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NEWS AND COMMENTARY

Alexander Disease Spectrum Continues to Expand

A new mutation in GFAP widens the spectrum of Alexander disease

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In this issue Nam *et al*[1] describe a novel case of Alexander disease that markedly expands the candidate patient population for this often fatal neurodegenerative disorder of astrocyte dysfunction. Astrocytes are a predominate cell type in the central nervous system; yet, despite their multiple critical activities, Alexander disease is the only genetic disorder presently known attributable to a primary defect in these cells (reviewed in Brenner *et al*[2]). The disease, defined by the abundant presence in astrocytes of protein aggregates termed Rosenthal fibers, was first described as a childhood leukodystrophy featuring the striking clinical signs of megalencephaly, seizures and psychomotor delay accompanied by massive white matter deficits in the frontal lobes. Subsequently, a later-onset form was added based on sharing the abundance of Rosenthal fibers, but with clinical signs that could be quite different, such as difficulty swallowing and speaking, autonomic dysfunction and ataxia. In addition, the radiologic abnormalities of the later-onset cases involve more caudal central nervous system regions, such as the cerebellum, brainstem and cervical spinal cord (see Prust *et al*[3] for a description of the two forms). A common etiology for the two forms was established by finding that about 95% of both are caused by mutations in the gene encoding glial fibrillary acidic protein (GFAP), an intermediate filament protein expressed strongly and predominantly in astrocytes.[4,5] All initial mutations discovered were heterozygous missense changes predicting production of both full-length mutant and wild-type proteins. This, together with the finding that GFAP null mice do not display signs of Alexander disease, led to the conclusion that the mutations cause disease by a dominant gain of toxic function.

The availability of a simple GFAP gene test for Alexander disease has led to discovery of more diverse and subtle clinical signs linked to GFAP mutations, especially in the adult population. A set of five MRI findings that proved highly diagnostic for the early-onset form[6] are much less reliable for later-onset cases, where atrophy and/or signal abnormalities in the brainstem and cervical spinal cord are more commonly found.[7] Similarly, the clinical manifestations displayed by patients have become more varied, and the catalogue of causative GFAP mutations now includes small in-frame insertions and deletions, in-frame skipping of an entire exon, and frameshifts at the extreme C-terminal end (eg, see Flint *et al*[8]).

The case report by Nam *et al* in this issue extends the scope of Alexander disease in all of its facets—presenting symptoms, MRI findings and mutation. The patient, a 67-year-old man, has none of the 21 clinical features associated with Alexander disease chronicled by Prust *et al*,[3] but instead has only the relatively generic complaints of headache and faulty short-term memory. The Nam *et al* case is also unusual for having neither of the MRI features suggested as common to late-onset cases—atrophy or signal abnormalities in the brainstem or cervical spinal cord.[7] Nevertheless, it was an MRI finding that prompted testing for Alexander disease—the presence of a scalloped-like garland of signal enhancement on axial FLAIR imaging along the outer rim of the lateral ventricle.[9]

The mutation discovered by Nam *et al* in this patient is heterozygous, as is the case for all other GFAP mutations found for Alexander disease patients. However, it is unique in being the first to produce an internal stop codon; a G to T change converts a glutamate GAG codon to a TAG nonsense codon, resulting in deletion of 121 amino acids. Like other intermediate filament proteins, GFAP consists of a central four-part alpha helical rod segment flanked by N-terminal head and C-terminal tail random coils. The E312ter mutation discovered results in deletion of about 2/3rds of the final 2B helical segment, and all of the C-terminal tail. This is the largest alteration of the GFAP gene observed in Alexander disease, the previous being a splice site mutation that caused skipping of exon 4, resulting in an internal deletion of 54 amino acids.[8] However, despite the major truncation caused by the E312ter mutation, the *in vitro* assays show that it still seems to act via a toxic gain rather than loss of function or haploinsufficiency.

Given the unique clinical features, radiologic findings and mutation for this patient, the question arises whether he indeed has Alexander disease, and whether the GFAP mutation is causative. The most definitive evidence would be finding that the mutation arose *de novo*, but the patient's parents are deceased and their DNA not available for analysis. Adding to the uncertainty, the only family member consenting to testing was an asymptomatic daughter, who also had the mutation. However, the mutant protein does meet several criteria for Alexander disease causation: it is produced in transfected cultured cells in reasonable amounts (about 50% the level of the wild type), it fails to form normal filaments in transfected cells, and it disrupts formation of normal filaments by wild-type GFAP in a dominant manner.

With the caveat that Alexander disease is not absolutely proven for this case, the commonality of the clinical symptoms of this patient has the potential to enormously increase the Alexander disease patient population. Chronic headache is estimated to occur at a frequency of ~4%[10] and deficits of short-term memory are in a similar range.[11] Thus, if even a small portion of these symptoms are caused by GFAP mutations, the incidence of Alexander

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disease could prove markedly higher than the current estimate of ~1 in a million.[12] Not far in the future it is likely that the entire genome of patients will be sequenced as a routine diagnostic, but until that time genetic testing for GFAP may be advisable for patients with essentially any neurological sign accompanied by suggestive radiologic findings for which the standard panel of tests is negative. ■

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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