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HIGHLIGHTS

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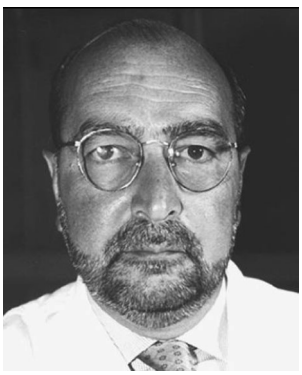

Antonio Federico
Editor-in-Chief

REVIEW ARTICLES

Genetic neuromuscular disorders: living the era of a therapeutic revolution. Part 1: peripheral neuropathies

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Recent advances in pathophysiological and genetic mechanisms of some neuromuscular diseases and a rapid progress in new pharmacological technologies led to an accelerated development of innovative treatments, generating an unexpected therapeutic revolution. In part 1, we report already commercially available drugs, just approved drugs and new therapeutic promises in the treatment of peripheral neuropathies. Hereditary transthyretin amyloidosis (hATTR) is a devastating disease due to amyloid accumulation in peripheral nerves, heart and autonomic system. The first specific drug approved for hATTR was tafamidis, a TTR tetramer stabilizer. In 2018, the positive results of two phase 3 trials have been reported leading to start of regulatory approval route for inotersen, an antisense oligonucleotide and patisiran, the first-ever RNA interference (RNAi) therapeutic. System biology targeting approach has indicated baclofen, naltrexone and sorbitol in combination (PXT3003) as candidate drugs for Charcot–Marie–Tooth disease type 1A. This hypothesis was confirmed in experimental models and in phase 2 and 3 clinical trials. Givosiran, another RNAi therapeutic, targeting 5-aminolevulinic acid synthase, has been positively tested in acute intermittent porphyria in phase 1/2 and ongoing phase 3 trials. Although allogenic hematopoietic stem cell transplantation resulted recently a long-term therapy in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), a new strategy is liver transplantation which is able to revert the severe biochemical and clinical imbalance of the disease. Recently, a gene therapy has been tested in a MNGIE murine model, indicating that it may become a new therapeutic option.

Genetic neuromuscular disorders: living the era of a therapeutic revolution. Part 2: diseases of motor neuron and skeletal muscle

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https://doi.org/10.1007/s10072-019-03764-z
This is the second part of a two-part document intended to discuss recent therapeutic progresses in genetic neuromuscular disorders. The present review is for diseases of motor neuron and skeletal muscle, some of which reached recently the most innovative therapeutic approaches. Nusinersen, anSMN2 mRNA splicing modifier, was approved as first-ever therapy of spinal muscular atrophy (SMA) by FDA in 2016 and by EMA in 2017. The orally administered small-molecule risdiplam, which increases SMN protein levels similarly but also in peripheral organs, is tested in ongoing phase 2 and 3 trials. After positive results with phase 1 treatment with AAV9-SMN, the first gene therapy for SMA, a phase 3 clinical trial is ongoing. Ataluren is the first approved drug for Duchenne muscular dystrophy (DMD) patients with premature stop codon mutations and its indication has been recently extended since the age of 2 years. Exon skipping technology was and is currently tested in many phase 3 trials, and

eteplirsen received a conditional approval by FDA for patients amenable to exon 51 skipping, but not by EMA. Many other compounds with different mechanisms of action are now tested in DMD byphase2 and 3 trials, including phase 1 gene therapy. Other innovative approaches are under investigation, i.e., gene therapy in X-linked myotubular myopathy and Pompe disease, and antisense oligonucleotides in myotonic dystrophy type1. Positive evidences are discussed about lamotrigine and ranolazine in non-dystrophic myotonias, chaperons in Pompe disease, and nucleosides in mitochondrial DNA depletion induced by thymidine kinase 2 deficiency.

ORIGINAL ARTICLES

Migraine and subclinical atherosclerosis: endothelial dysfunction biomarkers and carotid intima-media thickness: a case-control study

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https://doi.org/10.1007/s10072-019-3710-5

Background Migraine is a common neurovascular disease associated with vascular risks, especially in young adult females, but the mechanism underlying these associations remains unknown. This study evaluated the relationships between plasma endothelial dysfunction biomarkers and carotid intima–media thickness (IMT) in young adult females with migraine. Methods This case–control study included 148 female patients (age range: 18–50 years). Migraine was diagnosed according to the International Headache Society-IIIb criteria. Endothelial dysfunction biomarkers, such as von Willebrand factor (vWF), Creactive protein (CRP), homocysteine, total nitrate/nitrite concentration, and thiobarbituric acid-reactive substances (TBARS), were evaluated in plasma. Carotid IMT was measured by a radiologist with sonography. Results The CRP,TBARS,vWF, and IMTlevels were increased in the migraine compared with the control group ($p<0.001$, $p= 0.02$, $p<0.001$, and $p<0.001$, respectively). After adjusting for confounders, multiple linear regression analysis revealed that systolic arterial blood pressure, CRP, vWF, TBARS, and right and left internal carotid artery (ICA) IMT were independently positively correlated with migraine ($p<0.01$, $p=0.004$, $p=0.023$, $p=0.024$, $p=0.032$, and $p=0.048$, respectively). Multiple logistic regression analysis revealed that right ICA IMT was independently associated with ergotamine and triptan and left ICA IMT was independently associated with ergotamine ($p=0.013$, $p=0.026$, and $p=0.017$, respectively). In addition, significant correlations were found between LDL lipoprotein and carotid IMT in the migraine group ($p<0.05$). Conclusions Carotid IMT enhancement and elevated TBARS, vWF, and CRP levels in migraine subjects during a migraine attack could be regarded as consequences of migraine attack pathophysiology. The independent associations between triptan and ergotamine consumption and enhanced carotid IMT suggest that repeated use of these vasoconstrictive antimigraine agents may have additional effects on carotid IMT.

Evaluation of anxiety and depression scales and quality of LIFE in cervical dystonia patients on botulinum toxin therapy and their relatives

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In this study, quality of life and psychiatric comorbid disorders were investigated in patients with cervical dystonia and their spouses and we also investigated the effect of botulinum toxin (BTX) treatment on these parameters. Material and method Thirty patients with cervical dystonia (CD) on BTX treatment and their spouses (n=30) were included. Beck Depression Scale(BDS), State-Trait Anxiety Inventory Iand II (STAI-I,STAI-II), Hospital Anxiety Scale (HAS), Hospital Depression Scale (HDS) for psychiatric comorbid disease assessment, Toronto Western Spasmodic Torticollis Scale (TWSTRS) for disease ctivity assessment, and Craniocervical Dystonia Questionnaire (CDQ-24), Cervical Dystonia Impact Profile (CDIP-58), and Short Form 36 (SF-36) questionnaires for quality of life assessment were used. BDS, STAI-I and STAI-II, HAS, HDS, and SF-36 scales were also obtained from the spouses. The same tests were applied both before and 8 weeks after the BTX treatment. Conclusion In our study, an increase in psychiatric comorbid disorders such as depression and anxiety was observed and the quality of life was adversely affected in all areas in patients. In the spouses of the patients, the rates of psychiatric comorbid disorders such as depression and anxiety were found to be increased when compared to healthy subjects while vitality, mental health, and general health perception were found to be negatively affected. Patients showed improvements in anxiety level, disease activity, and overall quality of life scales after BTX treatment.

Exploring the feasibility of a mild and short 4-week combined upper limb and breathing exercise program as a possible home base program to decrease fatigue and improve quality of life in ambulatory and non-ambulatory multiple sclerosis individuals

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Purpose To evaluate the feasibility of a combined upper limb and breathing exercise for a home-based program and to explore its effect on primary fatigue and quality of life in ambulatory and non-ambulatory individuals with multiple sclerosis (MS) in a short time. Method Nineteen individuals with MS were assigned

into semi-controlled pre-post feasibility study based on Expanded Disability Status Scale (EDSS) status and divided into two groups: exercise (five ambulatory, five non-ambulatory; EDSS 1.0–8.0) and related control with no exercise (four ambulatory, five non-ambulatory; EDSS 1.0–7.5). Exercise group performed combined upper limb and breathing exercise in a controlled group (2 days/week, 60 min/session) accompanied by independent home exercise (3 days/week, ≥20 min/session). Participants underwent measures of fatigue impact (Modified Fatigue Impact Scale(MFIS) and quality of life (RAND Medical outcomes study 36-item short-form health survey (SF-36)) before and aftera 4 week period. Results The MFIS (physical, psychosocial, total) showed statistically significant group-by-time interaction in ambulatory (p= 0.033, d=1.60; p=0.039, d=1.59; p=0.033, d=1.62) and non-ambulatory individuals (p=0.009, d=2.42; p=0.018, d= 1.96; p=0.0008, d=3.92). Physical functioning (SF-36) showed statistically significant group-by-time interaction in ambulatory (p=0.014, d=2.14) but no significance in non-ambulatory (p=0.368, d=0.68) individuals. Despite the absent statistical significance, there were large intervention effects on MFIS cognitive scores for ambulatory (d=1.28) and non-ambulatory (d=1.47), and on other SF-36 scores for ambulatory (general health: d=1.76 and pain: d=1.02) and non-ambulatory (physical limitation: d=1.03 and emotional well-being: d=0.94) individuals. Conclusion Our 4-week program reduced some aspects of fatigue and improved some aspects of quality of life in a small group of ambulatory and non-ambulatory individuals with MS. Good feasibility and significant positive changes from baseline warrant further exploratory work.

What is the role of diffusion tensor imaging(DTI) in detecting subclinical pyramidal tract dysfunction in Behçet's and neuro-Behçet's cases?

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The aim of this study is to investigate the pyramidal tract integrity with DTI in Behçet's and neuro-Behçet's cases. The AA performed this technique in two subgroups of neuro-Behçet's patients (parenchymal and vascular), and Behçet's cases without neurological involvement and control group. Totally, 28 patients were investigated. The control group was composed of 14 healthy people. Cranial MR and DTI were performed in three patient groups and the control group. At DTI, circular regions of interest (ROI) were symmetrically drawn on axial slices on the left and right sides along the pyramidal tract pathway at two levels: middle one third of the cerebral peduncle and posterior limb of the internal capsule. Fractional anisotropy (FA) values for each ROI were obtained by averaging all voxels within the ROI. Calculated FA values on both sides (left and right) of the posterior limb of the internal capsule and cerebral peduncle are significantly lower in all three patient groups when compared to the control group. But there is no any difference of FA values in the selected brain regions of three patient groups. The study demonstrates that DTI can detect subclinical pyramidal tract dysfunction in neuro-Behçet's and Behçet's patients. Detection of subclinical nervous system involvement is crucial for morbidity in Behçet's disease. For this reason, studies based on DTI, which include a large number of patients and explore different brain regions, are needed to guide clinicians.

Dementia: new vistas and opportunities

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Over the past four decades, Alzheimer disease has become near synonymous with dementia and the amyloid/tau hypothesis as its dominant explanation. However, this monorail approach to etiology has failed to yield a single disease-modifying drug. Part of the explanation stems from the fact that most dementias in the elderly result from interactive Alzheimer and cerebrovascular pathologies. Stroke and dementia share the same risk factors and their control is associated with a decrease in stroke and some dementias. Additionally, intensive control of risk factors and enhancement of protective factors improve cognition. Moreover, anticoagulation of atrial fibrillation patients decreases their chance of developing dementia by 48%. Preliminary data suggest that treating blood pressure to a target of 120 mmHg systolic compared to a target of 140 mmHg decreases the chances of mild cognitive impairment by 19%. The Berlin Manifesto establishes the scientific bases of preventing dementia by preventing stroke. Enlarging our vista of dementia to include cerebrovascular disease offers the opportunity of preventing not only stroke, but some dementias, beginning now.

Typical clinical and imaging manifestations of encephalitis with anti-γ-aminobutyric acid B receptor antibodies: clinical experience and a literature review

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Objective To explore the clinical, imaging, and electroencephalogram (EEG) findings, as well as the treatment and prognosis of five patients with anti-γ-aminobutyric acid B receptor (GABABR) encephalitis and review the current literature to gain a deeper understanding and improve the clinical diagnostic ability of the disease. Methods Clinical data such as blood examination, imaging, computed tomography (CT), EEG, and magnetic resonance imaging (MRI) findings from five patients with anti-GABABR encephalitis were retrospectively analyzed. Results Based on the imaging data, autoimmune encephalitis with anti-GABABR antibodies displayed subacute onset of episodic memory loss, seizures, and confusion, in addition to signal changes in the medial temporal lobe and/or

hippocampus. Anti GABABR antibodies were found in blood and cerebrospinal fluid (CSF) in all five patients, although the CSF leukocyte count and the levels of protein, sugar, and chloride showed no obvious abnormalities. On MRI, only two patients presented with abnormal signals in the medial temporal lobe and/or hippocampus. The EEG showed a slow wave rhythm in all five patients. After treatment with methylprednisolone pulse therapy combined with antiepileptic treatment, all five patients recovered well, without any complications. Conclusions Autoimmune encephalitis with anti-GABABR antibodies may be a severe and refractory disease. Anti-GABABR antibodies tested in CSF and serum play a crucial role in the definitive diagnosis and treatment of autoimmune encephalitis. Early treatment is of vital importance to avoid serious complications and neurological sequelae

Expression analysis of long non-coding RNAs and their target genes in multiple sclerosis patients

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Multiple sclerosis (MS) is a progressive chronic autoimmune-mediated disease. Recently, long non-coding RNAs (lncRNAs) are characterized to participate in the adjustment of immune responses. Here, the AA evaluated the expression levels ofGSTT1-AS1and IFNG-AS1 lncRNAs and their targets (TNF and IFNG, respectively) in Iranian MS patients. In this case-control study, 50 relapsing-remitting MS patients and 50 healthy subjects were recruited. Expressions of GSTT1AS1andIFNG-AS1lncRNAs, as well as TNF and IFNG genes, were assessed in their peripheral blood samples by SYBR Green based Real-time quantitative PCR. Expression levels of GSTT 1-AS1 and IFNG-AS1l nc RNAs were both significantly down regulated (p values 0.032 and 0.013, respectively). On the other hand, the expression of TNF and IFNG showed increased levels, however, did not reach statistical significance after our analysis ($p>0.05$). Spearman correlation analysis showed that GSTT1-AS1 had a significant positive moderate correlation with IFNG-AS1 ($r=0.541$, $p<0.0001$), IFNG ($r=0.329$, $p=0.001$), and TNF ($r=0.204$, $p=0.041$). Also, IFNG-AS1 revealed the same correlation with IFNG ($r=0.475$, $p<0.0001$) as well as TNF ($r=0.399$, $p<0.0001$). Furthermore, GSTT1-AS1($r=0.313$, $p=0.027$) and (IFNGr=0.478, $p<0.0001$) demonstrated a significant positive correlation with age at onset. Briefly, the current study provided for the first time dysregulation of GSTT1-AS1 and IFNG-AS lncRNAs network in MS, which highlights the significant role of epigenetic pathways in this autoimmune disorder. Larger sample size and further investigation assays could shed light on the underlying mechanisms in this area of science.

Methylphenidate modifies activity in the prefrontal and parietal cortex accelerating the time judgment

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Methylphenidate produces its effects via actions on cortical areas involved with attention and working memory, which have a direct role in time estimation judgment tasks. In particular, the prefrontal and parietal cortex has been the target of several studies to understand the effect of methylphenidate on executive functions and time interval perception. The current study investigates the influence of the acute use of methylphenidate in both performance and judgment in the time estimation interpretation through the alpha band absolute power activity in the prefrontal and parietal cortex. This is a double-blind, crossover study with a sample of 32 subjects under control (placebo) and experimenta l(methylphenidate) conditions with absolute alpha band power analysis during a time estimation task. The AA observed that methylphenidate does not influence task performance ($p >0.05$), but it increases the time interval underestimation by over 7s ($p<0.001$) with a concomitant decrease in absolute alpha band power in the ventrolateral prefrontal cortex and dorsolateral prefrontal cortex and parietal cortex ($p <0.001$). Acute use of methylphenidate increases the time interval underestimation, consistent with reduced accuracy of the internal clock mechanisms. Furthermore, acute use of methylphenidate influences the absolute alpha band power over the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and parietal cortex.

Pictures portrayed by children with migraine with aura: a Turkish case series

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https://doi.org/10.1007/s10072-019-3713-2

Background Migraine is one of the most debilitating disorders with its chronic nature seen in childhood characterized by episodic bilateral or unilateral throbbing pain on the head that strikes at any time. It is divided into two categories as with or without aura and is diagnosed according to the 2013 International Headache Society criteria. Aim and method This study aims to present the pictures depicted by adolescents aged 14–18 who were diagnosed with migraine with visual aura by Ankara Training and Research Hospital Child Neurology Department. Results They were told to draw their visual auras as a picture that they depict or as a draft via changing another picture. In this article, five adolescents with migraine and their pictures related to their visual aura were presented. Conclusion

The diagnosis of migraine with visual aura in patients under18years of age would be supported by picturing of their visual images. Thus, pediatric patients could better express themselves and the clinician would better manage the process both in diagnosis and follow-up of the migraine with aura.

BRIEF COMMUNICATIONS

Migrants seeking help for cognitive disturbances: exploratory data from an Italian memory clinic

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Introduction The phenomenon of dementia occurring in migrants and minority groups constitutes a n emerging issue for Western countries. Nevertheless, it has been poorly explored from the perspective of Breal-world clinical services. The AA aimed to quantify the number of migrants from LMIC attending an Italian university memory clinic and to document its modifications over time. Methods All the subjects undergoing a first neurological and cognitive assessment between 2001and 2017were considered for the present analyses. Results The proportion of subjects from LMIC performing a first cognitive evaluation was found to remain substantially stable between 2001 and 2017. No statistically significant difference was found between BHIC and BLMIC individuals with regard to sociodemographic and clinical characteristics. Conclusion These findings seem to indicate that cognitive disorders in LMIC migrants still constitute a marginal public health issues for Italian dementia services. Nevertheless, the identification of eventual sociocultural and healthcare barriers may help to understand the real magnitude and relevance of this phenomenon.

Crossed obsessive-compulsive personality disorder and impaired theory of mind in temporal lobe epilepsy

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People with epilepsy often suffer psychiatric symptoms or exhibit maladaptive personality characteristics which can impact them more than seizures. This case illustrates a selective association of a Theory of Mind dysfunction, including an impaired comparison of reality and others' behavior, with an obsessive-compulsive personality disorder in a patient with left temporal lobe epilepsy and crossed cognitive functions. The patient revealed visual memory deficits and impaired interpretation of other people's behavior, mental rigidity, and a tendency to formulate inflexible judgements. Moreover, she shows impairment in understanding and sharing the emotional states of others in reference to herself (Empathic Quotient); her social relations are limited to her parents. Patients with right temporal lobe epilepsy frequently report persistent and rigid actions and thoughts, and this can have substantial psychological and social consequences for every day life. The AA suggest that this could be a case of crossed cognitive functions, in particular ToM, and crossed psychobehavioral functions linked to right-hemisphere damage.

Effect of pallidal deep-brain stimulation on articulation rate in dystonia

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Pallidal deep-brain stimulation of the internal globus pallidus (GPi-DBS) is an effective treatment for dystonia. However, GPiDBS may cause important stimulation-induced side effects such as hypokinetic dysarthria, which is particularly manifested by articulation rate abnormalities. However, little data regarding the effect of the location of the electrode and stimulation parameters for pallidal stimulation on articulation rate in dystonia is available. Speech data were acquired from 18 dystonic patients with GPiDBS and 18 matched healthy controls. Each of dystonic patients was tested twice within 1 day in both the GPi-DBSON and GPiDBS OFF stimulation conditions. Compared to healthy controls, the decreased diadochokinetic rate and slower articulation rate in dystonic patients were observed in both stimulation conditions. No significant differences in speech rate measures between stimulation conditions were detected with no relation on contact localization and stimulation intensity. The findings do not support the use articulation rate as a surrogate marker of stimulation-induced changes to the speech apparatus in dystonia.