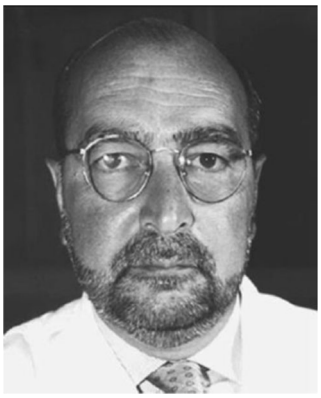
Neurological Sciences (2019) 40:231–234
https://doi.org/10.1007/s10072-019-3715-0

HIGHLIGHTS

Highlights of the Issue 2, 2019

Published online: 15 January 2019



Prof. Antonio Federico

REVIEW ARTICLES

Efficacy and safety of edaravone in treatment of amyotrophic lateral Sclerosis — a systematic review and meta-analysis

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https://doi.org/10.1007/s10072-018-3653-2
Based on the results of randomized, double-blind, placebo-controlled trials, the benefit and safety of edaravone in the treatment of amyotrophic lateral sclerosis remain controversial. The AA performed a meta-analysis to evaluate the efficacy and safety of edaravone in the treatment of this disease. They searched PubMed, the Cochrane Library, and Embase from the inception of electronic data to April 2018. We included randomized, double-blind, placebo-controlled trials reporting amyotrophic lateral sclerosis patients receiving 60-mg intravenous edaravone or intravenous saline placebo for 24 weeks. The primary efficacy evaluation was changed in Amyotrophic Lateral Sclerosis Functional Rating Scale score from baseline to after the trial. Measure of safety was the frequency of investigated adverse events and serious adverse events. Data synthesis and analysis and evaluation of risk of bias were performed using RevMan 5.3 software. Heterogeneity among studies was evaluated with the I2 statistic. A total of 367 patients were analyzed across three randomized controlled trials (183 patients receiving intravenous edaravone; 184 receiving placebo). A difference in ALSFRS-R score between groups at 24 weeks was found (mean difference [MD] = 1.63, 95% confidence interval [CI] 0.26–3.00, $P = .02$). No differences in the frequency of adverse events (odds ratio [OR] = 1.22, 95% CI 0.68–2.19, $P = .50$) or serious adverse events (OR = 0.71, 95% CI 0.43–1.19, $P = .20$) were found. Conclusion Intravenous edaravone is efficacious in amyotrophic lateral sclerosis patients, with no severe adverse effects. Additional reliable randomized controlled trials with larger sample sizes will further assess the efficacy and safety of edaravone in amyotrophic lateral sclerosis.

Vis-à-vis: a focus on genetic features of cerebral cavernous malformations and brain arteriovenous malformations pathogenesis

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https://doi.org/10.1007/s10072-018-3674-x
Cerebrovascular malformations include a wide range of blood vessel disorders affecting brain vasculature. Neuroimaging differential diagnosis can result unspecific due to similar phenotypes of lesions and their deep localization. Next-generation sequencing (NGS) platforms simultaneously analyze several hundreds of genes and can be applied for molecular distinction of different phenotypes within the same disorder's macro-area. The AA discuss about the main criticisms regarding molecular bases of cerebral cavernous malformations (CCM) and brain arteriovenous malformations (AVM), highlighting both common pathogenic aspects and genetic differences leading to lesion development. Many recent studies performed on human CCM and AVM tissues aim to detect genetic markers to better understand molecular bases and pathogenic mechanism, particularly for sporadic cases. Several

genes involved in angiogenesis show different expression patterns between CCM and AVM, and these could represent a valid starting point to project a NGS panel to apply for differential cerebrovascular malformation diagnosis.

ORIGINAL ARTICLES

The clinical and imaging features of hypertrophic pachymeningitis: a clinical analysis on 22 patients

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https://doi.org/10.1007/s10072-018-3619-4

Objective To explore the clinical and imaging features of patients with hypertrophic cranial pachymeningitis (HCP). Methods A retrospective study was performed on 22 patients with HCP diagnosed at the Affiliated Hospital of Xuzhou Medical University from February 2014 to September 2017. Results A headache was present as an initial symptom in 18 patients. The headache was associated with the loss of vision (2 cases), facial pain (1 case), and unsteady walking (1 case). Other symptoms included cranial nerve dysfunction (15 cases), cerebellar ataxia (4 cases), and sinus thrombosis (3 cases). In the laboratory tests, 7 patients showed an increased number of white blood cells, higher levels of C-reaction protein (CRP), and erythrocyte sedimentation rate (ESR). An elevated level of immunoglobulin G4 (IgG4) and the presence of the anti-neutrophil cytoplasmic antibody (ANCA) were found in 3 and 2 patients respectively. There were 17 patients who had abnormalities in their cerebrospinal fluid (CSF) on lumbar puncture. On magnetic resonance imaging (MRI), a local or generalized thickening was observed in the cerebral falx, the tentoriumof the cerebellum, the fronto-parietal lobe, the occipito-parietal lobe, and the dura of skull base. A dural biopsy obtained in one case showed a variety of inflammatory changes. An immunohistochemical analysis revealed the positivity of CD138, IgG, and IgG4 in some cells. All 22 patients had a good response to corticosteroids. Conclusion HCP mainly leads to a headache and the paralysis of multiple cranial nerves. A biopsy and MRI are often required and serve as the basis for the diagnosis and effective therapy.

Association of olfaction dysfunction with brain microstructure in prodromal Parkinson disease

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https://doi.org/10.1007/s10072-018-3629-2

Although olfaction dysfunction is now considered as an established clinical marker of prodromal Parkinson disease (PD), little is known about the neural underpinnings of olfaction dysfunction in the prodromal phase of PD. The aim of this study was to examine the microstructural association of olfaction in prodromal PD compared to early stage drug-naïve PD patients. Methods Diffusion MRI connectometry was conducted on 18 early PD and 17 prodromal PD patients to investigate the differences in group in terms of altered connectivity, i.e., integrity of white matter tracts, and subsequently to study the correlation of University of Pennsylvania Smell Identification Test (UPSIT) score to white matter integrity in each group using a multiple regression model considering age, sex, RBD, and MoCA, as covariates. Individuals with prodromal PD had significantly higher quantitative anisotropy (QA) comparing with PD patients in bilateral middle cerebellar peduncles and right arcuate fasciculus. Multiple regression analysis in prodromal PD demonstrated positive association between UPSIT score and connectivity in left and right subgenual cingulum, right inferior fronto-occipital fasciculus, left corticospinal tract, left parietopontine, left corticothalamic tract, and the body and the splenium of corpus callosum.

Conclusion These results indicate that PD and prodromal PD patients, which were matched for sex, UPSIT, and MoCA scores, have different white matter fiber architecture. Thus, it is postulated that olfaction dysfunction in prodromal and early clinical phases of PD may involve distinct pathogenesis. Increased network connectivity in prodromal and early PD may suggest the neural compensation.

Factors associated with freezing of gait in patients with Parkinson's disease

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https://doi.org/10.1007/s10072-018-3625-6

Freezing of gait (FOG) is a common and debilitating problem in patients with Parkinson's disease (PD). The aim of this study was to estimate the prevalence of FOG, and to identify factors that independently contribute to FOG in patients with PD. Method We included 157 PD patients. FOG was assessed using the FOG Questionnaire (FOG-Q). Patients with or without FOG were defined as item 3 in the FOG-Q. One hundred eleven (70.7%) out of 157 PD patients presented with FOG. Patients with FOG were older, had long disease duration, were taking higher doses of dopaminergic agents, and had higher motor and non-motor scores than those without FOG.

Multivariate linear regression analysis showed that high modified Hoehn and Yahr (mHY) stage, Unified PD Rating Scale (UPDRS) part II score, and non-motor symptom assessment scale for PD (NMSS) total score were significant predictors of a high FOG-Q score. Patients with FOG had significantly higher scores for cardiovascular, gastrointestinal tract, urinary, and miscellaneous NMSS domains than those without FOG. FOG in PD was associated with higher mHY stage,

UPDRS part II score, and total NMSS score. Therefore, clinicians should consider non-motor, motor features and activities of daily living states for the proper management of FOG.

A novel homozygous nonsense mutation in CCDC88A gene cause PEHO-like syndrome in consanguineous Saudi family

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https://doi.org/10.1007/s10072-018-3626-5

Progressive encephalopathy, edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome is an unusual Mendelian phenotype of unidentified origin that causes profound intellectual disability, optic nerve/cerebellar atrophy, epileptic seizures, developmental progress, pedal edema, and early death. Uncharacteristic affected individuals are often classified as having PEHO-like syndrome, although they may be misdiagnosed as having epileptic encephalopathy, a potential result of early birth. In this study, we report a consanguineous Saudi family with a novel homozygous nonsense mutation of the CCDC88A gene causing PEHO-like syndrome.

The children were suffering from developmental delay, epilepsy, mental disability, optic nerve/cerebellar atrophy, and pedal edema. Whole exome sequencing was conducted for the members of the family who have the disorder to study the novel mutation. Whole exome sequencing data analysis, confirmed by subsequent Sanger sequencing validation, identified a novel homozygous nonsense mutation c. 1292G > A, which was caused by p.Trp431* stop gain. This mutation was ruled out in 100 unrelated healthy controls. The nonsense homozygous mutation detected in this study has not yet been reported as pathogenic in the literature or various databases. In conclusion, a complete loss of protein function due to premature stop gain was caused by a mutation in exon 12 of CCDC88A. This loss may lead to PEHO phenotype. CCDC88A gene may therefore play an important and critical role for multiple aspects of normal human neurodevelopment.

Lack of association between dopamine transporter loss and non-motor symptoms in patients with Parkinson's disease: a detailed PET analysis of 12 striatal subregions

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https://doi.org/10.1007/s10072-018-3632-7

Patients with Parkinson's disease (PD) present a variety of non-motor symptoms. However, it remains unclear whether dopamine depletion is related to non-motor symptoms, and which non-motor symptoms are significantly dependent on dopaminergic deficit. Forty-one patients with PD who underwent positron emission tomography imaging of dopamine transporters (DATs) were recruited for this study. The striatum was divided into 12 subregions, and DAT activity, as striatal dopaminergic concentration, was calculated in each subregion. In addition to measuring motor symptoms using the Unified Parkinson's Disease Rating Scale-part III (UPDRS-III), various non-motor symptoms were assessed using the Montreal cognitive assessment, frontal assessment battery, Beck depression inventory (BDI), Beck anxiety inventory, PD sleep scale (PDSS), PD fatigue scale, and non-motor symptoms scale (NMSS) for PD. For simple linear regression analyses, dopaminergic depletion in all striatal subregions was negatively correlated with the UPDRS-III score. The most relevant non-motor symptom assessment related to dopaminergic loss in the 12 subregions was NMSS, followed by BDI and PDSS. However, following multiple linear regression analyses, dopaminergic depletion in the 12 striatal subregions was not related with any of the non-motor symptoms. Conversely, dopaminergic deficit in the right anterior and posterior putamen was associated with the UPDRS-III score. Striatal dopaminergic depletion was not significantly correlated with any of the various non-motor symptoms in PD. Our findings suggest that non-dopaminergic systems are significantly implicated in the pathogenesis of non-motor symptoms in patients with PD.

Intrathecal nusinersen treatment for SMA in a dedicated neuromuscular clinic: an example of multidisciplinary and integrated care

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https://doi.org/10.1007/s10072-018-3622-9

Nusinersen is now available in Italy for all SMAtypes. We describe the experience with intrathecal treatment with nusinersen in 50 patients with SMA at the NEMO Center (NEuroMuscular Omniservice Clinical Center) in Milan, a neuromuscular patient centered clinic hosted within Niguarda Hospital, a National Public General Hospital. Our results indicate that the pathway of care described outweighs the burden due to the repeated intrathecal injections. Irrespective of age and severity, the treatment is feasible, accessible, and replicable provided that there is a multidisciplinary team having experience and training in SMA.

Clinical variability of children with anti-N-methyl-D-aspartate receptor encephalitis in southern Brazil: a cases series and review of the literature

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https://doi.org/10.1007/s10072-018-3648-z

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated disease of the central nervous system (CNS). The aim of this study was to describe the variability of clinical presentation in anti-NMDAR encephalitis, treatment and outcomes in a case series of children and adolescents. Retrospectively the AA analyze patients diagnosed with anti-NMDAR encephalitis, from 2010 to 2018. The study population consisted of nine children with anti-NMDAR encephalitis from southern Brazil, six females and three males, aged 5 months to 16 years (mean 5 years). The time of follow-up varied between 1 and 7 years, with a mean of 3 years. The most frequent first manifestation consisted of seizures. All patients described had psychiatric symptoms and a wide spectrum of neurologic findings. Five patients had unilateral symptoms. Magnetic resonance imaging and electroencephalogram were normal in most patients. Cerebrospinal fluid pleocytosis occurred in five patients. All patients were administered immunoglobulin and/or steroids. Seven patients (78%) required cyclophosphamide and/or rituximab. Almost half of the patients fully recovered from all symptoms. A wide variety of symptoms were observed in this study and, although unilateral symptoms are rarely reported in the literature, a high frequency was observed among Brazilian children. Alternatives to first-line therapy should be considered in patients with clinical suspicion, even if they have not had a good response with first-line therapy.

MR evaluation of encephalic leukoaraiosis in sudden sensorineural hearing loss (SSNHL) patients

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https://doi.org/10.1007/s10072-018-3647-0

Epidemiological evidence suggests a strict correlation between sudden sensorineural hearing loss (SSNHL) and cerebrovascular disorders. Leukoaraiosis represents a diffuse alteration of the periventricular and subcortical white matter. The aim of our study was to verify if the presence of white matter hyperintensity (WMH) was higher in patients affected by SSNHL compared to controls and evaluate the correlation betweenWMH and the cardiovascular risk factors, hearing level, and the response to therapy in SSNHL patients. The study group included 36 subjects affected by unilateral SSNHL. Thirty-six age- and sex-matched normal subjects with a negative history of SSNHL were used as controls. All patients underwent magnetic resonance imaging (MRI) (1.5 Tesla GE Signa) and the extent of leukoaraiosis was assessed with the Fazekas scale. The results of the present study demonstrate a high prevalence of WMH in SSNHL patients compared to controls confirming the hypothesis of a vascular impairment in SSNHL patients. The higher recovery rate in patients with greater periventricular white matter hyperintensity (PWMH) may suggest a vascular etiology that is still responsive to medical treatment.

BRIEF COMMUNICATION

The performance of patients with Parkinson's disease on the Face-Name Associative Memory Examination

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https://doi.org/10.1007/s10072-018-3560-6

In this study, the AA examined the performance of patients with Parkinson's disease (PD) with different cognitive profiles on the Face-Name Associative Memory Examination (FNAME). They evaluated 71 patients with a comprehensive neuropsychological battery. The results revealed that the group with executive and additional visuospatial deficits demonstrated significantly lower scores on FNAME. This finding indicates the possible clinical utility of FNAME for screening patients with PD with distinct cognitive profiles.