Hereditary diffuse leukoencephalopathy with axonal spheroids

More than just a rare disease

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Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is a progressive white matter disease with a wide range of clinical symptoms, including dementia, behavioral changes, seizures, pyramidal signs, ataxia, and parkinsonism.[1–3] Affected individuals develop symptoms in their early 40s, with an average survival time of 10 years. HDLS is inherited as an autosomal dominant trait. Recently, mutations in the colony-stimulating factor 1 receptor gene (*CSF-1R*) were identified as the genetic cause of HDLS.[4] White matter lesions, easily demonstrated on MRI studies, involve predominantly the frontal lobes and corpus callosum, with subsequent cortical atrophy. MRI abnormalities are present prior to symptom onset.[5,6] Histopathology shows widespread myelin and axon destruction with axonal dilations termed spheroids, as well as pigmented macrophages.

In the current issue of *Neurology*®, Konno et al.[7] report detailed genetic, clinical, imaging, and neuropathologic investigations of Japanese patients with HDLS. The authors selected patients with HDLS due to mutations in the *CSF-1R* gene, carefully reviewed clinical and sequential brain MRI data, and performed a number of in vitro experiments using brain tissue and cellular models in an attempt to understand the mechanisms involved in disease pathogenesis. They identified 6 *CSF-1R* mutations in 7 patients from unrelated families, all of them located within the tyrosine kinase domain. Five of the 6 mutations were novel, with 3 missense, 1 splice-site, and 1 frameshift mutation, the latter leading to a premature stop codon predicted to induce nonsense-mediated decay. In support of this mechanism was the finding of a marked reduction of mutant mRNA expression compared to that of the normal allele. Further, the authors performed Western blot analysis on brain tissue and demonstrated a lower expression of the CSF-1R protein in patients with HDLS compared to controls. Using a cellular model, they examined the functional properties of mutant CSF-1R and demonstrated that mutations severely alter constitutive as well as ligand-induced autophosphorylation, indicating that mutations induce significant structural and functional changes in the CSF-1R protein. They went on to show that mutant CSF-1R does not affect autophosporylation of wild-type CSF-1R, arguing against a dominant-negative effect.

Overall, the clinical characteristics of the patients studied matched those of previously reported cases, with predominantly cognitive/behavioral symptoms associated with parkinsonism, pyramidal signs, and seizures. In 4 patients there was no family history, raising the possibility of de novo mutations or reduced penetrance. Using a previously proposed HDLS MRI rating scale,[5] they provided new data on early involvement and progression of disease. Alteration of the corpus callosum appears to be an early feature. Thin-sliced CT scans showed multiple spotty calcifications mostly within the frontal white matter. Neuropathologic examination revealed loss of myelin sheaths and axons with severe gliosis and axonal spheroids. Distribution of activated microglia was spatially restricted, with microglia and phagocytic cells appearing to be segregated. Interestingly, CSF-1R immunopositivity was weaker in activated microglia from patients compared with controls.

The study by Konno et al. provides important insights into HDLS caused by *CSF-1R* mutations. First, it further extends the widespread distribution of the disease, with families reported in Europe, Australia, the United States, and Japan, indicating that HDLS is not restricted to selected populations. Given the high level of clinical heterogeneity, it is likely that the disease frequency is underestimated and that many more families will be identified in the future. Nonspecific MRI abnormalities frequently lead to misdiagnosis of HDLS as multiple sclerosis or small-vessel disease. In this regard, the early involvement of the corpus callosum found by Konno et al. may prove useful to identify potential HDLS cases, prompting genetic testing for *CSF-1R* mutations.

The second important contribution of the present study is the identification of new mutations in *CSF-1R*, particularly the frameshift mutation leading to a premature stop codon. The results of the in vitro experiments indicate that haploinsufficiency (lack of

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expression of the mutated allele with about 50% of the normal protein available) is sufficient to cause disease. This is important and consistent with the idea that a dominant-negative effect (the mutated RNA or protein alters expression of the wild-type allele) is unlikely to play a substantial role in the pathogenesis of HDLS. Given that all known *CSF-1R* mutations are clustered within the tyrosine kinase domain, genetic screening can easily be performed. However, not all patients with autopsy-confirmed HDLS harbor a *CSF-1R* mutation, including the original family,[1,3] which suggests genetic heterogeneity. In addition, mutations in *CSF-1R* also occur in families with a closely related disease, pigmentary orthochromatic leukodystrophy (POLD).[8] This should not pose problems for clinicians given that HDLS and POLD are clinically and pathologically almost indistinguishable and are likely part of the same disease spectrum (adult-onset leukoencephalopathy with axonal spheroids and pigmented glia).[2,8]

The third finding that has strong clinical relevance is the presence of multiple punctate calcifications in the frontal white matter. This has not been emphasized previously, but others have made similar observations.[9] In addition to being a potentially useful marker for diagnosis, calcifications may be relevant for understanding pathogenesis, given the role of CSF-1R in osteoclast cytoskeletal reorganization.

Finally, neuropathology and immunohistochemistry evaluations displayed a pattern of spatially segregated microglia with low immunopositivity for CSF-1R, to some degree reminiscent of the abnormalities observed in mice homozygous for a null mutation in *Csf1r* and in the CSF-1 ligand gene ($Csf1^{op/op}$). Taken together with other data from mouse studies, this indicates that altered CSF-1R-mediated microglial repair of axonal degeneration may contribute to the development of HDLS. More studies are needed, however, to fully understand the pathogenic process involving microglia, axons, and myelin sheaths that leads to progressive white matter destruction.

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