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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Focused Ultrasound in Parkinson's Disease: Going Beyond Tremor

By Michael G. Kaplitt, MD, PhD, and Alexander Ramos, MD, PhD

Dr. Kaplitt is Professor and Vice Chairman for Research, Weill Cornell Medical College. Dr. Ramos is Resident, Department of Neurological Surgery, Weill Cornell Medical College.

SYNOPSIS: In this randomized controlled trial, patients with asymmetric Parkinson's disease were assigned to noninvasive, focused ultrasound-mediated subthalamotomy or sham procedure. The authors reported improved motor function in the focused ultrasound group, with adverse events including weakness, dyskinesia, and gait disturbances.

SOURCE: Martínez-Fernández R, Máñez-Miró JU, Rodríguez-Rojas R, et al. Randomized trial of focused ultrasound subthalamotomy for Parkinson's disease. *N Engl J Med* 2020;383:2501-2513.

Magnetic resonance-guided focused ultrasound (MRgFUS) is a promising noninvasive procedure that can be used to precisely lesion deep brain structures. Ablation of the ventral intermediate nucleus of the thalamus is approved by the Food and Drug Administration for the treatment of essential tremor (ET) and parkinsonian tremor.

Martinez-Fernandez et al investigated the use of subthalamic nucleus (STN) ablation with MRgFUS for treatment of the cardinal motor symptoms of Parkinson's disease (PD) as an alternative method to deep brain stimulation (DBS) for normalization of dysfunctional motor circuits.

Patients with highly asymmetric PD refractory to dopaminergic medication were enrolled in a double-blind, sham-controlled study. The researchers enrolled 40 patients: 27 received MRgFUS targeting the dorsolateral STN and 13 received sham treatment. The primary outcome was change from baseline of the more affected side in the well-validated Movement Disorder Society-revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) at four months following MRgFUS. Unblinded assessment at 12 months was a secondary outcome. Several additional secondary outcomes also were assessed, including quality-of-life scores and change in dopaminergic medication use.

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At four months, the treatment group had a decrease in mean MDS-UPDRS score from 19.9 ± 5.0 to 9.9 ± 4.9 vs. a change from 18.7 ± 5.5 to 17.1 ± 6.0 in the control group. The between-group difference in change was 8.1 points and was highly significant ($P < 0.001$). A similar decrease in mean MDS-UPDRS score after four months was seen in 12 of the 13 subjects in the sham treatment group who crossed over to treatment. Secondary outcomes were not adjusted for multiple comparisons. Therefore, there was no ability to determine statistical significance. With that limitation, most of the secondary outcomes, including change in dosage of dopaminergic medication, trended in the same direction as the primary outcome. There was a similar reduction in MDS-UPDRS score at the 12-month follow-up.

The authors described a significant rate of adverse events. Dyskinesia occurred in 12 patients (44%), half of whom were in the off-medication state. These symptoms persisted in four patients at four months, with three patients having off-medication dyskinesia. Five patients (19%) had weakness immediately after treatment; three patients recovered, and two patients had persistent symptoms at 12 months. Speech disturbance (56%) and gait disturbance (42%) after the procedure were common but resolved in the majority of affected patients at four months.

■ COMMENTARY

This is the first randomized trial to demonstrate efficacy in the treatment of the non-tremor PD motor symptoms with MRgFUS, which represents a significant advance in the application of this technology. The study was well-designed and controlled by a gold-standard sham procedure. There was a significant improvement in motor symptoms in the treatment group, and this was comparable to other surgical interventions when accounting for the unilateral procedure. The trial focused on patients with severely asymmetric disease, a reasonable patient population for a proof-of-principle first clinical trial. Most patients with PD have bilateral symptoms and most DBS patients receive bilateral surgery. A trial of bilateral MRgFUS thalamotomy for ET is currently ongoing, and future PD trials should examine the safety and efficacy of bilateral MRgFUS.

Although the benefit in reducing PD motor symptoms is clear, the authors reported a high rate of adverse events. Most, but not all, resolved at four months. These deficits included gait disturbance, speech disturbance, weakness, and dyskinesia, all of which could have a significant impact on quality of life. It is unclear in the current trial if these potential deficits outweighed the benefits of treatment. Notably, the authors did examine post-procedural magnetic resonance imaging of patients with new deficits after the procedure and found no evidence of permanent structural damage, in keeping with the transient nature of the majority of these symptoms. Avoidance of off-target effects with new targeting paradigms should be a major focus going forward. The rate of adverse events, such as speech and gait disturbance, while mostly transient, seems to be far greater than with MRgFUS thalamotomy.[1] This could be caused by off-target effects on the nearby corticospinal tract. Refinements, such as diffusion tractography to map out adjacent white matter tracts, might help to avoid off-target lesioning and adverse effects.[2] Also, it is possible that some adverse events, such as worsening dyskinesia, could be avoided by choosing another target for MRgFUS. An encouraging pilot study of MRgFUS pallidotomy has been reported,[3] and a large, multicenter randomized trial is nearing completion.

A key advantage to focused ultrasound is avoiding permanent implantation of hardware and surgery in patients who may be too sick for such a procedure. DBS is proven as efficacious in PD over a long period of time with an extremely low rate of adverse events. The long-term efficacy and safety profile of MRgFUS lesioning of the STN and other targets must be studied and refined further, but this trial represents a promising first step. ■

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ABSTRACT & COMMENTARY

Deficits in Neurotransmitters and Behavioral Disturbances in Frontotemporal Lobar Degeneration

By Makoto Ishii, MD, PhD

Assistant Professor of Neuroscience and Neurology, Feil Family Brain and Mind Research Institute, Department of Neurology, Weill Cornell Medical College.

SYNOPSIS: In subjects with a syndrome associated with frontotemporal lobar degeneration, gamma aminobutyric acid and glutamate deficiency in the right inferior frontal gyrus was associated with greater degrees of impulsivity.

SOURCE: Murley AG, Rouse MA, Jones PS, et al. GABA and glutamate deficits from frontotemporal lobar degeneration are associated with disinhibition. *Brain* 2020;143:3449-3462.

Behavioral disturbances such as disinhibition are common manifestations of syndromes associated with frontotemporal lobar degeneration (FTLD), which includes behavioral variant frontotemporal dementia (bvFTD) and progressive supranuclear palsy (PSP). These behavioral symptoms not only are distressing to caregivers, but also are associated with increased loss of functional independence and increased mortality. Because there are no specific treatments for these behavioral symptoms, elucidating the underlying mechanisms is necessary to develop targeted therapies.

Previous studies, mainly in animal models, and postmortem human studies have found evidence for deficiency in gamma aminobutyric acid (GABA) and glutamate signaling in FTLD. However, there is limited evidence relating these neurotransmitters with the behavioral phenotype. Therefore, Murley et al examined whether changes in GABA and glutamate are seen in FTLD and whether changes in these neurotransmitters are associated with greater impulsivity.

Forty-four patients with FTLD carrying a clinical diagnosis of bvFTD or PSP (either PSP-Richard's syndrome or PSP-Frontal syndrome) were recruited from the Cambridge Centre for Frontotemporal Dementia, Cambridge Centre for Parkinson-Plus, and the "Join Dementia Research" patient register. The researchers recruited 20 age- and sex-matched subjects with no history of a neurological or psychiatric illness as controls. All subjects underwent cognitive and neuropsychological assessments.

To measure impulsivity or response inhibition, a stop-signal type response inhibition task was used. To measure GABA and glutamate concentrations in the brain in vivo, all subjects underwent scanning with 7T 1H-magnetic resonance spectroscopy (MRS) targeting the right inferior frontal gyrus as the experimental region of interest and the right occipital lobe as a negative control. To compare gray and white matter volumes, voxel-based morphometry was conducted on T1-weighted MP2RAGE structural sequences.

[Previous studies, mainly in animal models, and postmortem human studies have found evidence for deficiency in gamma aminobutyric acid and glutamate signaling in frontotemporal lobar degeneration.]

Compared to control subjects, FTLD subjects had, as expected, reduced gray matter volumes in frontal lobes, including the right inferior frontal gyrus, temporal lobes, basal ganglia, thalamus, and cerebellum, with relative preservation in the occipital lobe. For the neurotransmitters, after correcting for age, sex, and partial volume, GABA concentrations were significantly reduced in the right inferior frontal gyrus but not the right occipital lobe in FTLD subjects, while glutamate concentrations were similar in both brain regions. For the behavior task, compared to control subjects, FTLD subjects exhibited greater impulsivity in the stop-signal reaction time, with nine FTLD subjects unable to complete the task. Finally, both glutamate and GABA concentrations in the right inferior frontal gyrus in FTLD subjects were inversely correlated with the stop-signal reaction time, which is consistent with loss of these neurotransmitters being associated with greater impulsivity or disinhibition.

■ COMMENTARY

A major strength of this study is the use of in vivo imaging to measure two neurotransmitters, glutamate and GABA, in the same individual and to correlate these

neurotransmitters to a measure of impulsivity or disinhibition. The study results were consistent with earlier animal and postmortem human studies that found deficiencies in GABA and glutamate signaling in FTLD. Collectively, these studies suggest that restoration of GABA and glutamate signaling could improve behavioral symptoms in patients with FTLD.

However, the study had several limitations, including a relatively small study population, combining two potentially distinct diseases (bvFTD and PSP) as one FTLD group, and a relatively high number of FTLD subjects (nine, or 20% of total recruited) excluded from final analysis for being unable to complete the behavior task. Additionally, the MRS was restricted to prespecified regions of interest.

Although investigating the right inferior frontal gyrus was reasonable, other brain regions pertinent to the behavioral symptoms in FTLD may be involved. It is not clear if deficits in GABA and glutamate would be seen in other brain regions or if this is specific to the right inferior frontal gyrus. Classically, GABA is an inhibitory neurotransmitter, while glutamate is an excitatory neurotransmitter. At first glance, it would seem odd that deficiency in both an excitatory and inhibitory neurotransmitter in the same brain region would contribute to the same phenotype. Importantly, as the findings are correlative, GABA and glutamate deficiencies may not be the underlying culprit for the behavioral symptoms and instead simply may reflect neurodegeneration or loss of cells synthesizing or releasing these neurotransmitters in this brain region.

To determine any causative role for GABA and glutamate deficiency, longitudinal clinical studies and mechanistic studies in animal models would be essential. Furthermore, as mentioned by the study investigators, it may be too simplistic to assume that these are the only neurotransmitters involved, and others in this or other brain regions are likely to contribute to the behavioral phenotype.

Despite these limitations, this study lays the foundation for future studies that combine MRS with behavior or cognitive testing. By conducting similar studies in patients with neurodegenerative or other brain disorders, new insights into the relationship between neurotransmitters and the clinical phenotypes could be gained. This could lead to the future development of targeted therapies that ameliorate specific behavior impairment or cognitive deficits by restoring key neurotransmitter signaling in these disorders. ■

ABSTRACT & COMMENTARY

Cognitive Benefit of Rivastigmine in Parkinson's Disease Dementia with Orthostatic Hypotension

By Lynda Nwabuobi, MD

Assistant Professor of Clinical Neurology, Assistant Attending Neurologist, New York Presbyterian/Weill Cornell Medical College

SYNOPSIS: Individuals with Parkinson's disease dementia and orthostatic hypotension (OH) have more robust cognitive improvement from rivastigmine compared to those without OH. This greater response possibly is mediated by the anti-OH effect of rivastigmine.

SOURCE: Espay AJ, Marsili L, Mahajan A, et al. Rivastigmine in Parkinson's disease dementia with orthostatic hypotension. *Ann Neurol* 2021;89:91-98.

Orthostatic hypotension (OH) is a common nonmotor symptom in Parkinson's disease (PD), with an overall prevalence of 30%, which increases to 65% as the disease progresses. Untreated, it can independently contribute to cognitive impairment in PD individuals, presumably as the result of a reduction in cerebral perfusion pressure. In individuals with Parkinson's disease dementia (PDD), the presence of untreated OH could negatively affect the efficacy of cholinesterase inhibitors used to treat PDD. Rivastigmine is approved for the treatment of cognitive impairment in people with PDD.

Using available clinical trial datasets, the authors tested the hypothesis that the cognitive effect of rivastigmine is reduced in patients with PDD with OH compared to those without OH.

A post-hoc analysis was performed on three Novartis-sponsored studies of rivastigmine in PDD in which orthostatic blood pressure measurements were recorded: a 24-week randomized, double-blind, placebo-controlled trial of patients with PDD at least two years after diagnosis; a 24-week open-label extension (a total of

48 weeks) in the same population; and a 76-week trial comparing the rivastigmine capsule vs. the transdermal patch. The main outcome was change from baseline in the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog) in patients with OH vs. patients without OH treated with rivastigmine compared to placebo. A secondary endpoint was change in Mini-Mental State Examination (MMSE) from baseline. The 76-week study used the Mattis Dementia Rating Scale (MDRS) as the outcome measure. The 24-week study was used for the main analysis because it was the only study with a placebo comparator. Statistical analysis included analysis of covariance (ANCOVA) model, with 95% confidence intervals for the difference between the treatment groups; P values were provided without adjustment for multiple comparisons.

In the rivastigmine vs. placebo study, the mean maintenance daily dose of rivastigmine for the 10 weeks preceding the study endpoint at week 24 was 8.7 mg (standard deviation [SD] = 3.4 mg); 9.8% of all OH patients were receiving OH treatment. There was a larger improvement in ADAS-Cog in the OH group at 24 weeks (5.6 ± 1.2 vs. 1.9 ± 0.9; $P = 0.0165$). MMSE also was significantly improved by rivastigmine compared to placebo, but only in patients with OH (2.2 ± 4.7 vs. -0.7 ± 3.9; $P < 0.001$). At 48 weeks, with both groups on rivastigmine, the favorable effect of rivastigmine on ADAS-Cog in the OH group was attenuated (3.2 ± 2.1 vs. -1.1 ± 1.1, $P = 0.0741$).

In the rivastigmine patch vs. capsule study, the daily dose during the maintenance period ranged from 8.80 mg/day to 8.87 mg/day in patients who received the rivastigmine capsule and from 9.20 cm^2 to 9.40 cm^2 in patients who received the rivastigmine patch (10 cm^2 patch releases 9.5 mg/24 hours). At week 76, the change in MDRS was significantly greater for OH patients compared to individuals without OH, but only for those on rivastigmine capsules (10.6 ± 2.9 vs. -1.5 ± 3.0 on transdermal patch; $P = 0.031$).

At the end of the 24-week study, the prevalence of OH among the patients who had OH at baseline was reduced to 28.3% in the rivastigmine group and 44.6% in the placebo group. Of the OH-negative patients, 5% converted to OH in the placebo arm compared to 1.7% in the rivastigmine arm. Syncope was more common in the OH placebo group (9.2%) compared to the OH rivastigmine group, which had no cases of syncope.

[Contrary to their hypothesis, the authors found that rivastigmine had a greater cognitive benefit in Parkison's disease dementia patients with orthostatic hypotension (OH) compared to individuals without OH, despite similar severity of cognitive impairment at baseline .]

■ COMMENTARY

Contrary to their hypothesis, the authors found that rivastigmine had a greater cognitive benefit in PDD patients with OH compared to individuals without OH, despite similar severity of cognitive impairment at baseline. Also, it appeared to have a protective effect of reducing OH, given the lower prevalence at the end of the 24-week study and no episodes of syncope in the rivastigmine group. This paradoxical effect may be explained by an anti-OH effect of the medication, as seen in a related ganglionic acetylcholinesterase inhibitor, pyridostigmine, which has been shown to reduce OH. These findings suggest a potential role of rivastigmine as an adjunct treatment strategy for OH in PD. An interesting subanalysis would be to investigate whether treatment with OH medications contributed to the amount of cognitive improvement seen in OH patients. If this is the case, it brings up the question whether all PDD patients should be on OH medications to boost the effectiveness of cholinesterase inhibitors. ■

ABSTRACT & COMMENTARY

Prednisone vs. Placebo in Short-Term Prevention of Episodic Cluster Headaches

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Prednisone, given at 100 mg for five days and then tapering by 20 mg every three days, is a safe and effective short-term prevention for episodic cluster headaches while waiting for longer-acting preventive agents to be initiated.

SOURCE: Obermann M, Nägel S, Ose C, et al. Safety and efficacy of prednisone versus placebo in short-term prevention of episodic cluster headache: A multicentre, double-blind, randomised controlled trial. *Lancet Neurol* 2021;20:29-37.

Cluster headache is a primary headache disorder characterized by attacks of severe, unilateral facial and head pain accompanied by trigeminal autonomic symptoms, with attacks lasting 15-180 minutes and occurring from once every other day to up to eight times a day in clusters lasting between one week and several months.

Treatments for acute attacks include high-flow oxygen, triptans, and intranasal lidocaine. Preventive medications, such as verapamil and lithium, reduce the number of attacks and potentially terminate the cluster episode. However, they need to be titrated gradually to avoid side effects and can take several weeks to achieve efficacy. Although headache guidelines recommend treatment with oral corticosteroids to break the initial cluster episode while waiting for preventive medications to take effect, this recommendation has not been rigorously assessed. The purpose of this trial was to assess the safety and efficacy of prednisone 100 mg for the short-term prevention of episodic cluster headaches.

The study was a multicenter, randomized, double-blind, placebo-controlled trial performed at 10 specialized pain and headache centers throughout Germany. Eligible patients were 18-65 years of age and met criteria for episodic cluster headache as defined by the International Classification of Headache Disorders. To avoid confounding data caused by spontaneous remission, the authors included patients whose prior cluster episodes lasted at least 30 days. Patients could use triptans, high-flow oxygen, intranasal lidocaine, ergotamine, and oral analgesics as needed. Patients were randomized to receive either oral prednisone or placebo. Prednisone was given at a dose of 100 mg for five days and then was tapered by 20 mg every three days. Oral verapamil was initiated at a dose of 40 mg three times a day at the same time and increased every three days to a maximum daily dose of 360 mg. Patients also were given 20 mg of pantoprazole daily to prevent gastrointestinal side effects from corticosteroids.

Patients used diaries to record the number and severity of cluster attacks, associated autonomic symptoms, and the use of acute rescue medication. The primary endpoint was the mean number of cluster attacks within the first week of treatment compared with placebo.

Over five years, the study trial pre-screened 157 patients and randomized 116 to participate in the study, 57 (49%) to the prednisone group and 59 (51%) to the placebo group. The mean number of attacks within the first week of treatment was 25% less in the prednisone group (7.1; standard deviation [SD] 6.5 vs. 9.5; SD 6.0, $P = 0.002$) compared to the placebo group. In addition to improvement in the primary endpoint, the prednisone group also performed better in terms of the number of cluster attacks after 28 days (15.6 vs. 20.2), the number of cluster attacks after seven days (3.9 vs. 5.1), and the number of days with cluster attacks at 28 days (8.8 vs. 11.0). After seven days, cluster attacks had ceased in 35% of the prednisone group vs. 7% of the placebo group. At least a 50% reduction in attack frequency at day 7 was seen in nearly 50% of the prednisone group vs. only 15% in the placebo group. The need for acute medication also was higher in the placebo group.

There were no significant differences in the frequency or severity of adverse events between the two groups. The Clinical Global Impressions scale showed significant differences between groups, with 15% of patients in the prednisone group (but none in the placebo group) rated as "normal" at seven days.

■ COMMENTARY

This small, randomized, double-blind study supports the clinical impression and prior societal recommendations that prednisone, starting with 100 mg and with gradual reduction over 17 days, is of value in the management of acute cluster attacks. Patients treated with prednisone had significantly fewer cluster attacks, with more than one-third of patients reporting complete cessation of their cluster attacks after seven days, nearly one-half reporting at least a 50% reduction in attacks, and marked reduction in the number of days with cluster attacks as well as the need for acute medication. Prednisone, given at 100 mg for five days and then tapering by 20 mg every

three days, is a safe and effective short-term prevention for episodic cluster while waiting for longer-acting preventive agents to be initiated.

The study was limited to small numbers in each group because of funding difficulties and the challenges of recruiting patients who may have been exposed to the treatment medications previously. The results need to be interpreted with caution since many patients with cluster headache will have spontaneous remissions; limiting the study to patients with prior cluster periods lasting more than 30 days offset this concern. In future studies, oral prednisone could be compared with occipital nerve block and other long-term preventive agents. ■

ABSTRACT & COMMENTARY

Clinical and Genetic Characterizations to Diagnose Sarcoglycanopathies

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Sarcoglycanopathies, caused by various genetic mutations, may cause limb-girdle forms of muscular dystrophy early in life. Although there are no specific treatments for these disorders at this time, the clinical and genetic characterizations will assist in more precise diagnosis that will be critical to develop new molecular-based therapies.

SOURCE: Guimarães-Costa RG, Fernández-Eulate G, Wahbi K, et al. Clinical correlations and long-term follow-up in 100 patients with sarcoglycanopathies. *Eur J Neurol* 2021;28:660-669.

Sarcoglycanopathies, caused by mutations of the α-, β-, γ-, or δ-sarcoglycan (SG) genes, are autosomal recessive limb-girdle muscular dystrophies (LGMD 2C, 2D, 2E, 2F), characterized by slowly progressive proximal muscle weakness of the pelvic and shoulder girdles with various degrees of cardiorespiratory involvement, most often of childhood onset, and resulting in premature death. Little is known regarding the prevalence or predictors of disease progression. Hence, this multicenter retrospective study encompassing 100 patients from 80 families was undertaken.

Medical records of genetically confirmed sarcoglycan patients seen at the neuromuscular centers of Pitie-Salpetriere, Raymond Poincare, Necker, and Armand-Trousseau Hospitals' Nord-Est/Ile-de-France, and in the cardiology department of Cochin Hospital in Paris, were reviewed. Neurologic, cardiac, and pulmonary evaluations, muscle biopsy data, and ethics committee approval were obtained. Muscle strength was measured in 15 muscle groups using the Medical Research Council (MRC) scale. Pulmonary insufficiency was defined as forced vital capacity (FVC) < 70% of predicted value, cardiomyopathy by a left ventricle ejection fraction (LVEF) < 50% based on transthoracic echocardiography, and skeletal muscle disease severity by the age at loss of ambulation (LoA). All patients underwent sarcoglycan gene analysis, and immunohistochemistry (IHC) was performed on muscle biopsies for dystrophin, dysferlin, and sarcoglycans, with muscle protein analysis done by multiplex Western blot. Statistical analysis encompassed Student *t* test, Chi-square test, and regression analyses, with statistical significance established at $P \leq 0.05$. Among 100 patients in the study, 54% women and 46% men, consanguinity was observed in 44%, with γ-SG patients accounting for 54%, α-SG patients for 41%, and β-SG patients for 5%. Most γ-SG patients (88.9%) came from North Africa (Algeria, Morocco, and Tunisia), most α-SG patients from Europe (70.7%), and one each of the β-SG patients came from Europe and Guadeloupe, and three from Tunisia. Mean age at symptom onset was 7.6 years, ranging from birth to 42 years, earliest in the γ-SG group (5.5 years of age), and latest in the β-SG group (24.4 years of age), usually with gait difficulties (54%), rarely with elevated creatine kinase (4%), and with exercise intolerance or myalgia (11%). Among 58 patients who underwent muscle biopsy, sarcoglycan expression was absent in 52.4% and decreased in 47.6%.

At last examination, mean age 30.8 years, all patients demonstrated proximal weakness in all four limbs, with joint contractures in 69%, axial weakness in 65%, LoA in 63%, calf hypertrophy in 48%, and scapular winging in 44%. Low FVC was seen in 66%, with 30% requiring ventilation, and dilated cardiomyopathy was seen in 21%, particularly the γ-SG group. Earlier time to LoA was associated with younger age of onset and absence of sarcoglycan on muscle biopsy, with the former an independent predictor of both severity and time to LoA. Age of onset should be considered in any future clinical trials for new therapies.

■ COMMENTARY

All four sarcoglycans are glycosylated transmembrane proteins, essential for membrane integrity during muscle contraction, forming a tetrameric complex linked to the major dystrophin glycoprotein complex (DGC). Missense mutations comprise the majority of

sarcoglycanopathies, resulting in absence or decreased amounts of sarcoglycan. Curiously, although absence of other DGC proteins results in aberrant neuromuscular junctions (NMJ), deficiency of γ-SG results in no detectable NMJ structural defect. However, age-related NMJ structural alteration has been reported recently in aging mice with reduced α-SG expression, such that overexpression of α-SG mitigated these alterations by preventing degradation of LRP4. How this is accomplished remains a mystery. ■

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CME QUESTIONS

1. **In the treatment of Parkinson's disease with focused-ultrasound subthalamotomy, which of the following benefits was observed?**
   a. Improved quality of life
   b. Significant reduction is the Unified Parkinson's Disease Rating Scale score
   c. Improvement in gait and balance
   d. Improvement in speech
2. **In a recent study investigating neurotransmitters and behavioral phenotypes in subjects with syndromes associated with frontotemporal lobar dementia (FTLD), which of the following is true?**
   a. FTLD subjects had higher levels of gamma aminobutyric acid (GABA) in the right inferior frontal gyrus compared to control subjects.
   b. FTLD subjects had higher levels of GABA in the right occipital lobe compared to control subjects.
   c. GABA levels in the right inferior frontal gyrus were inversely associated with impulsivity or disinhibition.
   d. GABA levels in the right occipital lobe were inversely associated with impulsivity or disinhibition.
3. **In patients with Parkinson's disease and dementia, rivastigmine has which of the following effects?**
   a. Reduces parkinsonian tremor
   b. Improves cognitive functions
   c. Improves balance and gait
   d. Worsens orthostatic hypotension
4. **Which of the following is *not* the result of a short course of oral prednisone given at the onset of a cluster headache attack?**
   a. A reduction in the number of cluster attacks in seven days
   b. A 50% reduction in cluster attacks in half of the patients
   c. A reduction in the autonomic symptoms associated with cluster attacks
   d. The cessation of cluster in one-third of patients within seven days
5. **Which of the following statements about sarcoglycanopathies is *false*?**
   a. They are caused by mutations of the α-, β-, γ-, or δ-sarcoglycan genes.
   b. They most often begin in mid-adult life.
   c. They are associated with various degrees of cardiorespiratory involvement.
   d. They are forms of autosomal recessive limb-girdle muscular dystrophies.