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ABSTRACTS

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ASYMMETRY OF PERMUTATION ENTROPY IN EARLY CREUTZFELDT-JAKOB DISEASE: A CLUE TO A SPECIFIC PATHOLOGICAL PROCESS?

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Objective: We used permutation entropy (PE) to disclose abnormalities of cerebral activity in patients with early genetic or sporadic Creutzfeldt-Jakob disease (CJD), as compared to patients with steroid-sensitive subacute encephalopathies (SSE) and healthy controls (HC). Methods: We evaluated 16 EEG of CJD patients (7 males, 9 females; age 37-79 years, median 58), 20 of SSE patients (7 males, 13 females age 27-71, median 50), and 33 of HC (10 males, 23 females, age 46-70, median 56). Diagnosis of probable sporadic CJD was made on the basis of revised criteria (1) in 8 patients; genetic CJD was confirmed by mutation of PrP gene in 8. EEG of CJD patients were performed at an early stage and didn’t show periodic sharp wave complexes. Diagnosis of SSE was established on clinical (subacute evolution of neurological disorders) and laboratory data (serum positivity to anti-GAD, anti-VGKC, anti-NMDAR or anti-TPO). All SSE patients had prompt response to IV steroids; EEG was performed before steroid initiation. PE was estimated channel by channel, and average PE of all channels as well as the mean PE values of channels belonging to right and left hemispheres was calculated in all subjects. The following variables were analysed: age at inclusion, sex, total average PE and mean interhemispheric PE differences. Chi-square and one-way analysis of variance were performed to assess differences among groups, followed by a post-hoc test (Tukey-Kramer) for multiple comparisons. Outliers were detected with Tukey method. Significance level was set at 0.05.

Results: The groups did not differ significantly for age and sex. No outliers were detected for average PE; for interhemispheric PE differences, 4 outliers were identified and excluded (2 in SSE group and one each in CJD and HC groups). Average PE was significantly lower in CJD patients as compared to HC (mean 0.72, SD 0.03 vs. mean 0.75, SD 0.02, p=0.01). Mean interhemispheric PE difference was higher (mean 0.009, SD 0.006) in CJD patients as compared to both SSE (mean 0.005, SD 0.003) and HC groups (mean 0.004, SD 0.004) (p<0.02).

Discussion: The lower average PE value in CJD as compared to HC group demonstrates a reduction of EEG complexity that suggests a severe thalamo-cortical disconnection since the early phases of disease. Moreover, subjects with CJD showed a significant interhemispheric asymmetry in PE values, pointing towards the possibility that the pathological process of CJD may be initially asymmetric, as reported by MRI and PET studies (2,3).

References:

BRAIN AND MUSCLE BIOENERGETICS ABNORMALITIES IN DM1 PATIENTS


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Objective: To evaluate brain and skeletal muscle bioenergetics in patients with myotonic dystrophy type 1 (DM1).

Materials: 24 consecutive DM1 patients (14 males and 10 females), aged from 22 to 71 years (mean 38 years), were recruited at the IRCCS, Istituto delle Scienze Neurologiche di Bologna, Bologna.

Methods: All 24 DM1 patients underwent a standardized MR conventional imaging evaluation, and 22 patients underwent brain single voxel proton magnetic resonance spectroscopy (1H-MRS) with PRESS sequence (TR=1500 ms, TE=288 ms). (1) Fifteen subjects also performed skeletal muscle phosphorus (31P)-MRS at rest, during and post-aerobic exercise and, as previously described, we calculated bioenergetics parameters, such as the rate of PCr post-exercise resynthesis, reflecting mitochondrial ATP production. All MR acquisitions were performed by using a 1.5 T GE scanner.

Results: All patients showed typical white matter hyperintensities on T2-weighted imaging with variable degree of severity. 1H-MRS evaluations evidenced a pathological accumulation of lactate in the cerebral spinal fluid of lateral ventricles in 5 patients (Lac/H20=0.04±0.005, mean ±sd) and only trace levels in other 5. 31P-MRS in resting calf muscle showed a significant reduction of phosphocreatine (PCr)/inorganic phosphate ratio (5.04±2.08) compared to a sample of 14 age matched controls (7.17±1.03; p =0.002). Aerobic exercise in calf muscle was performed in 11 patients, disclosing a slow rate of PCr post-exercise resynthesis (45.90±21.67 sec vs 25.93±0.02 in controls; p<0.002).

Discussion: Our study is the first describing a pathological accumulation of brain lactate in lateral ventricles, an index of oxidative phosphorylation deficit. We also demonstrated an impairment of skeletal muscle bioenergetics, as previously reported in vivo and by plasmatic and biochemical studies. (3) These findings suggest a multisystem mitochondrial dysfunction in DM1 patients.

Conclusions: These findings provide new pathophysiological clues and suggest possible new therapeutic interventions for DM1.

References:

HIGH-DOSE THIAMINE AS POSSIBLE MEDICAL TREATMENT FOR SPINOCEREBELLAR ATAXIAS

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Thiamine (vitamin B1) is a cofactor of fundamental enzymes of energetic cellular metabolism; its deficiency causes disorders in peripheral and central nervous system. The role of thiamine has been described in spino-cerebellar ataxias: some studies reported normal thiamine values in blood but low levels in cerebrospinal fluid. Moreover, several authors observed dysfunction of pyruvate-dehydrogenase complex in Friedreich ataxia (FRDA). In previous papers, we described the improvement of fatigue and motor symptoms in some patients with spino-cerebellar ataxia type 2 (SCA2) and FRDA, treated for three months with intramuscular injections of thiamine. The aim of our study was to investigate the symptomatic effect of long-term treatment with thiamine in some types of spino-cerebellar ataxia.

Materials and Methods: From July 2012 we recruited twenty-three FRDA patients, two SCA2 patients and two patients with sporadic idiopathic ataxia. All the patients had been assessed at baseline with the Scale for the Assessment and Rating of Ataxia (SARA) and then have been continuously treated with i.m. 100 mg of thiamine twice a week, without any change to personal therapy. The patients were re-evaluated after one month and then every three months during treatment.

Results: In all the patients basal levels of plasma thiamine were normal. Thiamine treatment led to significant improvement of motor symptoms. In FRDA group, total SARA scores improved from 26.7±8.3 to 23.5±8.3 (p<0.0001, t-test for paired data). Moreover, 13 out of 17 patients, with absence of deep tendon reflexes at baseline, showed normal deep tendon reflexes after one month of treatment; swallowing improved in more than 50% of patients with dysphagic symptoms at baseline. At SARA scale both patients with SCA2 improved of 50%, while the two patients with sporadic ataxia improved of 25% and 50%.

Discussion: Long-term and continuous administration of high doses of thiamine was effective in improving motor symptomatology in ataxic patients; this clinical improvement was stable during follow-up. We hypothesize that a focal, severe thiamine deficiency due to a dysfunction of thiamine metabolism could cause a selective neuronal damage in the cerebral areas involved in spino-cerebellar degeneration, depending on different genetic mutations. The abnormalities in thiamine-dependent processes could be overcome by diffusion-mediated transport at supra-normal thiamine concentrations.

Conclusions: Thiamine could have restorative and neuroprotective action in spino-cerebellar ataxias. Further studies are necessary to exclude placebo effect and to investigate thiamine role in pathogenesis and neuroprotection in spino-cerebellar ataxias.

THE NOVEL GRN G.1959 1960DELGT MUTATION IS ASSOCIATED WITH BEHAVIOURAL VARIANT FRONTOTEMPORAL DEMENTIA

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Objectives: Mutations in progranulin gene (GRN) represent a common cause of autosomal dominant Frontotemporal dementia (FTD) and are associated with low plasma progranulin levels (1). Here, we describe two families with a novel mutation in GRN.

Case reports: Patient #1. Male, at 68 years developed initial language deficits, one year later showing markedly altered behaviour (including disperceptions, sexual disinhibition and imporarity). His family history was positive for dementia (mother and maternal aunt affected by Alzheimer’s disease and Lewy body dementia, respectively). Neurological examination was unremarkable and neuropsychological testing (MMSE = 28/30) showed disiblishion, lack of attention, and insufficient performance in daily self-care activities (ADL=5/6, IADL=2/8). MRI showed asymmetric frontal and temporal cortical atrophy (right>left). FDG-PET showed bilateral frontal and temporal hypometabolism. Cerebrospinal fluid biomarkers were normal (Amyloid beta=731 pg/ml; tau=181 pg/ml; Ptau=29 pg/ml). Patient #2. Male, age 66, suffering from relevant mood alterations, anosognosia and loss of personal interests, developed subsequently diffuse cognitive deficits. Neuropsychological assessment (MMSE 28/30) showed deficits in attention and executive functions with reduced daily-living activities (ADL 5/6, IADL 4/5). His family history was positive for FTD (father and sister). Electromyography and Magnetic Evoked Potentials were normal, while brain CT showed bilateral temporal atrophy. Brain FDG-PET, using SPM5 software, showed areas of hypometabolism mainly on the right side in fronto-temporal regions and thalamus, frontal cortex and insula (p<0.001).

Materials and Methods: Progranulin plasma levels were evaluated through an ELISA kit (Adipogene, Korea), after the ethical committee approval and patients’ consent, subsequently we sequenced Progranulin gene (GRN).

Results: Both patients met the criteria for probable bvFTD (2) and their progranulin plasma levels were below the detection threshold (<15ng/ml). We found a novel mutation in exon 5: g.1159_1960delTG, that leads to a frameshift, which in turn creates a stop codon (c.445_446delTG, p.Cys149fsX10). Two additional family members of Patient#1 were asymptomatic carriers of the mutation and they showed low plasma progranulin levels as well. Other family members who did not carry the mutation had normal progranulin plasma levels (>61 pg/ml).

Conclusion and discussion: Here, we described two patients with a novel mutation in GRN. Both families originate from the same region (central Italy), suggesting that they could derive from the same founder. Notably, progranulin plasma levels were undetectable, even in presymptomatic carriers, suggesting that biological changes associated with the mutation occur soon before clinical manifestations of the disease. In accordance with MRI data on other GRN mutation carriers, this new variant showed atypical atrophy (3).

References:

A GLOBAL IMMUNEDEFICIT IN ALZHEIMER AND MILD COGNITIVE IMPAIRMENT DISCLOSED BY A NOVEL DATA MINING PROCESS

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Background/Aim: A growing awareness exists that pro-oxidative state and neuroinflammation are both involved in Alzheimer’s Disease (AD) and (Mild) Cognitive Impairment (MCI). Due to the expected nonlinear correlations between oxidative and inflammatory markers in such complex diseases, we believe that the use of traditional statistics may be