N.A. Visser, MD
K.P.J. Braun, MD, PhD
W.M. van den Bergh, MD, PhD
F.S.S. Leijten, MD, PhD
C.R.B. Willems, MD
L. Ramos, MD
B.J.C. van den Bosch, PhD
H.J.M. Smeets, PhD
J.H.J. Wokke, MD, PhD

**JUVENILE-ONSET ALPERS SYNDROME: INTERPRETING MRI FINDINGS**

A previously healthy 20-year-old woman was admitted to the department of neurology of our hospital after 2 generalized tonic-clonic seizures in the preceding 2 weeks. Since the first seizure, she had been seeing bright spots. Neurologic examination at admission was normal. EEG showed slowed background activity and continuous epileptic activity in the left occipital lobe. MRI revealed asymmetric but bilateral areas of increased signal intensity in the occipital cortex, most prominent in the left hemisphere (figure, A). During the following weeks, symptoms expanded, as she developed epilepsy partialis continua of her right arm and leg. Repeat brain MRI showed increase and extension of the occipital lesions, now including hyperintensity of the pulvinar region in the left thalamus (figure, B). We considered a diagnosis of juvenile-onset Alpers syndrome, mitochondrial encephalopathy with lactate acidosis and stroke-like episodes, cerebral vasculitis, or Rasmussen encephalitis. Urgent DNA sequencing of all protein encoding exons and at least 40 nucleotides of the flanking introns of the POLG1 gene, the gene encoding the mitochondrial DNA (mtDNA) polymerase γ, confirmed a homozygous c.1399G>A mutation (p.A467T) as the only mutation or variant present in this gene. The family history was negative for disorders possibly related to POLG1 mutations. Despite treatment with several combinations of antiepileptic drugs, avoiding valproic acid, she developed a generalized status epilepticus and was admitted to the ICU. Eight weeks after the initial symptoms, she died of refractory status epilepticus with renal failure.

**Discussion.** In 2008, a similar phenotype of POLG1 mutations has been reported, referred to as juvenile-onset Alpers syndrome. Features are the combination of refractory epilepsy and visual symptoms in a previously healthy adolescent. In contrast, typical Alpers (Huttenlocher) syndrome, also a POLG1 mutation phenotype, usually presents in early childhood with the classic triad of developmental delay, intractable seizures, and liver failure.

POLG1 encodes the catalytic subunit of mtDNA polymerase γ, which is the only polymerase involved in mtDNA replication. POLG1 mutations have been identified in a variety of diseases, ranging from progressive external ophthalmoplegia to Alpers syndrome. Inheritance is mostly autosomal recessive, although autosomal dominant transmission and sporadic mutations have been described. The most common POLG1 mutation is p.A467T, with a human gene frequency of 0.2%–0.6% in certain European populations; this mutation can cause both mild and severe phenotypes (http://tools.niehs.nih.gov/polg/).

Our case is exceptional with respect to the rapid progression of the disease, which is highly unexpected in patients with a homozygous p.A467T mutation. Previously, compound heterozygotes with a p.A467T mutation showed a shorter survival compared to patients with a homozygous p.A467T mutation. A series of 19 patients with 3 different POLG1 mutation genotypes, one of which was the homozygous p.A467T mutation, had an overall survival time of 8 years after onset of epilepsy, but individual survival times were not reported. As other variants in POLG1 were excluded, a possible explanation of the severe phenotype of this patient could be a concurrent mutation in the mtDNA or in one of the many genes involved in mtDNA maintenance, affecting either the replisome or nucleotide pools. However, so far no solid evidence exists for digenic inheritance due to a combined effect of 2 mutations in different genes on the function of the mtDNA replication system and it may also be difficult to prove causality in a single case.

The magnetic resonance abnormalities in our patient are characteristic of the previously described occipital lobe epilepsy phenotype within the spectrum of POLG1 mutation syndromes. Progressive occipital and thalamic magnetic resonance lesions, as well as increased signal intensities in the cerebellum, have been reported in both typical and juvenile-onset Alpers phenotype. The increased cortical signal intensity on diffusion-weighted imaging with areas of decreased apparent diffusion coefficient might be mistaken for ischemia. The apparent diffusion coefficient evolution, however, suggests a combination of both cytotoxic injury and vasogenic edema. Whether
these cortical and thalamic diffusion changes are specific for mitochondrial dysfunction, or merely reflect the consequences of long-lasting and intractable status epilepticus, remains unclear. Previous studies have demonstrated magnetic resonance lesions in the pulvinar region of the thalamus in patients with partial status epilepticus arising from the posterior quadrants of the brain, probably reflecting the extent of thalamocortical connections within the epileptic circuitry.7

The diagnosis of juvenile-onset Alpers syndrome should be considered in patients with (partial) status epilepticus of unknown origin and occipital symptoms or lesions on MRI. Early recognition of this syndrome has important consequences; valproic acid is contraindicated in patients with a (suspected) POLG1 mutation phenotype, because of severe hepatotoxicity.3,5 Urgent DNA analysis can confirm the diagnosis and genetic counseling can be offered.


CRYPTOCOCCAL MENINGOENCEPHALITIS IN IMMUNOCOMPETENT PATIENTS: CHANGING TRENDS IN CANADA

Cryptococcosis can range from asymptomatic pulmonary colonization to life-threatening meningitis and disseminated disease. Most infections occur in immunodeficiency states, though recent reports suggest that immunocompetent individuals may be at risk with some varieties of the yeast. Cryptococcus neoformans var grubii and Cryptococcus neoformans var neoformans infect immunocompromised individuals, whereas Cryptococcus neoformans var gattii occurs predominantly in immunocompetent patients and has a strong male preponderance. This variety is found in the tropics in the decaying heartwood of a number of tree species and the outbreak in 2002 on Vancouver Island suggests this region to be the primary ecologic niche of the organism in Canada. To date, no cases of C neoformans var gattii in immunocompetent patients have been reported outside British Columbia. We describe clinical features of 3 such patients from Edmonton, Alberta.

Case reports. Case 1. A 52-year-old previously healthy man presented with a 2-day history of fever, drowsiness, and neck stiffness. In the previous month, he had experienced new onset headaches, excessive daytime sleepiness, decreased mobility, and occasional disorientation, though routine investigations, including brain CT scan, had been normal. His family had moved from British Columbia in 2006. His HIV serology and chest X-ray were normal. CSF had lymphocytic pleocytosis. Brain CT showed hypodensities in basal ganglia, which appeared as multiple septated cysts (cryptococcema) on MRI with no enhancement or surrounding edema (figure, A–F). CSF India ink stain was positive for cryptococcus and cultures grew C neoformans var gattii. Induction therapy with amphotericin B and flucytosine was instituted with daily lumbar punctures for raised intracranial pressure. Subsequently, fluconazole was initiated for 2 weeks followed by maintenance dose for 6 weeks. His condition improved substantially. A month later, he became febrile and had a generalized seizure. CSF opening pressure and cryptococcal antigen titers were elevated and brain MRI revealed ruptured cryptococcoma. Despite aggressive therapy, the patient worsened and died.

Case 2. A 59-year-old woman presented with chills, confusion, nausea, dizziness, vertigo, headache, and word-finding difficulties. She had been admitted with a TIA-like episode 2 weeks previously and brain CT/MRI and bloodwork results were normal. She had traveled to Niagra, China, and to Pender Island in British Columbia during the last year. She was afebrile and mildly aphasic. Repeat brain CT and MRI and routine blood studies were normal. CSF had elevated protein (1.7 g/L), reduced glucose, and lymphocytic pleocytosis (108 cells/µL) with elevated cryptococcal antigen titer (1/1024). CSF culture grew C neoformans var gattii. With aggressive induction and maintenance therapies, her condition improved rapidly to baseline.

Case 3. A 54-year-old man developed confusion and fever suddenly while on a sabbatical in Germany. He had visited his brother in Nanaimo, British Columbia, 3 months previously. CSF and serum antigen titers were positive for cryptococcal antigens. Brain MRI demonstrated diffuse meningoencephalitis (figure, G and H). He was transferred to Edmonton and rapidly improved after initiation of induction therapy (amphotericin B and flucytosine) followed by maintenance therapy with fluconazole.

Discussion. Our cases demonstrate some of the challenges in managing cryptococcosis in immunocompetent hosts. Variable clinical manifestations mandate clinicians to have a high suspicion in patients with subacute meningitis and CSF lymphocytic pleocytosis. Travel history is critical. Meningoencephalitis is the most common neurologic manifestation of cryptococcosis and headache the most frequent symptom (>75%). Other symptoms include nausea and vomiting, lethargy, memory loss, personality change, stupor, and coma. Cryptococcoma can cause raised intracranial pressure (50%),
JUVENILE-ONSET ALPERS SYNDROME: INTERPRETING MRI FINDINGS
Neurology 2010;74:1231-1233
DOI: 10.1212/WNL.0b013e3181d90005

This information is current as of May 7, 2010

Updated Information
& Services
including high-resolution figures, can be found at:
http://www.neurology.org/cgi/content/full/74/15/1231

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
MRI
http://www.neurology.org/cgi/collection/mri
DWI
http://www.neurology.org/cgi/collection/dwi
Adolescence
http://www.neurology.org/cgi/collection/adolescence
Status epilepticus
http://www.neurology.org/cgi/collection/status_epilepticus
All Genetics
http://www.neurology.org/cgi/collection/all_genetics

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/misc/Permissions.shtml

Reprints
Information about ordering reprints can be found online:
http://www.neurology.org/misc/reprints.shtml