In the Literature

Mitochondria and AIDS


The capture by a proto-eukaryote of an endosymbiotic α-Proteobacterium closely related to the obligate intracellular parasite Rickettsia prowazekii several hundred million years ago provided the latter with not only an energy factory, but also a key regulator of apoptosis. Mitochondria contain their own genomes, which are maternally inherited as a single haplotype and which replicate independently of the chromosomal genome. Evolution over the millennia has led to the development of a variety of mitochondrial DNA (mtDNA) genotypes that may differ not only in sequence, but also in functional activity. It is not surprising that variations in mtDNA have been associated with a variety of disease states. To examine their potential role in the progression of human immunodeficiency virus type 1 (HIV-1) infection, Hedrickson and colleagues compared outcomes with mtDNA haplogroups in 1833 American HIV-1–infected patients of European origin.

Subjects were placed into 1 of 3 major groups on the basis of findings from an examination of 6 mitochondrial single-nucleotide polymorphisms (SNPs). Those in the N haplotype group, which indicated European origin, underwent further interrogation of key European mtDNA polymorphisms to define haplogroups. Statistical analysis demonstrated a number of significant associations of haplogroup with the course of HIV-1 infection. For instance, the J haplogroup was associated with accelerated progression to AIDS and AIDS-related death, and the U5a haplogroup was associated with accelerated loss of CD4 cells to counts <200 cells/μL. In contrast, haplogroups IWX and H3 were associated with a delay in onset of AIDS.

Genetic variation in mtDNA has been associated with varying risk of a number of disease states, including hereditary optic neuropathy and other neurodegenerative diseases, such as Parkinson disease. In addition to the relationship between the various haplogroups and outcome of HIV-1 infection reviewed here, haplotype H is reported to be associated with improved survival in sepsis.

The association of mtDNA haplotypes with outcome of HIV-1 infection should not be too surprising, given the already known roles of mitochondrial dysfunction in this disease. Thus, progression to AIDS is associated with depletion of mtDNA and loss of related energy production, and many adverse effects associated with use some nucleoside reverse-transcriptase inhibitors (e.g., lipodystrophy, lactic acidosis, hepatic steatosis, and peripheral neuropathy) have been ascribed to mitochondrial toxicity.

The discovery that a 32–base pair deletion in the CCR5 gene provides almost absolute protection from HIV-1 infection in homozygotes and delayed progression in heterozygotes opened a window into the vigorous examination of the role of host genetic factors in this disease. Since that finding, a wide variety of human genetic polymorphisms have been shown to affect the course of HIV-1 infection, including those associated with human leukocyte antigen, mannose-binding lectin, chemokines, and chemokine receptors, in addition to CCR5, Trim5, and interleukin-10. Although the work of Hedrickson and colleagues requires additional confirmation, it appears that mtDNA polymorphisms can be added to this list.

Arboviral Infections of the Central Nervous System in the United States


Until the appearance of West Nile virus (WNV) in the United States in 1999, the diagnosis of arboviral infection in this country was a relatively infrequent event. Reimann and colleagues have reviewed cases of neuroinvasive autochthonously acquired arboviral disease reported to the Centers for Disease Control and Prevention during the period 1990–2007.

Although the incidence of cases of arboviral disease due to St. Louis encephalitis virus significantly decreased after the initial detection of WNV, the incidence of cases due to both California serogroup and Eastern equine encephalitis virus remained stable. As expected, WNV dominated during the examined time period, with 11,125 cases of neuroinvasive disease reported, starting with a total of 78 cases in the first 2 years, peaking at 2865 cases in 2003, and ending with 1221 cases in 2007. California serogroup viruses, which caused a total of 895 cases during the period examined and which primarily affected children, were the second most frequently identified viruses, but with no obvious temporal trend. Species differentiation of California group viruses, which was first applied beginning in 2005, identified 407 of 412 viruses as La Crosse virus; the remaining 5 were not speciated. Most cases were detected in Appalachia and the upper Midwest (West Virginia, 235 cases; Ohio, 152 cases; North Carolina, 126 cases; Tennessee, 111 cases; Wisconsin, 168 cases; Minnesota, 48 cases; and Illinois, 939 cases). The reported mortality rate for the cases in which the outcome was known was 2%.

St. Louis encephalitis virus was the third most frequently reported arboviral cause of neuroinvasive disease; 87% of cases identified in Louisiana, Texas, Arizona, Michigan, and Mississippi were due to St. Louis encephalitis virus. The incidence was highest among individuals aged ≥40

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years, with three-fourths of cases occurring in this age group. Eighty cases were due to Eastern equine encephalitis virus, with the highest cumulative incidence occurring in counties along the Atlantic and Gulf coasts. The case-fatality rate among those for whom this information was available was 32%. Finally, there were 14 cases of neuroinvasive disease attributed to Powassan virus and 1 case each due to Western equine encephalitis and Cache valley virus.

Knowledge of the geographic clustering of cases of arboviral infection facilitates focused preventive interventions and provides valuable information to clinicians confronted with patients with apparent viral infections of the central nervous system. With the modest exceptions of WNV and California serogroup viral infection, the numbers of cases are quite small. As the authors point out, however, it is highly likely that these reported cases represent a significant underestimate of the true incidence of these infections.

**Neurocysticercosis, Calcium, Brain Edema, and Seizures**


Seizures in patients with neurocysticercosis have generally been thought to be triggered by an inflammatory reaction initiated as the result of larval death. Calcified cysticercal cysts are generally considered to be the end stage of infection, resulting from the death of the worm; nonetheless, they are also associated with recurrent seizures. In contrast to a common assumption that calcified lesions are inert is the observation that perilesional edema may be seen in association with calcified cysts, suggesting an ongoing pathophysiologic process. In fact, a recent study by the investigators of the study under review previously identified perilesional edema in approximately one-third of patients presenting with seizures who had only calcified lesions on imaging studies. This finding may also, however, occur in patients who are asymptomatic. Thus, the relationship between edema associated with calcified cysts and seizure occurrence has been uncertain.

In a study from Peru by The Cysticercosis Working Group, 110 adults (106 with a history of seizures and 4 with severe headache) who had only calcified lesions of neurocysticercosis were prospectively observed. On the occurrence of a seizure, the individual was then matched with an asymptomatic control subject from the same study population; both were then assessed by magnetic resonance imaging (MRI) of the brain. During a median duration of follow-up of 32–33 months, 29 patients (26.4%) had a new seizure; 24 of these underwent MRI within 5 days, and 12 (50%) had perilesional edema. In contrast, MRI identified perilesional edema in only 2 (8.7%) of 23 control subjects who had been matched for age, sex, and number of calcifications—a robustly significant difference.

The strong association of perilesional edema with seizure occurrence provides potential insight into the pathophysiology of the event (although one-half the patients had no edema). The edema is believed to be the result of intermittent antigen release, intermittent recognition of antigen, or both. The hypothesis that seizures result from local activation of the inflammatory response points the way to possible therapeutic interventions.

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