

populations.² Only 10% of patients in the Korean population and 28% of the current Taiwanese series had mutations in this more centromeric section of the chromosome.

No patient with the R544C mutation in either the Taiwanese or Korean study was from a common pedigree, suggesting a “founder effect” from a common remote ancestor. Such population genetics would be expected in island populations and for a disorder such as CADASIL that occurs later in life and does not affect fertility.

In the current study, six intracerebral hemorrhages (ICHs) were found in five patients (24%), all of whom had a history of hypertension, three having prior treatment with aspirin. All of these patients had R544C mutations. MRI showed white matter hyperintensities in the anterior temporal lobe in 43%, in contrast to the recent British study, which showed sensitivity of 89% and specificity of 86% for this finding. MRI localization appears to correlate with genetics, since all of the patients in the current study with mutations in exons 2–6 had anterior temporal lobe findings, while only one of the patients with R544C in exon 11 had involvement of this area. In addition, the Korean cohort again seems to match the Taiwanese much more closely showing on 20% anterior temporal lobe involvement. Similarly, the Korean population had a 25% hemorrhage rate (all having the R544C mutation). None of the patients in the British series were reported to have hemorrhage.

■ COMMENTARY

One weakness of Lee’s study is that skin biopsies were either negative or not done, limiting pre-genomic diagnostic accuracy to clinical and radiologic grounds. Nevertheless, these data provide an elegant example of how the clinical spectrum of a disease can be closely correlated with its population genetics. While the precise mechanism through which a NOTCH3, exon 11, R544C mutation might produce CADASIL is unknown, its unique clinical phenotype is easily recognizable. Asian patients lack the classical anterior temporal leukoariosis seen in Western cohorts, but more often present with hypertension and ICH. Whether hypertension and CADASIL interact in an additive fashion to produce ICH is unknown. From a therapeutic perspective, aspirin therapy might be prescribed for patients presenting primarily with ischemic disease, but might be withheld from Asians at risk for bleeding.

Lee’s study is a fascinating example of how a syndrome with varied clinical features might be a direct manifestation of heterogeneity in its underlying genetics. The next step is to investigate how these

various genotypes can functionally produce such marked differences in brain pathology.

References

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2. Markus HS, Martin RJ, Simpson MA, et al. Diagnostic strategies in CADASIL. *Neurology* 2002; 59: 1134. ■

Inclusion Body Myositis: A Final Word

ABSTRACT & COMMENTARY

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Dr. Rubin reports that he receives grant/research support from Pfizer and is on the speaker’s bureau of Athena Diagnostics.

Synopsis: *Inclusion body myositis remains a mystery—the underlying cause and pathogenesis have yet to be fully understood.*

Source: Karpati G, O’Ferrall EK. Sporadic inclusion body myositis: pathogenic considerations. *Ann Neurol* 2009;65: 7-11.

SPORADIC INCLUSION BODY MYOSITIS (IBM) IS THE most common acquired myopathy with onset over the age of 50 years. Unresponsive to therapy, its etiology remains a puzzle. In this paper, the last published in his lifetime, George Karpati, who in 1978 first described IBM as a distinct clinical and pathological entity, offers a final word on its pathogenesis.

Categorized as an inflammatory myopathy, both degenerative and inflammatory changes are seen pathologically. Myonuclear abnormalities, including the presence of 18-nm tubular filaments, rimmed vacuoles, small-caliber muscle fibers, increased endomysial connective tissue, muscle fiber hypertrophy, and ragged red fibers suggesting mitochondrial abnormalities, comprise the degenerative changes reported. Cytoplasmic–amyloid accumulation, reputedly myotoxic, has been described by some, but not found by others. None of these findings are diagnostic in isolation but the constellation of these features is characteristic. Endomysial CD8⁺ lymphocyte and macrophage collections with partial invasion of these cells into nonnecrotic muscle fibers, as well as

endomysial dendritic and CD138⁺ plasma cells, encompass the inflammatory features of IBM.

Proposed pathogenic paradigms ascribe either a primary role to inflammation with degenerative changes the resulting byproduct, or the reverse, with degenerative changes believed to be primary, and inflammation a secondary phenomenon. The firm skeptic (George Karpati) accepts neither scenario. Inflammation-first advocates suggest that an antigenic trigger, perhaps a virus, provokes a process, including clonal expansion of CD8⁺ lymphocytes and release of proinflammatory cytokines and chemokines, which results in cell injury and death. Arguing against this scenario is the lack of therapeutic benefit with immunosuppression, the paucity of necrosis and regeneration in sporadic IBM, and the absence of inflammatory changes in the inherited form. Degeneration-first advocates offer that, well before clinical symptoms begin, alterations of the myonuclear matrix putatively develops, resulting in transcriptional or RNA-handling dysregulation and nuclear membrane dissolution, with rimmed vacuole and tubular filament formation. Subsequent inflammatory changes may be immune mediated. Hereditary IBM lacks these inflammatory changes, arguing against this theory as well. Most plausibly, inflammatory and degenerative changes occur independently, the consequence of hitherto undiscovered agents, and it is to these agent(s) provocateurs that future research should best be directed to resolve the controversy and ultimately offer efficacious treatment.

■ COMMENTARY

George Karpati, 1934–2009, was a man of epic achievements. Husband, father, teacher, mentor, physician, scientist, Chevalier de l'ordre National du Québec, and—his proudest accomplishment (personal communication)—officer of the Order of Canada, Canada's highest civilian honor, George Karpati still had much to contribute. This writer had the privilege to be trained under him and owes his professional advancement, at least in part, to him. Always available for counsel and advice, either professional or personal, by phone or email, he was able to quickly recognize the issue at hand, direct listeners on the best course of action, and intervening himself if he felt it warranted. Many will miss him. ■

Long-term EEG Monitoring: 'Holter' Monitor for the Brain

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

Synopsis: *The authors in this retrospective study review their experience in long term EEG monitoring (LTM) and utility in the clinical diagnosis and classification of epilepsy.*

Source: Yogarajah M, Powell HW, Heaney D, et al. Long term monitoring in refractory epilepsy: the Gowers Unit experience. *J Neurol Neurosurg Psychiatry* 2009;80:305-311.

HISTORICALLY, THE GOLD STANDARD IN ESTABLISHING or refuting a diagnosis of epilepsy or seizures has been the electroencephalogram. Advances in neurophysiology, including digital long-term monitoring, have helped increase the yield of capturing and characterizing paroxysmal symptoms. In response to this ever-growing technology, the International League Against Epilepsy (ILAE) released a 2007 position paper outlining the recommended applications for long-term recording, including detection, characterization, and quantification of electroclinical seizures in epilepsy, differentiation of epileptic and non-epileptic events, and identification of subclinical seizures in comatose patients. In this article, the authors scrutinize their own database of long-term monitoring cases over a consecutive one-year period and report their findings in the context of the established guidelines.

From 2005–2005, 364 patients at the Gowers Center were retrospectively identified and met criteria for inclusion into the study. Patients who had been previously monitored at the center were excluded. Patients were admitted to the unit for either inpatient ambulatory EEG or inpatient video EEG. Both the admitting and discharge diagnoses were recorded for each case. The reason for admission was divided into three distinct categories: diagnostic clarification, medication changes, and presurgical evaluation. For those admitted for diagnostic clarification, pre- and post-admission diagnoses were compared. Patients were then stratified into one of three categories after long-term monitoring: no change in diagnosis, refinement in diagnosis, and change in diagnosis. All epilepsy diagnoses were classified as focal, idiopathic generalized,

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