marked calcification in severe lesions in the advanced patient. Calcification can be considered to accompany the progression of white matter degeneration.

CSF1R is a cell surface receptor for the cytokine CSF1, which regulates the survival, proliferation, differentiation, and function of mononuclear phagocytic cells, including microglia and macrophages of the CNS (17). Moreover, several functions of CSF1R signaling that contribute to the white matter development, remyelination, or neuronal maturation have been reported (8,18,19); it is unknown which of these functions may be affected most in the pathogenesis of HDLS. Perturbation of CSF1R signaling by haploinsufficiency has recently been reported in HDLS patients (8). Our immunohistochemical and immunoblotting results also suggest that CSF1R is generally expressed at lower levels on microglia in HDLS patient brain tissues. In particular, the findings in tissues from the patient who was considered to be asymptomatic indicate that microglia with low CSF1R expression were diffusely dispersed in the white matter even in the early phases of disease, before axonal damage or myelin loss. We consider it likely that CSF1R signaling may be broadly impaired in the microglia during the patients' younger years—before the clinical onset of disease. Then, vulnerable axons in the subcortical white matter may gradually become impaired, followed by subcortical demyelination. In middle age, the lesions may become confluent and widespread, and this level of pathologic severity may be sufficient to generate clinical symptoms. Finally, the pigmented microglia and axonal spheroids may become sparse with the progression of white matter destruction.

One limitation of our study is that the patient who was considered to be asymptomatic could not be examined with the use of intensive radiologic or cognitive tests because of active tuberculosis and respiratory failure. Thus, we cannot completely exclude the possibility that this patient experienced slight impairments in high-order functions. However, on the basis of bedside neurologic examinations and information supplied by the patients' families, it appears likely that the patient was asymptomatic and pathologically represented an extremely early picture of the pathology associated with HDLS.

In conclusion, HDLS lesions initially develop multifocally in subcortical white matter regions. Moreover, the pigmented microglia seen in HDLS brains express CSF1R at lower levels compared with controls and spread diffusely in white matter in the early stages of disease, and their appearance precedes axonal damage and myelin loss.

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