME MEASURE FOR MUSCLE INVOLVEMENT IN MYOTONIC DYSTROPHY TYPE 1 (DM1): A SMALL PILOT STUDY

Alessia Perna¹, E. Rinninella², M. Cintoni², M. Ricci¹, T. Nicoletti¹, S. Rossi¹, G. Miggiano², A. Gasbarrini³, M. Mele³, G. Silvestri¹

¹ Dept. of Neurology - Catholic University of Sacred Heart - Rome

² Clinical Nutrition and Dietetics - Catholic University of Sacred Heart - Rome

³ Dept of Internal Medicine, Gastroenterology Area - Catholic University of Sacred Heart - Rome

Abstract: in DM1 progression of muscle involvement is slowly; current objective outcome measures are not able to detect significant variations in the time span of a therapeutic trial. Therefore we assessed the reliability of BIA as objective measure of muscle involvement, in parallel with MIRS score, which evaluates severity of muscle disease in DM1 patients. Preliminary data suggest that BIA might be a potential outcome measure of muscle disease progression in DM1.

Background: Myotonic dystrophy type 1 (DM1) is the most common adult form of autosomal muscular dystrophy in adults. Muscular Impairment Rating Scale (MIRS), hand-held dynamometer, and muscle MRI represent validated clinical tools to assess the severity of muscle impairment in DM1 patients. However, none of these tools appears sensitive enough to detect progression of muscle deterioration in DM1 patients in a relatively short time span characteristic of clinical trials.

Aim: we performed a pilot study in a small cohort of DM1 patients aiming to test the reliability of multifrequency bioimpedance analysis (BIA) in correlation with MIRS, in order to estimate the malnutrition risk among DM1 patients.

Materials and Methods: 30 DM1 patients (50% males), stratified according to MIRS, underwent a multifrequency bioimpedance analysis (BIA) carried out using BodyStat 5000 (Bodystat LTD), evaluating two lean body mass measures, Phase Angle (PhA) at 50 kHz and Impedance Ratio (IR) at 200 kHz and at 5 kHz. Nutritional risk screening (NRS-2002) and body mass index (BMI) were also assessed as malnutrition predictors. Results were analyzed using Kruskal-Wallis test ($p < 0.05$ significant).

Results: Median age at the visit was 49 ys (range 37-60). 10% of DM1 patients had MIRS score =2, 43.3% =3, 30% =4 and 16.7% =5. 83.3% of DM1 patients had an NRS <3, meaning a low nutritional risk, and only one patient was undernourished

(BMI<18.5). Statistical analysis documented a highly significant correlation between MIRS score, PhA and IR values [$p=0.0001$].

Discussion and Conclusion: The main findings of this observational study are that malnutrition risk and undernutrition were unfrequent in our DM1 population, so the tight correlation between BIA parameters (PhA and IR) and severity of muscular involvement (MIRS), suggests that BIA might be a useful not invasive outcome measure of muscle progression in DM1. The evidence of this correlation suggest to extend our studies on a larger cohort of DM1 patients, to detect the muscular involvement in a longer time.

References: Lukaski HC, Kyle UG, Kondrup J. Assessment of adult malnutrition and prognosis with bioelectrical impedance analysis: phase angle and impedance ratio. *Curr Opin Clin Nutr Metab Care.* 2017 Sep;20(5):330-339.

Mathieu J1, Boivin H, Meunier D, Gaudreault M, Bégin P. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. *Neurology.* 2001 Feb 13;56(3):336-40.

Sedehizadeh S1, Brook JD2, Maddison P3. Body composition and clinical outcome measures in patients with myotonic dystrophy type 1. *Neuromuscul Disord.* 2017 Mar;27(3):286-289.

POEMS SYNDROME: AN UNCOMMON CAUSE OF BILATERAL PAPHILLOEDEMA AND REDUCED VISUAL ACUITY

Angela Romano¹, M. Sabatelli¹⁻², G. Bisogni¹, A. Di Paolantonio¹, P. M. Rossini¹, M. Luigetti¹

¹ Institute of Neurology - Catholic University of The Sacred Heart, Pol. A. Gemelli Foundation - Rome

² NEMO (NEuroMuscular Omniculture) Clinical Center - Serena Onlus Foundation-Pol. A. Gemelli Foundation - Rome

Introduction: POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes) is a rare multisystemic disorder associated with a monoclonal plasma cell dyscrasia. Its main features include polyradiculoneuropathy, clonal plasma cell disorder, organomegaly, endocrinopathy and skin changes, but it's also possible to have papilloedema, extravascular volume overload, sclerotic bone lesions and thrombocytosis/polycythemia. Among the variety of disease manifestations, ocular signs and symptoms are more common than generally thought, affecting about half of all patients. Papilloedema is found in almost one-third of cases; other ocular symptoms include diplopia, blurred vision and ocular pain.



Objective: To describe a patient affected by POEMS syndrome presenting with bilateral papilloedema and severe loss of visual acuity.

Patients and Methods: A 40-year-old woman referred to our emergency room because of progressive visual loss and headache. She also complained a 5-month history of paresthesias, dysesthesias and distal weakness in lower limbs. Her past medical history was unremarkable except for hepatitis B.

Results: Neurologic examination revealed bilateral, distal muscle weakness, prevailing in lower limbs, paresthesias and dysesthesias with stocking distribution and generalized hypopallesthesia and areflexia. Cranial nerves were spared except for papilloedema with severe visual impairment. Extensive laboratory investigations revealed an IgA lambda monoclonal component in serum, a primary hypothyroidism and a thrombocytosis. Cerebrospinal fluid examination showed hyperproteinorrhachia without pleocytosis. Electrophysiological findings were suggestive of axonal and demyelinating sensory-motor neuropathy, more severe in lower limbs. A brain and spine MRI detected linear enhancement of the pachymeninges and enlargement and diffuse enhancement of the cauda equina nerve roots. A total body CT revealed splenomegaly, hepatomegaly, diffuse lymphadenopathy and minimal fluid effusion in the Douglas pouch. Visual evoked potentials showed bilateral absence of P100; ocular examination confirmed a severe bilateral visual loss (2/10).

Patient also underwent bone marrow aspiration, which revealed mild increase of plasma cell percentage, and immunophenotypic analysis of bone marrow, which didn't detect B-lymphocyte clonality; bone marrow biopsy was unremarkable.

Serum VEGF dosage was elevated and confirmed our clinical suspect of POEMS syndrome. Patient underwent high-dose chemotherapy (cyclophosphamide) followed by autologous peripheral blood stem cell transplantation. Six months follow-up showed slight improvement in limb weakness and in visual impairment.

Conclusions: POEMS syndrome should be considered in the differential diagnosis of patients with a bilateral papilloedema in which no other cause can be readily found, because its prompt treatment can determine improvement of neurologic manifestations reducing disability and preventing blindness.

- 
- References:** Dispenzieri A. POEMS syndrome: Update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2015 Oct;90(10):951-62.
- Kaushik M, Pulido JS, Abreu R, Amselem L, Dispenzieri A. Ocular findings in patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome. *Ophthalmology.* 2011 Apr;118(4):778-82.
- Kuwabara S, Misawa S, Kanai K, Suzuki Y, Kikkawa Y, Sawai S, Hattori T, Nishimura M, Nakaseko C. Neurologic improvement after peripheral blood stem cell transplantation in POEMS syndrome. *Neurology.* 2008 Nov 18;71(21):1691-5.



TOR VERGATA POLICLINICO ROMA

TMS EVALUATION IN MILD COGNITIVE IMPAIRED PATIENTS ACCORDING TO NEW CRITERIA FOR AD: A 36 MONTHS FOLLOW UP STUDY

Francesco Di Lorenzo, C. Motta, V. Ponzio, S. Bonni, C. Caltagirone, A. Martorana, G. Koch

Non-invasive Brain Stimulation Unit, Fondazione Santa Lucia Rome, Italy - Tor Vergata Policlinic, Rome - Rome

Background: Cortical plasticity mechanisms such as long-term potentiation (LTP), main neurophysiological correlates for learning and memory, can be assessed reliably and safely in humans by means of non-invasive repetitive transcranial magnetic stimulation. AD patients show a consistent impairment of LTP-like cortical plasticity. Such remarkable impairment of LTP-like cortical plasticity is independent from age of disease onset and is associated to a more aggressive clinical course.

Aim: In light of the new lexicon and the new diagnostic criteria, aim of the current work is to investigate the different outlines of cortical plasticity in cognitive impaired (CI) patients admitted for the first time in the memory clinic and stratified according to CSF biomarker profile; moreover we followed patients up to a period of three years to explore the relationship between neurophysiological and CSF biomarker and clinical progression.

Methods: 47 patients were recruited at memory clinic admitted for their first visit for complaining memory symptoms and underwent CSF sampling. They undertook investigation of LTP with intermittent Theta Burst Stimulation (iTBS). According to new criteria of AD we divided patients in basis of evidence of in vivo biomarkers (as assessed by CSF analysis) resulting in two groups: 1) Mild Cognitive Impaired (MCI) patients (n=22) and Prodromal AD (PROAD) patients (n=25). At 36 months the rate of converters to a state of dementia was obtained in both group. Finally a Kaplan Meier analysis was run in order to detect the predictor of clinical progression

Results: iTBS protocol showed differences among the two groups with a paradoxical reversal of LTP for PROAD and a poor response for MCI patients. The 80% of PROAD and the 57% of MCI patients converted to a state of dementia. LTP impairment was the only common feature between the converters in both groups. Kaplan-Meier analyses showed that in both group CI patients expressing the worst LTP values were the ones to progress faster in a 36 months time.

Conclusions: LTP impairment drives the clinical progression in CI patients at prodromal stages even without evidence of biomarker positivity, confirming its pivotal role in determining cognitive decline.



MULTIFOCAL MOTOR NEUROPATHY UNCOMMONLY OCCURRING AFTER ACUTE MOTOR AXONAL NEUROPATHY: TWO STAGES OF THE SAME DISEASE?

Silvia Bocci, F. Ginanneschi, G. Capoccitti, L. Franci, L. Africa, F. Giannini

Neurology and Clinical Neurophysiology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy

Background. AMAN and MMN share more common features than what previously assumed: both are characterized by exclusive motor involvement and association with anti-gangliosides antibodies, and have been included in the “nodo-paranodopathies”⁽¹⁻³⁾. We report the case of a young woman who developed definite MMN, some years after AMAN.

Case Report. A 35-years-old woman, reporting an episode of gastroenteritis one week earlier, was admitted due to burning pain in her upper limbs since 4 days, followed by severe hands weakness and diffuse distal paresthesia. The first electrophysiological study (EDX) showed absent CMAP in Median and Ulnar nerves, increased distal motor latencies, marked reduction of CMAP amplitudes and F wave absence in Peroneal and Tibial nerves without CB or sensory conduction abnormalities. CSF analysis and stool examination for *CJ* were negative, whereas serum anti-GM1 IgG were positive with a high-titre. Cervical MRI showed swelling and gadolinium-enhancing of anterior C7 left root. Due to rapid worsening up to flaccid tetraplegia, right facial nerve paresis, dyspnea, dysphagia and cardiac ventricular dysrhythmia, the patient was transferred to ICU and treated with intravenous immunoglobulins (IVIg) 2g/kg. A second EDX, 3 weeks after onset, revealed acute denervation activity more severe in distal upper limbs. The patient recovered with residual asymmetrical weakness and atrophy in hands and legs muscles. About 3 years later, the patient began to suffer from relapse of symptoms, such as worsening of distal weakness in right forearm and left leg, painful cramps and patchy paresthesia, often preceded by an infective illness. Despite no evidence of new EDX abnormalities and absence of serum anti-ganglioside antibodies (notably anti-GM1 or anti-GD1a IgM), whole-spine MRI showed gadolinium-enhancement of anterior lumbar roots. A first high dose steroid therapy had unremarkable effect, whereas IVIg (2 g/kg) induced clear clinical improvement. The short-time disease evolution from “stepwise” to “chronic” time course required a periodic IVIg treatment (2 g/kg every 4 weeks). After an attempt to reduce IVIg regimen, the patient experienced a premature “end-of-dose” relapse complicated by

right facial palsy and diplopia. The EDX follow up at this time, firstly revealed a definite motor CB in left Ulnar nerve.

Discussion. As pointed out by some authors various pathophysiological similarities support the hypothesis that AMAN and MMN are part of the same spectrum⁽¹⁻³⁾. Nevertheless, clinical continuity of such diseases has never been reported to our knowledge. History and clinical/electrofisiological findings of the current patient suggest the possibility that MMN could develop after AMAN.

References: Uncini A et al. Natura non facit saltus in anti-ganglioside antibody-mediated neuropathies. *Muscle Nerve* 2013;48(4):484-487.

Yuki N Acute Motor Axonal Neuropathy and Multifocal Motor Neuropathy: more in common than not. *Muscle Nerve* 2013;48(5):693-695.

Léger JM et al. The pathogenesis of multifocal motor neuropathy and an update on current management options. *Ther Adv Neurol Disord* 2015;8(3):109-122.

WOLFRAM SYNDROME: CLINICAL AND GENETIC FEATURES OF A NEW ADULT CASE

Giulia Peppoloni¹, I. Di Donato¹, A. Mignarri¹, F. M. Santorelli², M.T. Dotti¹

¹ Department of Medicine, Surgery and Neuroscience, University of Siena

² Molecular Medicine, IRCSS Stella Maris, Pisa

Background: Wolfram syndrome (WS) is a rare genetic disorder characterized by juvenile-onset diabetes mellitus, diabetes insipidus, optic nerve atrophy, hearing loss and neurological disturbances. Diabetes mellitus is typically the first manifestation, usually diagnosed around 6. Other common symptoms are urinary tract problems, ataxia and autonomic dysfunction. A Wolfram gene (*WFS1*) has been mapped to chromosome 4p16.1 which encodes an endoplasmic reticulum membrane-embedded protein. The prognosis is currently poor with the median age at death being 30 years (range 25-49).

Case report: We report a 25-year-old boy who presented with a juvenile-onset diabetes mellitus (age 6), sensorineural hearing loss at high frequencies, around age 14 and bilateral optic nerve atrophy from the age of 20. Around age 24 the patient suffered from bladder dysfunction and upper urinary tract dilatation; one year later central diabetes insipidus was diagnosed. At examination we observed scoliosis, ligamentous laxity, flatfoot and ogival palate; neurological exam showed limb ataxia, mydriasis, mild anisocoria (right

> left) and rotatory nystagmus. Brain MRI revealed bilateral optic nerve atrophy and loss of the physiological hyperintense signal of the neurohypophysis. Genetic investigation was performed; the patient carries an homozygous mutation in *WFS1* (c.2099G>A).

Discussion: We report the case of a typical presentation of a rare disease as Wolfram syndrome. The minimal criteria for diagnosis are juvenile-onset diabetes and optic atrophy, but additional features can be found, hence the acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness) is used. Our patient fulfilled all the criteria and genetic test led us to a certain diagnosis. Unfortunately there is currently no cure for WS, but there are treatments for some of the complications, as desmopressin and insulin for diabetes, hearing aids for deafness and catheterization for renal problems.

Conclusion: When we approach a patient with a juvenile-onset diabetes associated with optic nerve atrophy, the diagnosis of WS should always be considered and further investigations should be performed. Despite the absence of an effective treatment, an early diagnosis is important in order to limit associated complications, to improve the prognosis and to perform genetic counseling for family members.

EYE TRAKING AND SACCADES ANALYSIS IN THE CLINICAL PRACTICE

Domenica Zaino, A. Rufa

Eye tracking and Visual Application Lab (EVA Lab) – Neurology and Neurometabolic Unit, Department of Medical and Surgical Sciences and Neurosciences, University of Siena, Italy

Background: The analysis of eye movements is an important tool for the study of cognitive and motor brain functions.

Aims: Through the emergent eye-tracking technology, a reliable, user friendly and non-invasive method for the investigation of brain activity, clinicians might obtain powerful information about functioning of several areas and networks of the central nervous system (CNS). This diagnostic method allows to define the burden of neurodegenerative diseases on various networks and brain functions.

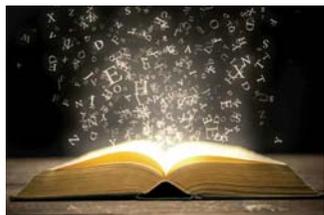
Materials and methods: *Eye-trackers* are special devices including a light source (often infrared light source), cameras tracking the image of the eye, software finding particular ocular structures and estimating the point of gaze. This examination is available for all collaborative patients able to maintain a sitting position. Chin and forehead rests are



applied to minimize head movement. We use specific tasks developed to investigate *prosaccades*, *antisaccades*, *trail-making-test eye-tracker version*, *memory-guided saccades* and *fixations*. Many parameters of the various tasks have been considering in the signal processing: latency, velocity, duration, amplitude, accuracy, gain. Saccades analysis are performed through a semiautomatic *ad-hoc* software by a trained neurologist.

Results: We found specific alterations of ocular movements in extrapyramidal pathologies (Parkinson's disease, atypical parkinsonisms), acquired or hereditary cerebellar affections (including spinocerebellar ataxias, spastic paraparesis), genetic neurometabolic defects.

Conclusions: Alterations of ocular movements may help to confirm diagnosis of neurological diseases especially those involving the CNS. Significant correlations are found between gaze control and cognitive functions. Eye tracking might be used even for a cognitive assessment “hand and speech free” in patients who lost motor and language function as in amyotrophic lateral sclerosis.



RINGRAZIAMENTI

SI RINGRAZIANO

FB HEALTH

NOVARTIS

TEVA



