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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

The Course of Headache in Idiopathic Intracranial Hypertension

By Louise M. Klebanoff, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Klebanoff reports no financial relationships relevant to this field of study.

SYNOPSIS: In a prospective study of 35 patients with newly diagnosed idiopathic intracranial hypertension confirmed by diagnostic lumbar puncture and treated with standard medication regimens, 43% of patients had excellent headache outcome at 12 months, with the major improvement seen within the first month of diagnosis. Chronic headache was seen in another 43% of patients despite identical treatment, normalization of intracranial pressure, and resolution of papilledema.

SOURCE: Yri HM, et al. The course of headache in idiopathic intracranial hypertension: A 12-month prospective follow-up study. *Eur J Neurol* 2014;21:1458-1464.

Idiopathic intracranial hypertension (IIH), a condition defined by elevated intracranial pressure (ICP) of unknown etiology, primarily affects young women. More than 90% of patients present with severe headache. Patients are at risk for developing chronic headache and permanent visual loss due to papilledema and secondary optic nerve atrophy. In many patients, chronic headache persists even after papilledema and other signs of intracranial hypertension have resolved. Data on the long-term outcome of IIH headache are sparse. This prospective study aimed to describe the course of headache and papilledema during the first year after the IIH diagnosis and to define possible predictors of headache outcome.

The study included patients with newly diagnosed IIH referred within 7 days of diagnostic lumbar puncture. All patients underwent detailed neurological examinations, brain imaging studies (including magnetic resonance or computed tomography with venous sequences) and comprehensive neuro-ophthalmological examination (Snellen visual acuity, Humphrey automated visual fields, Ishihara color-plates, motility, slit-lamp, and fundus examination) to confirm the diagnosis. Papilledema was quantified by optical coherence tomography measures of peripapillary retinal nerve

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fiber layer thickness. Standardized lumbar puncture ICP manometry was performed at diagnosis and after 3 months. Headache history and follow-up were obtained by a standardized structured interview that included details of headache onset, frequency, duration, intensity, character of pain, location, accompanying symptoms, pre-existing headache, and detailed medication history (including over-the-counter analgesics). Following diagnostic lumbar puncture, treatment with acetazolamide and/or topiramate was initiated. Weight loss was encouraged and dietician consultations were offered. Simple analgesics were allowed up to 14 days per month; other than topiramate, no medications for headache prophylaxis were allowed.

Forty-four patients with newly diagnosed IIH were included in the study. The median age was 27.5 years; all but one patient was female. Eighty-nine percent had papilledema. Pre-existing headaches were noted in 45% of the patients. Sixty-eight percent of the headaches reported fulfilled diagnostic criteria for migraine, and 82% if headache attacks < 4 hours were included. Headaches were frequently exacerbated by cough or strain (70%), bending forward (52%), or physical activity (64%). Acetazolamide (750-2225 mg/day) was the sole medication in 36 patients, two patients were treated solely with topiramate, and three were treated with a combination of the two medications. Three patients underwent ventriculoperitoneal shunting during the study period, two due to progressive visual deterioration and one due to intractable headache and medication intolerance. Thirty-five patients (80%) completed the 12-month follow-up.

The most dramatic improvement in headache was seen within the first month following diagnosis. At the 1-month follow-up, headache index had reduced by > 75% in two-thirds of patients and almost one-third of patients reported that the headache had completely resolved. The prevalence of constant headache improved from 64% to only 13%. Proportions of patients reporting daily occurring headache reduced from 86% to 41%. The median intensity of daily occurring headache reduced from 7.5 to 5.0 on the 0-10 visual analogue scale. There was only a minor reduction in headache characteristics between the 1-month and 12-month follow-up.

Forty-three percent of patients reported persisting headache at the 12-month follow-up. Half of these patients had a history of pre-existing headache. Young age at onset and high opening pressure were both associated with better odds of being headache-free or having infrequent (< 1 day/month) headache after 12 months.

The extent of papilledema at diagnosis was linearly associated with the diagnostic ICP and inversely correlated with age at onset. Papilledema improved significantly within the first 3 months of treatment. At 12 months, there was no difference in retinal nerve fiber layer thickness between patients and controls. Visual outcome was excellent in most cases. At 3- and 12-month follow-up, visual fields and acuity were normal in the majority of eyes. Severe deterioration of vision of organic origin was found in only one patient with fulminant IIH.

■ COMMENTARY

In 43% of patients, there was significant improvement or complete resolution of headache, with most of the improvement occurring within the first month of diagnosis and treatment. Despite identical treatment, an equal number of patients had persistent chronic headache. Young age at onset and high opening pressure at the time of diagnosis were associated with better headache outcome. Short duration of headache prior to diagnosis and subsequent weight loss did not improve the chance of headache resolution. Normalization of ICP at the 3-month follow-up was also not related to headache resolution, supporting the concept that elevated ICP alone is not responsible for the headache in IIH. Although half of the patients with persistent headache reported a pre-existing headache syndrome, half of the patients had no prior headache syndrome, suggesting the development of a de novo chronic headache syndrome induced by IIH despite the normalization of ICP. The mechanism of chronification of headache in IIH is unknown. One possible mechanism is the sensitization of central pain pathways, although the lack of correlation of symptom duration and headache outcome in this group of patients argues against this mechanism. Headache in IIH is likely attributed more complex mechanisms than ICP elevation alone. ■

ABSTRACT & COMMENTARY

Varicella-Zoster Virus and Fingolimod: Much Ado about Not Much?

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Safdieh reports no financial relationships relevant to this field of study.

SYNOPSIS: The risk of varicella-zoster virus infections in patients treated with fingolimod is slightly higher than placebo, but is overall quite low.

SOURCE: Arvin AM, et al. Varicella-zoster virus in patients treated with fingolimod: Risk assessment and consensus recommendations for management. *JAMA Neurol* 2014;Nov 24 doi:10.1001/jamaneurol.2014.3065 [Epub ahead of print].

The rapidly evolving field of novel therapies for multiple sclerosis (MS) has led to FDA approval of a number of oral therapies. Fingolimod, the first oral therapy approved for MS, sequesters certain types of T lymphocytes in the lymph nodes by modulating sphingosine 1-phosphate receptors. Fingolimod lowers lymphocyte counts by 20-30% and, therefore, does increase the risk of infections. FDA labeling for fingolimod specifically notes a death from disseminated zoster infection and states that patients should be assessed for prior varicella infection or vaccination, or have varicella-zoster virus (VZV) serum antibodies assessed prior to initiation of therapy to ensure prior immunity. Nonimmune patients should be vaccinated prior to initiation of therapy. VZV is a herpesvirus that causes varicella (chickenpox) during initial infection and shingles (herpes zoster) during reactivation. Risk factors for reactivation (shingles) increase in settings of reduced T-cell immunity, including age, HIV infection, and immunosuppression by medications.

In this study, the authors calculated the rates of VZV infection in patients with MS treated with fingolimod. The rates were derived from a number of cohorts, including the patients enrolled in the completed Phase 2 and 3 trials for fingolimod and postmarketing reports since approval in 2010. It is important to note that the clinical trial included a cohort of patients receiving 1.25 mg/day, much higher than the eventual FDA-approved dose of 0.5 mg/day. Rates of VZV were calculated in patient-years.

Analysis of the data revealed that the rate of VZV infection in the fingolimod-treated patients in clinical trials was 11 per 1000 patient-years. The placebo rate was 6 per 1000 patient-years. In postmarketing data, the reported rate of VZV infection was 7 per 1000 patient-years, lower than the clinical trial patients but higher than postmarketing reports for all other disease-modifying MS therapies. Of note, two fatal cases of VZV were reported, one during the clinical trial in a patient receiving the high dose and another with standard dosing reported in postmarketing data. That patient was previously treated with natalizumab and was receiving 10 days of concomitant corticosteroid therapy. The majority of cases of VZV were uncomplicated, involving one or two dermatomes. Eight percent of cases involved more than two dermatomes. Non-cutaneous dissemination was extremely rare. Rates of serious VZV infections were not higher in fingolimod groups compared to other MS disease-modifying therapies.

Based on these results, the authors conclude that while the risk of VZV in fingolimod-treated patients is higher than placebo, the absolute numbers (11 per 1000 patient-years in the clinical trial and 7 per 1000 patient-years in postmarketing) are quite low and the vast majority of cases involved one or two dermatomes only. However, the authors do propose consensus guidelines to most effectively mitigate the risk of VZV in patients who are being considered for treatment or who are being treated with fingolimod. These include testing for VZV antibodies in patients with no clear history of varicella, vaccinating non-immune patients with varicella vaccination at least 1 month before initiating therapy, avoiding varicella vaccination during fingolimod therapy as it is a live-attenuated vaccine, limiting corticosteroid treatment for MS relapses to 3-5 days in patients receiving fingolimod, and having high vigilance for recognizing and treating zoster in patients on fingolimod therapy. Patients should be educated about signs and symptoms of shingles and told to report them to their physician if they suspect shingles. The consensus is to stop fingolimod in the setting of zoster only if disseminated and to treat VZV infections with antiviral therapy as per CDC guidelines. ■

ABSTRACT & COMMENTARY

Cerebrospinal Fluid ß-Amyloid 42 vs Amyloid PET Imaging in the Diagnosis of Alzheimer's Disease

By Richard S. Isaacson, MD

Associate Professor of Neurology (Education), Weill Cornell Medical College

Dr. Isaacson reports he is a retained consultant and on the speakers bureau for Novartis, and is a retained consultant for and receives grant/research support from Accera.

SYNOPSIS: Aß 42, measured in cerebrospinal fluid, may help determine whether patients have normal or increased cortical Aß deposition. Additionally, abnormal PET 18F-flutemetamol retention levels correlate with disease stage in patients with mild cognitive symptoms.

SOURCE: Palmqvist S, et al. Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid ß-Amyloid 42: A cross-validation study against amyloid positron emission tomography. *JAMA Neurology* 2014;71:1282-1289. doi:10.1001/jamaneurol.2014.1358.

The future of Alzheimer's disease (AD) treatment will rely on disease-modifying therapy that is begun as early as possible in the development of the disease. The most recent AD diagnostic criteria were reported in 2011, and most accurately reflect our current understanding of AD (National Institutes of Aging/Alzheimer's Association criteria). These new standards describe a spectrum of AD that starts many years, decades in fact, before the first symptoms occur. This new model breaks down AD into three different stages. It is important to note that before AD becomes manifest in the brain, patients may be classified in the prodromal stage, meaning the disease has not started and no symptoms have begun. Stage 1 refers to AD starting in the brain without symptoms ("preclinical" AD). Stage 2 refers to mild memory loss, but the person can still perform all of their usual daily activities (mild cognitive impairment due to AD). Stage 3 refers to dementia due to AD. For the most optimal effect, future drug treatments will need to be initiated at a preclinical or prodromal stage to offer the most clinically relevant neuroprotection.

Therefore, establishing diagnostic tools that identify AD pathology at an early stage is of paramount importance. A new cross-sectional study by Palmqvist and colleagues has found that in routine clinical practice (at three memory clinics in Sweden), Aß42 that was measured in cerebrospinal fluid (CSF) may help determine whether patients have normal or increased cortical Aß deposition. Additionally, amyloid positron emission tomography (PET) imaging with 18F-flutemetamolabnormal highly correlated retention levels with disease stage in patients with mild cognitive symptoms. The study population included patients with mild cognitive symptoms (n = 118 Stage 2 of AD, with validation cohort n = 38) from the Swedish BioFINDER (Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably) study (visit www.biofinder.se for additional information).

Results demonstrated very high agreement between Aß classification with CSF Aß42 and 18F-flutemetamol PET, with 92% of cases identically classified using an Aß42 cutoff of ≤ 647 pg/mL. In addition, CSF Aß42 accurately predicted abnormal cortical Aß deposition in all cortical regions.

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This is the first evidence helping to determine whether levels of CSF Aß42 can be used with validity and reliability to detect abnormal brain Aß deposition when analyzed consecutively over a few years within the context of routine clinical practice. While such CSF studies tend to be ordered more frequently in subspecialty memory clinics when diagnostic accuracy is in doubt, the vast majority of neurologists have not incorporated this testing into their diagnostic armamentarium. Proof-of-concept studies such as this are necessary prior to more widespread adoption of using CSF biomarkers as part of the diagnosis of Stage 2 and 3 AD. Considering known issues of variability of CSF biomarker levels, accuracy of CSF Aß42 measurements in clinical practice was quite good. High reliability and validity of CSF Aß42 levels for predicting cortical Aß deposition was also used when using 18F-flutemetamol PET as a more appropriate "gold standard." While controversial, of the currently available methods, amyloid PET is believed to be the most suitable surrogate in vivo marker for amyloid load due to the high correlation with histopathology.

At this time, from a practical clinical perspective, alteration in clinical practice by measuring CSF Aß42 to aid in diagnosis and help stratify patients cannot yet clearly be recommended. However, these data continue to expand upon recent progress in the diagnosis of AD at the earliest clinical stages, as well as prodromal AD, and will help to select patients for a future drug most optimally suited for AD prevention. ■

ABSTRACT & COMMENTARY

Is Exercise Harmful in Charcot-Marie-Tooth Disease?

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study.

SYNOPSIS: Unlike other neuromuscular disorders, physical exercise does not appear to worsen weakness in patients with Charcot-Marie-Tooth disease.

SOURCE: Piscosquito G, et al. Is overwork weakness relevant in Charcot-Marie-Tooth disease? *J Neurol Neurosurg Psychiatry* 2014;85:1354-1358.

Overwork weakness, defined as increased disease progression as a result of muscle overload, has been demonstrated in Duchenne muscular dystrophy, facioscapulohumeral muscular dystrophy, amyotrophic lateral sclerosis, and post-polio syndrome. As a result, patients are advised to relatively spare affected muscles during physical activity to prevent premature worsening. Does this apply to Charcot-Marie-Tooth disease (CMT)?

If overwork weakness were to play a role in CMT, hand strength would be expected to be superior in the non-dominant hand, because dominant hands do more work. Hence, to address this question, retrospective data review was undertaken on 271 CMT 1A patients, 108 men and 163 women, ages 18-70 years, recruited in the ascorbic acid in Charcot-Marie-Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK) double-blind, randomized trial. Muscle strength was graded using the MRC scale and tested in distal muscles most affected in CMT, including the first dorsal interosseous and abductor pollicis brevis in both hands, and tibialis anterior and gastrocnemius/soleus complex in both legs. Using a 9-hole peg test, manual dexterity was tested and expressed in seconds. Side-to-side comparisons were made, with asymmetry defined as an MRC grade differential of 1 or more between sides. Statistical analysis included the chi-square and Fisher's exact test, the Wilcoxon rank sum test or Kruskal-Wallis for comparisons, and the Shapiro-Wilk normality test, with statistical significance set at $P < 0.05$.

None of the patients demonstrated any significant side-to-side difference in hand or foot muscle strength for any muscle tested, while dexterity, as expected, was significantly better on the patient's dominant side. In all muscles studied, strength significantly decreased with increasing disease severity and with age, with no significant difference seen between dominant or non-dominant hands, but with a mild but significant difference found in gastrocnemius/soleus strength in older patients, which was greater on the dominant side. Gender affected neither symmetry nor strength between sides.

Overwork weakness does not appear to play a role in CMT 1A, and patients may be encouraged to exercise to their heart's content.

[Overwork weakness does not appear to play a role in Charcot-Marie-Tooth disease type 1A; patients may be encouraged to exercise to their heart's content.]

■ COMMENTARY

Although more than 75 gene mutations may result in CMT, in most North American and European countries, the most frequent forms of CMT are autosomal dominant, with CMT1 accounting for more than 80%, most of whom have the classical CMT phenotype, with median motor nerve conduction velocities of 38 m/s and nerve biopsies demonstrating decreased numbers of myelinated axons with "onion bulbs," comprising several layers of basal lamina, Schwann cells, and connective tissue surrounding thinly myelinated axons. Presently, CMT1 is sub-classified as CMT1A to CMT1F, with CMT1A caused by a 1.4-Mb duplication of chromosome 17 containing the peripheral myelin protein 22 gene (PMP22). Together with mutations affecting myelin protein zero (MPZ), mitofusin 2 (MFN2), and gap junction beta-1 protein (GJB1, also referred to as connexin 32, Cx32), these abnormalities comprise more than 80% of CMT patients in Western countries. While a cure remains a distant hope, our understanding of the underlying pathophysiology is advancing dramatically.[1] ■

REFERENCE

1. Tazir M, et al. Hereditary motor and sensory neuropathies or Carcot-Marie-Tooth diseases: An update. *J Neurol Sci* 2014;347:14-22. http://dx.doi.org/10.1016/j.jns.2014.10.013.

ABSTRACT & COMMENTARY

Somatic Mutations in Cerebral Cortical Malformations

By Eric Mallack, MD, MBE and Barry Kosofsky, MD, PhD

Dr. Mallack is Fellow, Department of Pediatrics, Division of Pediatric Neurology, Weill Cornell Medical College. Dr. Kosofsky is Chief, Division of Pediatric Neurology, Goldsmith Professor of Pediatrics, Neurology and Neuroscience, and Radiology, Weill Cornell Medical College.

Drs. Mallack and Kosofsky report no financial relationships relevant to this field of study.

SYNOPSIS: Targeted high-coverage sequencing for causal somatic mutations in patients with cortical malformations is more sensitive than traditional Sanger and whole-exome sequencing.

SOURCE: Jamuar SS, et al. Somatic mutations in cerebral cortical malformations. *N Eng J Med* 2014;371:733-743.

The role of somatic mutations in cancer has been well established. However, the analogous role of somatic mutations in normally dividing cells, and its relation to non-cancerous disease states, is less well described. This study evaluates the improved diagnostic sensitivity of targeted high-coverage DNA sequencing using "Next-Gen," a method used commonly in detecting somatic mutations in tumor samples, vs traditional Sanger sequencing in detecting cerebral cortical malformations. The authors analyzed DNA acquired from blood samples derived from human subjects with the double-cortex syndrome (subcortical band heterotopia), polymicrogyria with megalencephaly, periventricular nodular heterotopia, or pachygyria, and used this novel, high throughput, targeted DNA diagnostic approach to estimate the prevalence of mosaicism in each condition.

A total of 158 affected individuals were studied, all diagnosed with cortical malformations radiographically by MRI. Two targeted high-coverage gene panels were designed to detect a combination of 68 genes known to be the most frequent genetically identifiable causes of cerebral cortical malformations. To detect mosaicism, libraries of sequence data were generated from DNA isolated from peripheral blood samples and analyzed using this high-coverage sequencing method. The inclusion criteria for pathogenic mutations were defined as mutations that are known to cause the disorder, are absent from controls, alter the sequence of the encoded protein, and alter the function of the encoded protein (as predicted by SIFT or Poly-Phen-2 software algorithms).

The authors report that by using this sophisticated Next-Gen DNA diagnostic approach specifically designed to identify somatic mutations in a set of genes known to affect structural brain development, study of peripheral blood samples revealed the following:

1. 17% (n = 27) of the 158 subjects were found to have causative mutations.
2. 30% (n = 8) of the 27 were found to be somatic, non-germline, mosaic mutations by targeted high coverage sequencing: six occurred among 30 patients with Double-Cortex Syndrome who had a somatic mutation in either the DCX or LIS1 gene; one of eight patients with periventricular nodular heterotopia had a somatic mutation in the FLNA gene; one of eight patients with pachygyria had a somatic mutation in the TUBB2B gene.
3. As compared to Next-Gen sequencing, five of those eight mutations were misread by traditional Sanger sequencing as either undetected or classified as germline anomalies.
4. Standard (Sanger) DNA sequencing methods routinely identify a corresponding mutation only when it is present in at least 10% of circulating blood cells.

■ COMMENTARY

This study brings to light the practical exigencies that exist in our era of increasing options for and sophistication of genetic testing for developmental brain disorders and other neurologic diseases. It nicely illustrates the limitations of our current genetic testing methods. The authors have demonstrated that the traditional Sanger method of DNA sequencing has a lower sensitivity for correctly detecting and classifying somatic mutations vs targeted high-coverage sequencing, as shown by testing for DCX and LIS1 in the Double-Cortex Syndrome. Even more striking, with the promise of whole-exome sequencing as being a "diagnostic promised land," Next-Gen sequencing was able to detect a somatic mutation in a patient with pachygyria, whereas whole-exome sequencing returned a false negative result for the TUBB2B gene. This is consistent with other limitations of whole-exome sequencing, such as an inability to test for triplicate repeat disorders, requiring additional specific gene panels to be utilized for such testing.

The article also advances an understanding of the clinical severity secondary to somatic mosaicism in cerebral cortical malformations vs that of germline mutations. The DCX mutation (R186C) in the germline of one subject produced the expected phenotype of thick-band heterotopia in both anterior and posterior portions of the brain. The same mosaic mutation in a different subject in whom approximately only 10% of brain cells expressed that same mutation, produced a milder phenotype of predominantly anterior, thin-band heterotopia.

The study does make a critical assumption; the degree of mosaicism found in peripheral cells for a mutation is quantitatively reflective of that which exists in the brain. The reality of the matter is that in this study, brain tissue was not directly tested, so the corresponding incidence and expression of the somatic mutations reported from the blood in the brain is unknown. However, these same authors have additionally pioneered approaches to enable such single brain cell DNA diagnostics.[1]

In terms of shedding light on the full clinical picture of these disorders, the study showed the ability of targeted Next-Gen DNA sequencing to implicate new genes that may cause certain cerebral cortical

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Stroke Alert

By Matthew E. Fink, MD

Early, Intensive Rehabilitation Improves Outcome in Patients with Intracerebral Hemorrhage

SOURCE: Liu N, et al. Randomized controlled trial of early rehabilitation after intracerebral hemorrhage stroke: Difference in outcomes within 6 months of stroke. *Stroke* 2014;45:3502-3507.

At least 30% of strokes in China are caused by intracerebral hemorrhage, compared with approximately 10-15% in North America. There are a huge number of such cases in China, and interventions to reduce the effects would be important, but, to date, no significant therapies have been demonstrated to improve outcome, reduce mortality, or result in improved functional neurologic status. In this large multicenter, randomized, controlled study, with blinded outcome at 3 and 6 months, patients were randomized to receive standard care, which was family-directed physical therapy beginning 1 week after the hemorrhage, or standard care plus early rehabilitation, defined as professional rehabilitation started within 48 hours of hemorrhage. The primary outcome was survival. Secondary outcome measures included health-related quality of life using the SF 36 questionnaire, the modified Barthel index, and the Zung Self-Rated Anxiety Scale.

A total of 243 of 326 eligible patients were randomized (mean age = 59 years; 56% were men). At 6 months, patients who received standard care were more likely to have died (hazard ratio, 4.44), and for all morbidity outcomes, patients who received early rehabilitation had better outcomes, as measured by the SF 36 questionnaire, the modified Barthel index score, and the self-rated anxiety scale scores. The study strongly supports the benefit of early rehabilitation within 48 hours of intracerebral hemorrhage to improve survival and functional outcomes at 6 months in patients who were hospitalized in China. Whether these findings can be generalized to populations outside of China is uncertain, but it should certainly be evaluated and replicated if possible. ■

CT Angiography Is Most Cost-Effective Definitive Test to Identify Aneurysm in Perimesencephalic Subarachnoid Hemorrhage

SOURCE: Kalra VB, et al. Cost-effectiveness of angiographic imaging in isolated perimesencephalic subarachnoid hemorrhage. *Stroke* 2014;45:3576-3582.

Nontraumatic perimesencephalic subarachnoid hemorrhage is a distinct imaging and clinical entity that is found in approximately 5% of patients with subarachnoid hemorrhage. However, about 10% of these patients will have a hemorrhage caused by a ruptured posterior circulation aneurysm, and controversy exists regarding the most definitive and cost-effective test to use to diagnose these small number of aneurysms. Choices have been digital subtraction angiography, or CT angiography, with and without follow-up evaluation if the initial studies are negative. The authors developed a decision tree based on a meta-analysis of 40 studies in the literature, and performed base case and sensitivity analyses to assess cost-effectiveness of various strategies.

The most cost-effective strategy was to perform initial CT angiography with no follow-up angiographic studies needed in patients who had a clinical picture of perimesencephalic subarachnoid hemorrhage, if the CT angiogram was negative for an aneurysm. Even if one was willing to pay up to $1 million for evaluation, the same strategy remains most cost-effective, that is, an initial CT angiogram with no follow-up study required, assuming that the sensitivity of the initial study is greater than 97.9%. Under no circumstances was digital subtraction angiography felt to be superior, or more cost effective, than CT angiography as an initial study. ■

malformations, in this case pachygyria. The approach reports de novo mutations in two previously unknown genes: DYNC1H1 (which matched the genotype of two participants in a parallel study) and a novel mutation in KIF5C. It also implicated known genes KIF7, KIF1A, and KIF2A, thought previously to not play a role in disease. This may be the most important point of this research, as the multiple advanced genetic diagnostic modalities utilized in this study only identified 27 mutations (17%) in the 158 subjects diagnosed with a brain malformation. These investigators have confirmed that targeted high-coverage sequencing is an example of a novel approach to genetic testing that provides enhanced diagnostic sensitivity as well as the potential for discovering new disease-causing mutations, which can increasingly be applied to many developmental brain and neurologic disorders. ■

REFERENCE

1. Cai X, et al. Single-cell, genome-wide sequencing identifies clonal somatic copy-number variation in the human brain. *Cell Rep* 2014;8:1280-1289..

CME QUESTIONS

1. **In patients with newly diagnosed idiopathic intracranial hypertension, which of the following characteristics is associated with improved headache outcome?**
   a. High intracranial pressure at diagnosis
   b. Subsequent weight loss
   c. Normalization of intracranial pressure at 3 months
   d. Short duration of headache prior to diagnosis
2. **In clinical practice, recent evidence supports the use of CSF Aß42 levels to independently predict cortical amyloid deposition with very high accuracy, and may be most valuable for diagnostic workup of which stage of AD?**
   a. Prodromal
   b. Stage 1
   c. Stage 2
   d. Stage 3
3. **VZV infections in patients with multiple sclerosis are increased in those receiving disease-modifying immune-suppression therapies.**
   a. True
   b. False
4. **For which of the following disease(s) has overwork weakness, defined as increased disease progression as a result of muscle overload, been demonstrated?**
   a. Duchenne muscular dystrophy
   b. Facioscapulohumeral muscular dystrophy
   c. Amyotrophic lateral sclerosis
   d. Post-polio syndrome
   e. All the above
5. **Brain malformations are associated with which of the following genetic abnormalities?**
   a. There are no associated genetic abnormalities.
   b. Genetic abnormalities are rare.
   c. Approximately 15-20% of patients have causative gene mutations.
   d. Current technology is unable to diagnose genetic disorders.
   e. Genetic disorders are irrelevant to the causation of brain malformations.

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Update on Parkinson's disease

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