Anti-GABAbR antibody positivity in a patient with hereditary diffuse leukoencephalopathy with spheroids (HDLS): a case report

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Case report

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Abstract

Background: Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS), a rare autosomal dominant inherited leukodystrophy, is associated with the genetic mutations of colony stimulating factor 1 receptor (CSF1R). The clinical manifestations may be a combination of mental, neurological and physical symptoms that are easily misdiagnosed. And the magnetic resonance imaging (MRI) showed asymmetric white matter damage. Case presentation: We report a case which genetically confirmed hereditary diffuse leukoencephalopathy with spheroids with anti-GABAbR antibody positivity. A 30-year-old woman presented with a 30-month history of progressive limb weakness, aphasia, stiff and cognitive decline. Brain MRI revealed persistent white matter hyperintensities on diffusion-weighted images for 24 months. Sequence analysis of CSF1R showed a novel missense mutation c.1736G>A (p.R579Q). The presence of anti-GABAbR antibody did not report in patients with HDLS. After immunoglobulin and methylprednisolone steroid pulse therapy, the patient's condition improved and the Barthel index scale of daily living ability was increased from 40 to 60. Conclusions: HDLS is often misdiagnosed due to the diverse clinical manifestations and the lack of reliable laboratory indicators. The case may helpful for clinicians to further understand the disease. If a patient whose manifestations are progressive limb weakness and cognitive impairment with anti-GABAbR antibody positivity and the MRI shows asymmetric white matter damage, clinicians should consider the possibility of HDLS and recommend genetic testing.

Background

Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS) is a rare autosomal dominant inherited leukodystrophy, which was first reported by Axelsson in 1984.1 The magnetic resonance imaging (MRI) showed asymmetric white matter damage. Clinical manifestations may be a combination of psychiatric, neurological, and somatic symptoms1 and easy to be misdiagnosed. It's been proven that the only pathogenic gene of HDLS is colony stimulating factor 1 receptor (CSF1R) gene. The impact on tyrosine kinase domain caused by CSF1R gene mutation is the basis of white matter disease of HDLS.2 And more than 50 mutations in the HDLS patients have been reported up to now，including missense, frameshift and nonsense mutations, but also deletions and splice-site mutations, all mutations are located in the intracellular tyrosine kinase domain, encoded by exons 12-22.3 Here, we report a young female patient diagnosed HDLS with a new mutation of whom anti- GABAbR antibodies were detected.

Case Presentation

A 30-year-old, right-handed female patient admitted to our hospital for a 30-month history of progressive limbs weakness, aphasia and cognitive decline on June 27, 2016. At the beginning of the course of her disease, she showed only poor right-hand flexibility and was diagnosed with stroke, but the antiplatelet therapy was ineffective. Then she got a little bit of walking instability, pronouncing unclearly and drinking choked occasionally. The thoracic spine enhanced MRI showed abnormal intramedullary signals without enhancement on C6-T1 segment which referred to demyelination, the cervical spine enhanced MRI

showed C5-6 intervertebral disc protrusion. According to these results, the doctor thought she probablely had inflammatory demyelination of the central nervous system but cerebral autosomal dominant arteriopathy with subcortical infarcts leukoencephalopathy (CADASIL) cannot be excluded. The patient began to get worse and the limbs became weakness on March 2015. At the end of 2015, her legs were too weak to walk, and she slurred more serious. Three months later, she developed into mixed aphasia. Since illness, she frequently appeared forced laughing and had poor sleep. The urinary and fecal incontinence occurred occasionally. Except a history of mumps at age 3, there is no history of other common diseases and genetic disease, and her families were not affected. But her menstrual cycle is irregular. At the time of admission, her vital signs were normal. Because of aphasia, a complete neuropsychological test could not be performed. The pupil and eye movements are normal. She had the right side of limb weakness of grade 4 and bilateral pyramidal signs were positive. She didn't have sensory disturbance.

After admission, MRI showed multiple asymmetric hyperintense signal changes with no enhancement on DWI (Figure 1), and the ventricles are clearly dilated. The cerebrospinal fluid (CSF) examination revealed no obvious signs of inflammation and evidence of pathogen infection except leucocyte increased mildly (19/ul). But we found the anti-GABAbR antibody positivity in CSF. Therefore, we given the methylprednisolone and gamma globulin. The patient developed skin rash all over the body and got alleviated after treatment. Immunological examination showed positive anti-nuclear antibody (1:100). The laboratory tests for leukocyte, liver function, kidney function, prothrombin time and partial thromboplastin time were normal. Syphilis and HIV serology was negative. Dynamic erythrocyte sedimentation rate was faster than normal (25 mm/h). Cardiac evaluation including electrocardiogram and heart ultrasound was normal. Genetic testing revealed the presence of a heterozygous mutation c.1736G>A in the CSF1R gene leading to a change in the corresponding amino acid sequence (p.R579Q) Figure 2. Based on the clinical manifestations, imaging characteristics and genetic analysis of the patient, we diagnosed HDLS. And we treated her with immunoglobulin (5 days) and methylprednisolone steroids (2 weeks). After two weeks of treatment, the patient's symptoms improved and the Barthel index scale of daily living ability was increased from 40 to 60.

Because the patient was bedridden for a long time, she could not come to the hospital for a check. We only know from her father that she is currently completely aphasic and unable to take care of herself completely.

Discussion And Conclusions

HDLS is a rare autosomal dominant inherited leukodystrophy. The average age of onset is about 40 years (18-72 years), with a course of disease ranging from 2-30 years.3 The clinical symptoms and signs include3, 4: (1) impairment of higher cortical function (abnormal mental behavior, personality changes, cognitive dysfunction); (2) motor and sensory disturbances; (3) symptoms of Parkinson's disease and dystonia; (4) cerebellar and brainstem symptom. MRI showed asymmetric white matter damage without enhancement, especially the frontal and parietal lobes, and the corticospinal tract is normally involved at

the middle and late stages. With the white matter damage deteriorated, the ventricles may become enlarged and cause secondary brain atrophy change.5 The MRI findings of our patient were basically consistent with these manifestations. The severity of HDLS can be assessed using a total MRI severity score (0-57), according to the rating system, HDLS is divided into 3 grades: mild(1-6), moderate(7-15) and severe (16-57) .5 In addition, Some studies have found that patients with HDLS shown lower concentration of N-acetylaspartate (NAA) and glutamate (Glu), and higher concentration of choline-containing compounds (Cho) and myo-inositol (Ins) on magnetic resonance spectroscopy (MRS).6 This may be related to nerve damage and glial cell hyperplasia leading to decreased neurotransmitters.

HDLS is caused by mutations in the protein tyrosine kinase domain of the CSF1R, encoded by the CSF1R gene on chromosome 5q32.2. Before the pathogenic gene has been found, the only way to diagnose HDLS is pathologic examination of leukodystrophy, where axonal spheroid changes are demonstrated either by brain biopsy or by autopsy.1, 4 The histopathological features of the white matter lesion area were changes in axonal spheroid, myelin deleted, proliferative pigmented microglia which expressed CSF1R poorly, and lipid-rich macrophages.7, 8 The typical electron microscopy examination appearance of HDLS is axonal swelling, fulling of neurofilament arranged in a jumbled pattern and vacuolations of myelin sheath or demyelination and capillary basal lamina dilated. Postmortem examination showed that the microglia cells in the white matter were not evenly distributed, and the content of microglia-related proteins was reduced. 9 Immunohistochemical staining showed positive results of neurofilaments (NF), amyloid precursor protein (APP) and ubiquitin.10 Unfortunately, for economic reasons, our patient did not undergo pathological examination.

The main manifestations of this female patient is progressive limb weakness, slurred speech and cognitive impairment, consistent with previous reports.3 MRI-DWI showed multiple high signals of white matter and bilateral ventricles in bilateral frontal cortex, accompanied by diffuse high signals of white matter and corpus callosum，which was consistent with the imaging manifestations of typical HDLS. However, we first found a new gene mutation of HDLS, genetic analysis confirmed a novel heterozygous c.1736G>A mutation resulting in a R579Q substitution in exon 12. This mutation was not recorded in the Human Gene Mutation Database (HGMD). And there was no mutation frequency data in the normal population. This mutation may explain the positive anti-GABAbR antibody with HDLS. At the same time, the laboratory examination found that patients with anti-nuclear antibody positive (1:100), may be associated with genetic mutations can lead to immune abnormalities. Regrettably, the patient refused a biopsy, and we could not learn more about the pathological changes. Therefore, the possibility of HDLS should be considered in patients with anti-GABAbR antibody positive combined with leukodystrophy. From the perspective of imaging, CADASIL presented extensive white matter high signal in the brain with subcortical infarction, so our patient was suspected of CADASIL initially，but CADASIL can be detected with Notch3 gene mutation.11 Notably, HDLS was misdiagnosed as atypical Parkinson's,4 dementia (including Alzheimer's disease and frontotemporal dementia)12 and primary progressive multiple sclerosis (PPMS)13 in previous reports.

In conclusion, HDLS is often misdiagnosed due to the diverse clinical manifestations and the lack of reliable laboratory indicators. For patients with leukodystrophy, particularly with anti-GABAbR antibody positivity, and the clinical manifestations include dyskinesia, behavioral cognitive changes, Parkinson's syndrome, and psychiatric symptoms, doctors should consider the possibility of HDLS, and advise patients and their family members to perform genetic tests in order to make a clear diagnosis and reduce the birth of children with genetic defects through genetic counseling. Further studies are necessary to better understand the physiology-pathologic effects of CSF-1R mutations and the detailed molecular mechanisms leading to HDLS.

Notes

Hongyu Cao and Lei Yang are joint first authors.

Two authors have the same initials (LY) in the Authors' Contributions section, with LY1 corresponding to Lei Yang, with LY2 corresponding to Ling Yu.

List Of Abbreviations

HDLS: Hereditary diffuse leukoencephalopathy with axonal spheroids

CSF1R: colony stimulating factor 1 receptor

CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts leukoencephalopathy

CSF: cerebrospinal fluid

HGMD: Human Gene Mutation Database

APP: amyloid precursor protein

PPMS: primary progressive multiple sclerosis

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethical Committee of Beijing Chaoyang Hospital, Capital Medical University and the patient gave written informed consent prior to obtain the data.

Consent for publication

Written informed consent was obtained from the patient after treatment for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of data and materials

All data for this case report are included in this article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LY1 and HYC examined, evaluated the patient and drafted the manuscript. LY2, WQ and JZ analyzed the genetic test report, YL and SNY performed and interpreted the MRI studies. WLH participated in the design of the case-report and helped to draft the manuscript. All authors read and approved the final manuscript.

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Figures

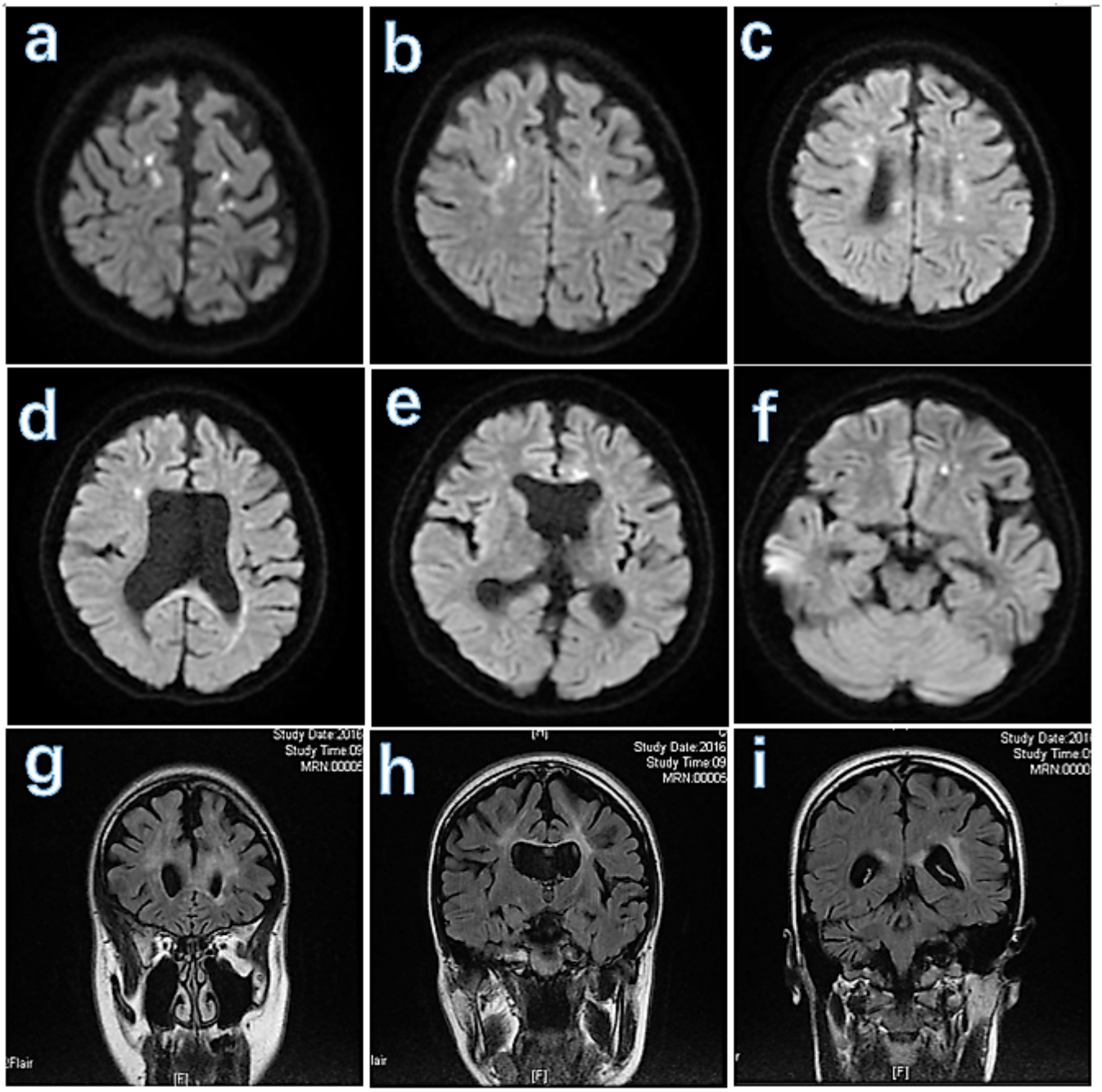

Figure 1

MRI showed multiple asymmetric hyperintense signal changes with no enhancement on DWI.

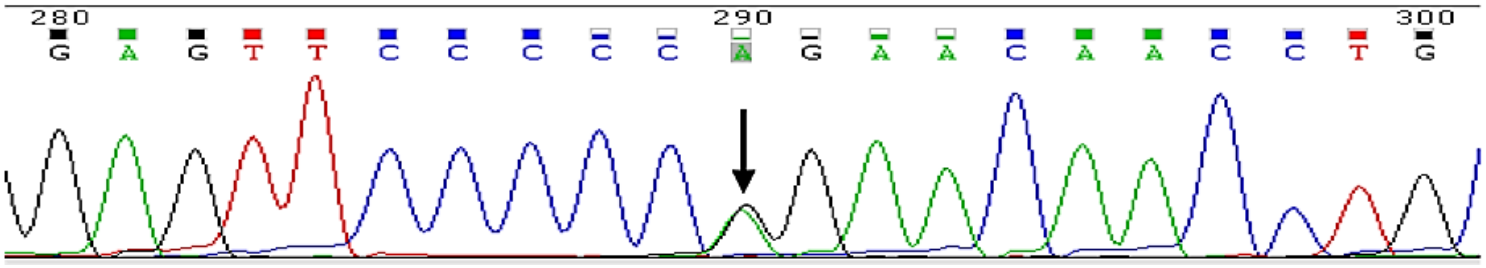

Figure 2

Gene analysis of CSF1R. A heterozygous c.1736G>A (p.R579Q) mutation in exon 12 of CSF1R was found in this patient (arrow).

Supplementary Files

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