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CASE REPORT

Suspected Perinatal Depression Revealed to be Hereditary Diffuse Leukoencephalopathy with Spheroids

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ABSTRACT

Early motor symptoms of neurodegenerative diseases often appear in combination with psychiatric symptoms, such as depression or personality changes, and are in danger of being misdiagnosed as psychogenic in young patients. We present the case of a 32-year-old woman who presented with rapid-onset depression, followed by a hypokinetic movement disorder and cognitive decline during pregnancy. Genetic testing revealed a mutation in the colony-stimulating factor 1 receptor gene, which led to the diagnosis of hereditary diffuse leukoencephalopathy with spheroids. Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is probably an under-recognized disease. HDLS should be considered in patients with rapidly progressing parkinsonian symptoms and dementia accompanied by white matter lesions.

Key Words Hereditary diffuse leukoencephalopathy with spheroids; parkinsonism; leukoencephalopathy; colony-stimulating factor 1 receptor.

Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is a rare, autosomal dominant inherited disorder with adult onset that leads to progressive cognitive decline and varying neurologic features, including ataxia, parkinsonism, dystonia and spasticity.[1] Psychiatric symptoms, including personality changes, apathy, drug abuse and depression, may proceed these symptoms.[2] The median age of onset is 45 years, and the median life expectancy after diagnosis is six years, although both parameters vary among affected patients,[3] who carry mutations in the colony-stimulating factor 1 receptor (*CSF1R*) gene on chromosome 5.[4] All known mutations lead to disturbed autophosphorylation after ligand binding.[5] CSF1R is the cell surface receptor for cytokine macrophage colony-stimulating factor 1 (CSF1) and IL-34, both of which play a role in regulating mononuclear phagocytic cells, including microglia.[6] Therefore, impaired microglia survival, proliferation and differentiation are assumed to be causative for HDLS. The typical MRI findings of HDLS are confluent FLAIR hyperintensities in the subcortex and deep white matter.[7] These MRI changes may be mischaracterized as ischemic small vessel disease, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) or demyelinating diseases, such as primary progressive multiple sclerosis, especially early in the disease. Bifrontal spotty calcifications have been described on CT in a small number of cases.[8]

CASE REPORT

A 32-year-old female patient developed depression, anxiety and subtle gait disturbances during the second trimester of her first, otherwise uncomplicated pregnancy. Her main complaint upon her first visit to the emergency department was having difficulty finding words and concentrating, as well as having a fear of falling while walking. She felt anxious and hopeless and showed mildly decreased cognitive function, achieving a score

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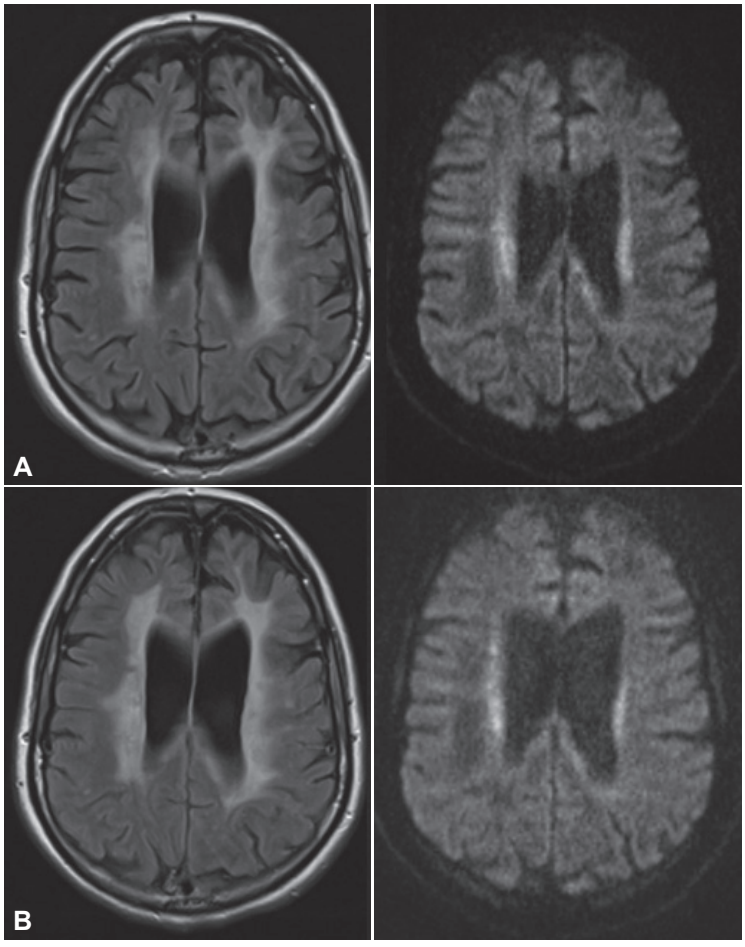

Figure 1. Cerebral MRI at the first visit (A) and nine months later (B). A: Cerebral MRI at the first visit. Confluent hyperintensities in the periventricular and deep white matter (FLAIR, left) with partly restricted diffusion (diffusion-weighted, right). B: Cerebral MRI nine months later: increasing hyperintensities affecting almost the entire white matter (FLAIR, left). FLAIR: fluid-attenuated inversion recovery.

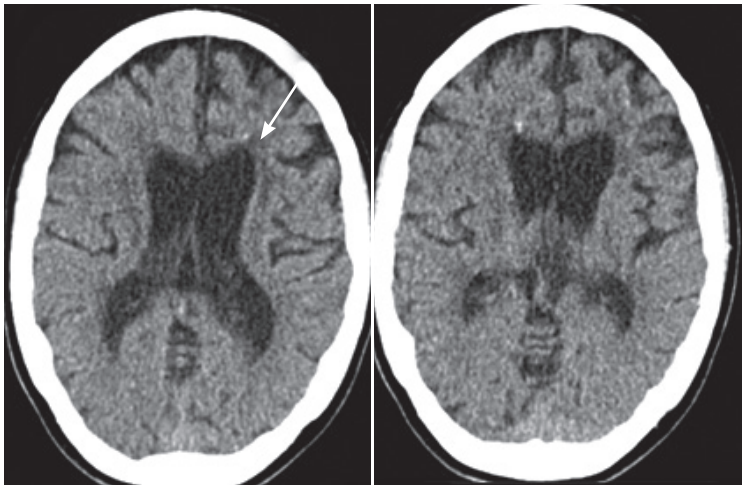

Figure 2. Cerebral CT at the first visit. Generalized supratentorial atrophy inconsistent with an age of 32 years and multiple spotty calcifications in the frontal white matter (arrow).

of 24 points on the Mini Mental State Examination. Perinatal depression was suspected, and she was treated by the Department of Psychiatry for six months without significant improvement in her symptoms. Upon completion of her treatment, the patient displayed an unusual wide-based, shuffling, very slow and highly fluctuating gait. She walked in small steps and sometimes staggered severely, but her symptoms were variable, and she did not fall. Therefore, her gait disturbances were classified as psychogenic. However, cerebral MRI showed confluent white matter lesions suspicious for CADASIL. The patient had been treated for mild hypertension since the age of 29 but had otherwise been healthy. Her family history was negative for any hereditary diseases, but her reported history was fragmented because she had broken off all contact with her father at the age of 18.

The patient subsequently presented to us ten months after symptom onset and six months after she had given birth to a healthy girl. She presented with conspicuous global bradykinesia with severe slowing and hesitation in her fine motor skills and symmetric rigidity in all her extremities, but without tremor. She also exhibited reduced spontaneous speech with slight amnestic aphasia and ataxic dysarthria, with loss of modulation. Her gait disturbances had worsened, as she could walk only short distances independently, and she had difficulty lifting her feet of the ground without external instruction but showed no typical freezing behaviors. Apraxia was an important finding, as it was evident in both her fine motor skills and her gait. Another MRI revealed the presence of increasingly symmetrical, confluent FLAIR hyperintensities with partly restricted diffusion, but without contrast enhancement (Figure 1). Wide-ranging blood and CSF analyses, as well as electrophysiological tests, were not suggestive of a diagnosis. In particular, there was no evidence of an infectious or autoimmune cause of her symptoms.

The marked parkinsonian features, which improved slightly on levodopa, combined with the progressive leukoencephalopathy and spotty frontal calcifications demonstrated by CT (Figure 2) led us to test for HDLS. Genetic testing revealed the presence of a heterozygous mutation (c.2541G>C) in the CSF1R gene leading to a change in the corresponding amino acid sequence (p.E847D). This mutation was first described in a patient who presented with cog-

nitive decline and spastic paraparesis at the age of 44.[3]

The patient exhibited signs of progressive pyramidal as well as extrapyramidal motor dysfunction and rapidly progressing dementia during the following months (Supplementary Video 1 in the online-only Data Supplement). Eighteen months after symptom onset, the patient was admitted to a nursing home. By that time, she was not able to sit, stand, communicate or recognize faces. She presented with a combination of rigid-spastic muscle tonus, pyramidal signs and primitive reflexes. The patient died 28 months after symptom onset.

DISCUSSION

This young woman's case was highly suspicious for infection or autoimmune disease due to its subacute onset and rapid progression during her pregnancy and shortly after her first childbirth. HDLS is caused by mutations in the *CSF1R* gene. CSF1R and its ligands, CSF1 and IL-34, are required for placental development.[9] We therefore hypothesize that the extensive adaptations of the maternal immune system that occur during pregnancy contribute to the clinical manifestations of the disease. Further research is needed to prove this theory.

In addition to the parkinsonian features, the spotty calcifications that were noted in the affected frontal white matter on CT were a hint to the diagnosis. These findings were first described by Fujioka et al.,[10] who reported the case of a female patient with a CSF1R mutation in 2013, and Konno et al.,[8] who presented the results pertaining to a set of patients in 2014. CSF1R signaling is known to be necessary for osteoclast cytoskeletal reorganization. Therefore, a direct pathogenic relationship between CSF1R signaling and calcification is conceivable. The calcifications seem to be specific for HDLS, but this specificity is not yet common knowledge. CT should be performed in suspected cases to confirm the diagnosis and to investigate the specificity of this finding further.

Early motor symptoms of neurodegenerative diseases, which often appear in combination with psychiatric symptoms, such as depression or personality changes, are in danger of being misdiagnosed as psychogenic in young patients, especially during and shortly after pregnancy. HDLS is probably an underrecognized disease. HDLS should be considered in patients with rapidly progressing parkinsonian symptoms and dementia accompanied by white matter lesions.

Supplementary Video Legend

Video 1. The video shows the patient at 16 months after symptom onset. She is distinctly bradykinetic and rigid, and her fine motor skills are slow and apraxic. She is not able to stand up without the help of two nurses and cannot walk due to spasticity and severe gait apraxia.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.16050.

Conflicts of Interest

The authors have no financial conflicts of interest.

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