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Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Effectiveness of Bariatric Surgery for the Treatment of Idiopathic Intracranial Hypertension

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Idiopathic intracranial hypertension is an important cause of intractable headaches and may cause permanent loss of vision as a result of chronic papilledema. Weight loss is an effective treatment, and this randomized study demonstrated superior outcomes for both weight loss and reduced intracranial pressure from bariatric surgery compared to community weight-loss programs.

SOURCE: Mollan SP, Mitchell JL, Ottridge RS, et al. Effectiveness of bariatric surgery vs community weight management intervention for the treatment of idiopathic intracranial hypertension: A randomized clinical trial. *JAMA Neurol* 2021; Apr 26. doi: 10.1001/jamanerol.2021.0659. [Online ahead of print].

Idiopathic intracranial hypertension (IIH) is a chronic, disabling neurological condition in which intracranial pressure (ICP) is elevated in the absence of an intracranial mass. The clinical syndrome is characterized by chronic headaches, vision loss, and reduced quality of life. The vision loss occurs as the result of increased ICP and the development of optic disc swelling or papilledema.

IIH occurs predominantly in women between the ages of 25 and 36 years; weight gain and obesity are major risk factors. As levels of obesity increase worldwide, the incidence of IIH also is increasing.

Although medications, including diuretics and carbonic anhydrase inhibitors, can improve IIH, weight loss, with a reduction of 3% to 15% of body weight, has been associated with disease remission as defined by normalization of ICP and resolution of papilledema. Although community management programs have been associated with modest weight loss, maintaining this weight loss is more

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challenging. Bariatric surgery has been associated with more sustained and more significant weight loss. Case studies have suggested that bariatric surgery is associated with remission in patients with IIH. The authors hypothesized that bariatric surgery would be superior to community weight management interventions in reducing ICP in patients with IIH.

The authors conducted a multicenter, randomized clinical trial comparing bariatric surgery with community weight management intervention to assess which approach was more effective in decreasing ICP in patients with IIH. The primary endpoint was ICP as measured by lumbar puncture (LP) opening pressure. Patients from five National Health Service hospitals in the United Kingdom were enrolled over a three-year period. At baseline, patients were required to have an ICP greater than 25 cm of cerebrospinal fluid (CSF) and papilledema. The patients were all female, ranging in age from 18 to 55 years, who met diagnostic criteria for IIH, had normal brain imaging studies (including magnetic resonance venography or computed tomographic venography), had a body mass index (BMI) of 35 or higher, and had not been successful in losing or maintaining weight loss. Patients were randomized in a 1:1 ratio to receive community weight management intervention with Weight Watchers or bariatric surgery. The primary outcome was the difference in ICP between the two groups at 12 months. Secondary outcomes included LP opening pressure at 24 months, visual acuity, and health-associated quality of life. The researchers assessed headache symptoms using the six-item Headache Impact Test, symptom frequency, and analgesic medication use.

Between 2014 and 2017, 74 women were assessed for eligibility, with 66 women enrolling in the study. Patients were randomly assigned to either the surgical arm (n = 33) or the weight management arm (n = 33). The clinical trial arms were balanced in terms of baseline characteristics, including age, ethnicity, duration of illness, and LP opening pressure. The mean standard deviation (SD) LP opening pressure in the study population was 35.7 (7.0) cm CSF. Sixty-four women remained in the trial for 12 months and 54 women (81.8%) completed the primary outcome measures; six patients declined surgical intervention and two patients dropped out of the weight management arm. Of the 27 women who had surgical intervention, 12 participants had Roux-en-Y gastric bypass, 10 had gastric banding, and five had laparoscopic sleeve gastrectomy. The mean number of face-to-face weight management sessions attended was 14.3, with 57.6% of participants attending at least one session.

ICP was significantly lower in the surgical arm vs. the weight management arm. At 12 months, the mean (SD) LP opening pressure decreased from a baseline of 34.8 (5.8) cm CSF to 26.4 (8.7) cm CSF in the surgery arm and from 34.6 (5.6) cm CSF to 32.0 (5.2) cm CSF in the weight management arm; the difference in the weight management arm did not reach statistical significance. The adjusted mean standard error (SE) difference in LP opening pressure between the two groups at 12 months was -6.0 (1.8) cm CSF (95% confidence interval [CI], -9.5 to -2.4 cm CSF; $P = 0.001$). At 24 months, this difference increased to -8.2 (2.0) cm CSF (95% CI, -12.2 to -4.2 cm CSF; $P = 0.001$). At 12 months, the mean (SE) percentage change in ICP was -32.1% (4.7%) in the surgical arm compared with -2.5% (3.9%) in the weight management arm.

At 12 and 24 months, all measured improvements in weight and BMI were significantly greater in the surgery arm vs. the weight management arm. In terms of percentage of excess weight loss, the mean (SE) difference between the two groups at 12 months was -18.3% (1.9%; 95% CI, -22.1% to -14.6%; $P < 0.001$); there were similar results at 24 months.

Papilledema was reduced in both arms. Differences in visual function, as measured by perimetric mean deviation between the two arms, was not significant at either 12 or 24 months. Analysis of quality of life using the 36-item Short Form Health Survey showed significant improvements in the domains of energy and fatigue, physical functioning, and general health. Notably, the severity of headache disability, as measured by the Headache Impact Test, was not significantly different between the two study arms.

■ COMMENTARY

This randomized clinical trial of bariatric surgery in female patients with IIH showed that bariatric surgery was superior to a community weight management program in terms of sustained reduction in ICP, disease remission, and quality of life measures at both 12 and 24 months. Patients undergoing bariatric surgery had significantly greater weight loss.

Interestingly, visual outcomes in the two groups were not significantly different, nor was there a significant difference in headache disability. The significant improvements in quality of life may be the result of the overall benefits of sustained weight loss. Going forward, differences in headache disability between the two interventions could be explored in more detail. However, this study supports the recommendation for consideration of bariatric surgery in patients with IIH who have not been able to attain or sustain adequate weight loss, the primary treatment for this disabling condition. ■

ABSTRACT & COMMENTARY

Association of Sleepwalking and REM Sleep Behavior Disorder in Men with Parkinson's

By Daniel A. Barone, MD, FAASM, FANA

Assistant Attending Neurologist, NewYork-Presbyterian Hospital, and Assistant Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: In this retrospective, cross-sectional study of men, both sleepwalking and rapid eye movement sleep behavior disorder were associated with the development of Parkinson's disease.

SOURCE: Zhang X, et al. Association of sleepwalking and REM sleep behavior disorder with Parkinson disease in men. *JAMA Netw Open* 2021;4:e215713.

Rapid eye movement (REM) sleep behavior disorder (RBD) is one of the most well-known and extensively studied sleep features of Parkinson's disease, both in terms of risk and as a sleep-related symptom. The non-REM parasomnia, sleepwalking, has less of an association and is not as well understood or studied. It has been suggested that sleepwalking may exhibit a significant prevalence in patients with Parkinson's disease (approximately 10%), and the presence of non-REM parasomnias is associated with worse symptoms, cognitive impairment, and depression in those with Parkinson's disease. However, despite these observations and the fact that sleepwalking is somewhat rare in adults (1% to 2%), no study comparing individuals without Parkinson's disease in direct comparison to those with Parkinson's disease for risk estimation has been done.

In this cross-sectional study by Zhang et al, the authors aimed to answer the question of whether the presence of sleepwalking in men, either alone or comorbid with RBD, is associated with higher odds of having Parkinson's disease. To accomplish this, they surveyed a cohort of 25,694 men from the Health Professional Follow-Up Study, which consisted of male health professionals in the United States followed from January 2012 until June 2018. The presence of probable sleepwalking and/or probable RBD was ascertained in 2012 via the Mayo Sleep Questionnaire, and the diagnosis of Parkinson's disease was determined by a movement disorder specialist through a review of medical records.

The mean age of this cohort was 75.6 years, and the authors found that 223 (0.9%) had probable sleepwalking, 2,720 (10.6%) had probable RBD, and 257 (1.0%) had Parkinson's disease. The presence of confounders, such as age, smoking, caffeine intake, chronic disease status, and other sleep disorders, was adjusted for in a two-tailed logistic regression analysis. This led to the observation that those with probable sleepwalking, probable RBD, or both probable sleepwalking and probable RBD had higher odds of Parkinson's disease ($P < 0.05$): probable sleepwalking, odds ratio (OR) = 4.80; probable RBD, OR = 6.36; both probable sleepwalking and probable RBD, OR = 8.44. Thus, it appears that both probable sleepwalking and probable RBD, alone and in conjunction, were significantly associated with higher odds of having Parkinson's disease. The authors pointed out that arousal regulation during sleep is likely to be affected by Parkinson's disease-related neurodegeneration.

■ COMMENTARY

As the authors pointed out, this is the first paper to date commenting on a non-REM parasomnia as a risk for Parkinson's disease. However, despite the novelty of this design, there are significant

limitations. This was a questionnaire-based methodology for assessing the presence of sleep disorders and a medical records review for making a diagnosis of Parkinson's disease. However, this new line of thinking should open the doors to prospective evaluation of the risk for development of Parkinson's disease in other parasomnias and sleep disorders. For example, in an earlier study based on the Health Professional Follow-Up Study, the presence of restless legs syndrome (RLS) was associated with increased odds of having constipation and probable RBD, both of which are risk factors for Parkinson's disease.[1]

Long-term studies evaluating the risk of neurodegeneration in those with non-REM parasomnias and other sleep disorders (such as RLS and periodic limb movements of sleep) are needed now, and perhaps this marks the beginning of a paradigm shift to a better understanding of the risk neurodegeneration in patients with sleep disorders other than RBD. ■

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ABSTRACT & COMMENTARY

Genetic Biomarkers of Immunoglobulin Response in Patients with CIDP

By Mary L. Vo, MD, PharmD

Assistant Professor of Neurology, Weill Cornell Medical College

SYNOPSIS: Nearly 25% of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) have a poor response to intravenous immunoglobulin treatment. Variations in the *PRF1* and *FCGR2B* genes in CIDP patients offer insights into the heterogenous treatment response.

SOURCE: Kuitwaard K, van Doorn PA, Bengrine T, et al. Genetic biomarkers for intravenous immunoglobulin response in chronic inflammatory demyelinating polyradiculoneuropathy. *Eur J Neurol* 2021;28:1677-1683.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy resulting in progressive weakness, sensory loss, and gait instability evolving over at least eight weeks. In the absence of a biomarker, diagnosis relies on clinical evaluation with confirmation of unequivocal demyelination on electrodiagnostic studies. Intravenous immunoglobulin (IVIg) is preferred over other treatments because of its rapid onset, accessibility, and favorable side effect profile. However, unpredictable treatment responses pose a significant clinical challenge, since one-quarter of CIDP patients either have a suboptimal response or are refractory to immunosuppressive treatment altogether.

Poor clinical response to IVIg may be the result of misdiagnosis, severe axonal loss, and disease course. Diagnostic pitfalls contribute to observations that nearly 40% patients diagnosed initially with CIDP had an alternate cause of their neuropathy.[1] The presence of severe axonal loss and the relapsing remitting course of CIDP can further complicate assessment of treatment response.

Moreover, pharmacodynamic and pharmacogenetic features may influence IVIg efficacy and account for differences in treatment response between patients. The mechanism of IVIg in CIDP is unknown, although studies suggest the predominant mechanisms include neutralizing pathogenic autoantibodies, inhibiting complement binding, and directly enhancing remyelination.[2] Recent studies have identified potential molecular biomarkers involved in FcγRIIb receptor modulation and axonal injury that may affect IVIg responsiveness in CIDP patients.[3]

The authors conducted a retrospective genetic association analysis focusing on six candidate genes previously associated with IVIg responsiveness in CIDP patients. Blood samples were taken from 172 patients with CIDP treated at Erasmus MC University Medical Centre in Rotterdam, Netherlands, between 1980 and 2018. Patients met clinical criteria for CIDP defined by the European Federation of Peripheral Neuropathies/Peripheral Nerve Society (EFNS/PNS) and were treated with at least one course of IVIg (2 g/kg). Treatment response was defined as > one-point improvement in the Modified Rankin Scale determined by a neuromuscular specialist.

Genetic variations in *GJB1*, *CNTN2*, *PRF1*, *SH2D2A*, *FCGRT*, and *FCGR2B* were analyzed. Chi-squared tests and Fisher exact tests were used to compare IVIg response among patients with different genotypes. A two-tailed P value < 0.05 was deemed significant. A multivariate logistic regression model was used to assess IVIg responsiveness.

Overall, 79% of the 172 CIDP subjects responded to IVIg. There were no significant differences in age, gender, or acute onset CIDP between the responder and non-responder groups. Genetic association studies for all six candidate genes were determined in 163 patients. Multivariate analysis showed that the *PRF1* p.Ala91Val variant was negatively associated with IVIg response (odds ratio [OR] = 0.57) and *FCGR2B* promoter 2B.4/2B.1 was positively associated with IVIg response (OR = 2.56). *PRF1* encodes for perforin, an essential component for the function of cytotoxic T-cells and NK-T cells. The *PRF1* p.Ala91Val variant causes a reduction in cytotoxic perforin activity. Patients harboring the p.Ala91Val variant of the *PRF1* gene were more likely to have a poor response to IVIg. *PRF1* variants are more prevalent in CIDP patients with axonal damage, a feature that predicts poor IVIg response.

CIDP patients with the 2B.4/2B.1 promoter genotype for *FCGR2B* were more likely to respond to IVIg. *FCGR2B* encodes for the FcγRIIb receptor expressed by monocytes, macrophages, dendritic cells, and B-cells. It has been suggested that the 2B.4 variant induces FcγRIIb receptor expression and may facilitate IVIg response by reducing cell activation, proliferation, and cytokine production. Variations in *CNTN2*, *FCGRT*, and *SH2D2A* were not associated with IVIg response. No disease-associated changes were observed in the *GJB1* gene.

This genetic association study is among the first to explore pharmacogenetic relationships affecting IVIG response in CIDP. *PRF1* and *FCGR2B* variants can influence IVIg responsiveness by identifying patients with axonal injury who would be less amenable to treatment and also offers insights into the predominant mechanisms influencing IVIg activity in CIDP.

■ COMMENTARY

The identification of molecular biomarkers influencing axonal injury and IVIg response sheds light on the complex pharmacogenetic mechanisms affecting IVIg response. Innovations in pharmacogenetic analysis to predict IVIg response would allow individualized treatment approaches early in the disease course and optimize clinical outcomes. Further prospective study is needed to corroborate these findings and elucidate the immunoregulatory mechanisms of IVIg. ■

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3. Dalakas MC. Potential biomarkers for monitoring therapeutic response in patients with CIDP. *J Peripher Nerv Syst* 2011; 16(Suppl1):63-67.

ABSTRACT & COMMENTARY

Long-Term Effects of Cholinesterase Inhibitors on Cognitive Decline and Mortality

By Michael T. Lin, MD

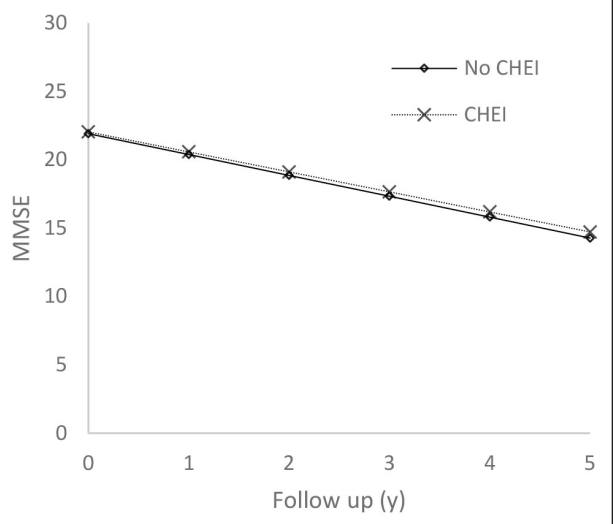
Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

SYNOPSIS: Cholinesterase inhibitors are one of the few drug classes approved by the Food and Drug Administration for the treatment of patients with Alzheimer's disease. This study shows a long-term benefit in slowing the decline of cognition, as measured by the Mini-Mental State Exam, but it is unclear if there is any benefit in quality of life.

SOURCE: Xu H, Garcia-Ptacek S, Jonsson L, et al. Long-term effects of cholinesterase inhibitors on cognitive decline and mortality. *Neurology* 2021;96:e2220-e2230.

Cholinesterase inhibitors (CHEIs) are the main Alzheimer's disease (AD) drug therapies. However, the follow-up in most randomized clinical trials of CHEIs is < 1 year, and there are few studies of their long-term effects. In their recent article, Xu and colleagues found that CHEIs were associated with sustained benefit in cognition and decreased mortality over five years. One specific CHEI, galantamine, also was associated with a lower risk of severe dementia. The authors used the Swedish Dementia Registry, established in 2007 to register all patients with incident dementia in Sweden and follow them annually. From 2007 to 2017, 39,196 patients with AD or mixed AD dementia were registered. Subjects were consideired CHEI nonusers if they were never given a CHEI and CHEI users if they were given a CHEI within three months of baseline Mini-Mental State Exam (MMSE). Subjects given their first CHEI more than three months after baseline were excluded because of faster decline. Without adjustment, CHEI nonusers were older, had lower baseline MMSE scores, had more comorbidities, and took more medications. To

Figure 1. MMSE Scores



MMSE: Mini-Mental State Exam

balance these potential confounders, a propensity score matching scheme was used. The final cohort consisted of 11,652 CHEI users and 5,826 nonusers, well-matched for demographics, comorbidities, and baseline characteristics. The investigators compared the groups with respect to cognitive trajectory, incidence of severe dementia, and mortality.

Over an average of five years of follow-up, MMSE scores in CHEI users were slightly higher than in CHEI nonusers at every time point, and the benefit increased slightly over time (0.13 points/year). The benefit increased with dose up to a certain point (donepezil 7.5 mg, rivastigmine 9 mg, galantamine 16 mg) and then plateaued. The different CHEIs produced similar degrees of improvement. For all CHEI users as a group, the risk of developing severe dementia (MMSE < 10) was slightly decreased compared to nonusers, but not statistically significant (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.63-1.13). However, for galantamine users, the decrease in risk of severe dementia reached the edge of statistical significance (HR, 0.69; 95% CI, 0.47-1.00).

The mortality rate was decreased for CHEI users as a group compared to nonusers (HR, 0.73; 95% CI, 0.69-0.77), as well as for each CHEI individually.

■ COMMENTARY

The strengths of this study are a large sample size and long follow-up period. However, it is observational and can provide only class III evidence. Also, the main criticism of CHEIs is their very modest benefit, and that remains the case here. Although the cognitive benefit was sustained, and even increased slightly over time, after five years, the benefit of CHEIs was less than 0.5 MMSE points. This difference typically is not noticeable, and a graph of the MMSE scores, as shown in Figure 1, illustrates that the CHEI user and nonuser trajectories are virtually superimposed. A 27% decreased risk of mortality over the follow-up period is of interest, but a more meaningful figure would be the duration of increased survival, presented as a Kaplan-Meier plot. It also is reasonable to ask whether prolongation of severe dementia even is desirable. Perhaps the most important question, still unanswered, is whether CHEIs produce long-term improvement in quality of life. It is important to make a distinction between a statistically significant improvement in a test and a quality-of-life improvement. ■

ABSTRACT & COMMENTARY

Prophylaxis for Tuberculosis in Patients with Myasthenia Gravis

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: In this observational study from an area with a high rate of endemic tuberculosis (TB), prophylactic treatment of TB was appropriate in those treated with high doses of prednisone and evidence of prior TB infection.

SOURCE: Steyn EC, Naidoo TM, Marais S, Heckmann JM. Tuberculosis in myasthenia gravis patients on immunosuppressive therapy in a high-risk area: Implications for preventative therapy. *J Neurol Sci* 2021;425:117447.

Treatment of myasthenia gravis (MG) often requires long-term corticosteroid therapy, resulting in a host of systemic side effects, including weight gain, diabetes, hypertension, cataracts, glaucoma, accelerated bone demineralization, and neuropsychiatric disturbances. QuantiFERON-TB Gold or tuberculin skin testing has been recommended before initiating corticosteroid therapy, with prophylactic tuberculosis (TB) therapy indicated for those who test positive from prior exposure. Although TB

prophylaxis has shown benefit in human immunodeficiency virus (HIV)-infected persons, potential side effects and the additional pill burden may give one pause before offering it in a more general manner. Accurate knowledge of the risk of developing TB in endemic areas would be useful in informing the judicious use of TB prophylaxis in immunosuppressed MG patients. To address this question, investigation of the incidence of, and risk factors for, TB in a South African cohort of MG patients receiving immunosuppressive therapy was undertaken.

Observational data collected between Jan. 1, 2010, and April 1, 2020, on MG patients followed at the MG Clinic at Groote Schuur Hospital in Cape Town, South Africa, who received immunosuppressive medication were reviewed. Patients were included if they were seen at least twice and followed for longer than six months. Data included age of MG onset, disease severity, immune therapies and duration, comorbidities (such as diabetes and HIV), and prior TB or opportunistic infections. Screening for TB was comprised of questioning for TB symptoms and chest radiograph prior to initiating immunosuppressive therapy. In the presence of a productive cough, sputum testing, microscopy, and culture also were performed. Statistical analysis included univariate analysis, the Chi-square and Fisher-exact tests, the Mann-Whitney U test/unpaired t-test, and rare events multiple logistic regression.

Among 539 MG patients seen in the clinic during the study period, 59 were excluded because of lack of inclusionary criteria, leaving 480 patients with a mean age of 43 years, of which 70% were women.

Following initiation of immunosuppressive therapy, 13 patients (3%) developed TB, 11 of which were proven by sputum analysis, and two proven by lymph-node biopsy. Among these 13 patients, five (38%) developed TB within six to 12 months of initiation of immunosuppressive therapy, and eight (62%) did so after five years. Of the five early cases, three were possibly new infections, with patients either having had a TB contact or normal chest radiographs. In two patients, a review of prior chest radiographs revealed findings suspicious for TB. Compared to those who did not develop TB, the TB group was more likely to have received higher maximum doses of prednisone (> 0.5 mg/kg/d), for longer durations (> six months), and manifested severe/refractory MG requiring two steroid-sparing agents in addition to prednisone. Overall, without receiving TB prophylaxis, more than 96% of patients did not develop TB. The incidence of TB in this cohort was similar to that of the general Cape Town population, suggesting that TB prophylaxis is not indicated in all MG patients initiating immunosuppressive therapy. In those with healed/fibrotic TB on chest radiographs, in whom higher doses (> 0.3 mg/kg/d) of prednisone are envisaged, TB prophylaxis for at least six months is justified.

■ COMMENTARY

As the authors noted, Cape Town has a high burden of TB, which may explain why the incidence of TB in their cohort was similar to that of the general population. Hence, the findings might not be generalizable to low TB areas. Yet, prior to initiating prednisone therapy, careful scrutiny of the chest radiograph is an excellent screen. In the United States, where MG patients generally undergo thymoma screening by chest computed tomography or magnetic resonance imaging, it is reassuring that TB likely will be identified early. Although low doses of prednisone do not mandate TB prophylaxis, its consideration is warranted when higher doses will be used in patients with evidence of prior TB on chest imaging. ■

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME QUESTIONS

1. **Bariatric surgery was shown to be superior to community weight management intervention for female patients with idiopathic intracranial hypertension, with the exception of:**
   a. weight loss.
   b. headache disability.
   c. quality of life.
   d. papilledema.

2. **Which of the following statements regarding sleepwalking and rapid eye movement (REM) sleep behavior disorder is correct?**
   a. Sleep disorders are common in the general population and not associated with other medical conditions.
   b. Sleepwalking occurs only in children.
   c. REM sleep behavior disorder may be a prodrome to Parkinson's disease.
   d. REM sleep behavior disorder always occurs in sleepwalkers.

3. **Variants in which gene are associated with poor response to intravenous immunoglobulin in chronic inflammatory demyelinating polyneuropathy patients?**
   a. *GJB1*
   b. *CNTN2*
   c. *PRF1*
   d. *FCGR2B*

4. **Cholinesterase inhibitors have been shown to have which of the following benefits in patients with Alzheimer's disease?**
   a. Improvement in memory
   b. Improvement in sleep maintenance
   c. Slowing the decline of memory impairment
   d. Improving quality of life for dementia patients

5. **Which of the following statements regarding tuberculosis (TB) prophylaxis is correct?**
   a. All treated patients with myasthenia gravis must receive TB prophylaxis.
   b. TB prophylaxis in myasthenia gravis patients only increases the pill burden with no clinical benefit ever.
   c. TB prophylaxis for at least six months is justified in those myasthenic patients who will receive high-dose prednisone (> 0.3 mg/kg/d) and have healed/fibrotic TB on chest radiographs.
   d. TB prophylaxis for at least six months is justified even in those myasthenic patients who will receive very low dose prednisone (< 0.1 mg/kg/d) and have healed/fibrotic TB on chest radiographs.