International Journal of General Medicine

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CASE REPORT

A Novel Missense Mutation of the *CSF1R* Gene Causes Incurable *CSF1R*-Related Leukoencephalopathy: Case Report and Review of Literature

This article was published in the following Dove Press journal:
International Journal of General Medicine

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Abstract: *CSF1R*-related leukoencephalopathy, mainly caused by the mutation of the *colony stimulating factor 1 receptor* (*CSF1R*) gene on chromosome 5, is an underestimated neurological disease typically presenting as early-onset cognitive decline and personality changes. Currently, there is no specific treatment for *CSF1R*-related leukoencephalopathy. Most clinicians failed to recognize this disease during an early disease stage, leading to a high rate of misdiagnosis. Although rare, an increasing amount of *CSF1R*-related leukoencephalopathy cases have been reported recently. In this study, we first report a 35-year-old woman with *CSF1R*-related leukoencephalopathy carrying a novel missense mutation c.2463G >C (p.W821C) of *CSF1R*. An extensive literature research was performed in order to better understand the broader genetic and clinical characteristics of *CSF1R*-related leukoencephalopathy. A total of 147 patients with *CSF1R*-related leukoencephalopathy confirmed either by the genetic test or brain biopsy were identified. Among them, 49 patients were sporadic, and the rest of individuals had a family history originating from 46 different families. Our study indicated that the average age of *CSF1R*-related leukoencephalopathy onset was 41.4 years. Typical clinical symptoms of *CSF1R*-related leukoencephalopathy include cognitive decline, movement disorders, behavior changes and mental disorders. Genetic studies have reported 93 missense mutations, 13 splicing mutations, 6 deletion/insertion mutations, 1 code shift mutation and 1 nonsense mutation of the *CSF1R* gene in patients with *CSF1R*-related leukoencephalopathy. Early genetic detection and brain biopsy would be helpful for a confirmed diagnosis, and more translational studies are needed to combat this devastating disease.

Keywords: *CSF1R*-related leukoencephalopathy, clinical symptoms, *CSF1R*

Introduction

CSF1R-related leukoencephalopathy is a rapidly progressive neurodegenerative disease. This disease is mainly caused by the mutations of the *colony stimulating factor 1 receptor* (*CSF1R*) gene located in the chromosome 5q32 and now considered as a primary central nervous system (CNS) microgliopathy.[1] Patients with *CSF1R*-related leukoencephalopathy present complex clinical symptoms which make this disease more difficult to recognize during an early disease stage and can often be misdiagnosed as multiple sclerosis,[2] frontotemporal dementia, corticobasal syndrome, Alzheimer disease, atypical cerebral autosomal dominant

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http://doi.org/10.2147/IJGM.S286421

arteriopathy with subcortical infarcts and leukoencephalopathy. Unfortunately, there is no specific treatment for this disease yet and patients may gradually lose their motor function, become bedridden and eventually die from lung infections or other secondary infections.[3–5] Thus, more effort is needed to understand this incurable disease and eventually improve the life quality of patients with *CSF1R*-related leukoencephalopathy.

Case Presentation

A 35-year-old woman was admitted to Department of Neurology at the affiliated hospital of Hebei University due to speech impairment and gait disorder for almost 3 months. She had no remarkable past medical history. This patient graduated from a junior college, while her speech was clumsy at admission. Specifically, she had difficulty in pronouncing certain words when she talked fast, often causing frustration. Cognitive function tests revealed that the Mini-Mental State Exam (MMSE) score was 29/30 and the Montreal Cognitive Assessment (MoCA) score was 28/30 at admission. Upon neurological evaluation, the pharyngeal reflex response was reduced and the uvula deviated toward the left side. The tendon reflexes of the limbs were slightly more active and other remarkable signs were not evident. Routine laboratory investigations indicated a sign of liver damage without apparent cause, evidenced by increased levels of alanine aminotransferase (52, normal range 7–40U/L) in the circulation. Sagittal T2-weighted fluid-attenuated inversion recovery (FLAIR) images showed periventricular white matter hyperintensities and abnormal signals on the bilateral semi-oval centers (Figure 1A). Ventricular enlargement, thinning of the corpus callosum and global brain atrophy were also noted on MRI scans (Figure 1A). Four months later, the patient experienced communication difficulties, dragging gait, posture instability, dysphagia, progressive cognitive decline and obvious tremors of the jaw and hands. Repeated routine laboratory investigations also showed an increased serum level of alanine aminotransferase (73, normal range 7–40U/L). Multiple patchy abnormal signals, global brain atrophy and thinning of corpus callosum were evident in bilateral lateral ventricles on MRI scans (Figure 1B). Glucocorticoids and therapeutic strategies controlling related clinical symptoms were then used. However, the patient continued to progressively deteriorate during follow-up period. Nine months after the first admission, the patient suffered from dysarthria, tongue muscle atrophy, upper body tremors and walking abnormalities. Most of the daily activities could not be performed by herself. Cognitive function, especially short-term memory, became worse with the MMSE score being 23/30 and the MoCA score being 22/30. Repeated MRI scans did not show any significant changes from the last time (Figure 1C). After 12 months, the patient could not walk and essentially restricted to bed much of day. Genetic testing results indicated that the *CSF1R* gene on chromosome 5 (exon 19) was reported as c.2463G >C (p.W821C) with a missense mutation (Figure 2A). The genetic code was mutated from GGA to GCA, leading to the changes of tryptophan number 821 to cysteine (Figure 2A). We confirmed this novel mutation c.2463G >C (p.W821C) by performing insilico analysis using different methods. The results are "probably damaging" (Polyphen); "deleterious" (Sorting Intolerant from Tolerant, SIFT) and "disease causing" (Mutation Taster) (Figure 2B). The predicted result using the Mutation Assessor is medium (Figure 2B and Supplementary Figure). The criterion is PM1 (the American College of Medical Genetics and Genomics, ACMG) since it is located at a mutational hot spot and/or critical and well-established functional domain. Whole exome sequencing was carried out with the consent of this patient's parents, sister and daughters. Genetic tests of patient's relatives did not show abnormalities. Our case is sporadic (de novo mutation), which has not been reported in genome databases. Pathological results of the brain tissue removed during biopsy reported that the structure of white matter was seriously damaged, in particular with axonal destruction. Numerous axonal spheroids, gliosis and proliferating phagocytic cells were also noted (pathological images were not shown since the brain biopsy was not performed in our hospital).

Discussion

We conducted a literature review by searching PubMed, WANFANG (old.g.wanfangdata.com.cn) and CNKI (www.cnki.net). The following keywords "axonal leukodystrophy", "adult-onset leukodystrophy with axonal spheroids", "*CSF1R*-related leukoencephalopathy" and "hereditary diffuse leukoencephalopathy with axonal spheroids" were used. Both English and Chinese articles were included (from 1987 to February 2020) in our study.[3,5–66] All patients with *CSF1R*-related leukoencephalopathy were confirmed either by the genetic test or brain biopsy. Individuals who presented similar symptoms in the family without genetic tests or brain biopsy were excluded in our study. We extracted the following information:

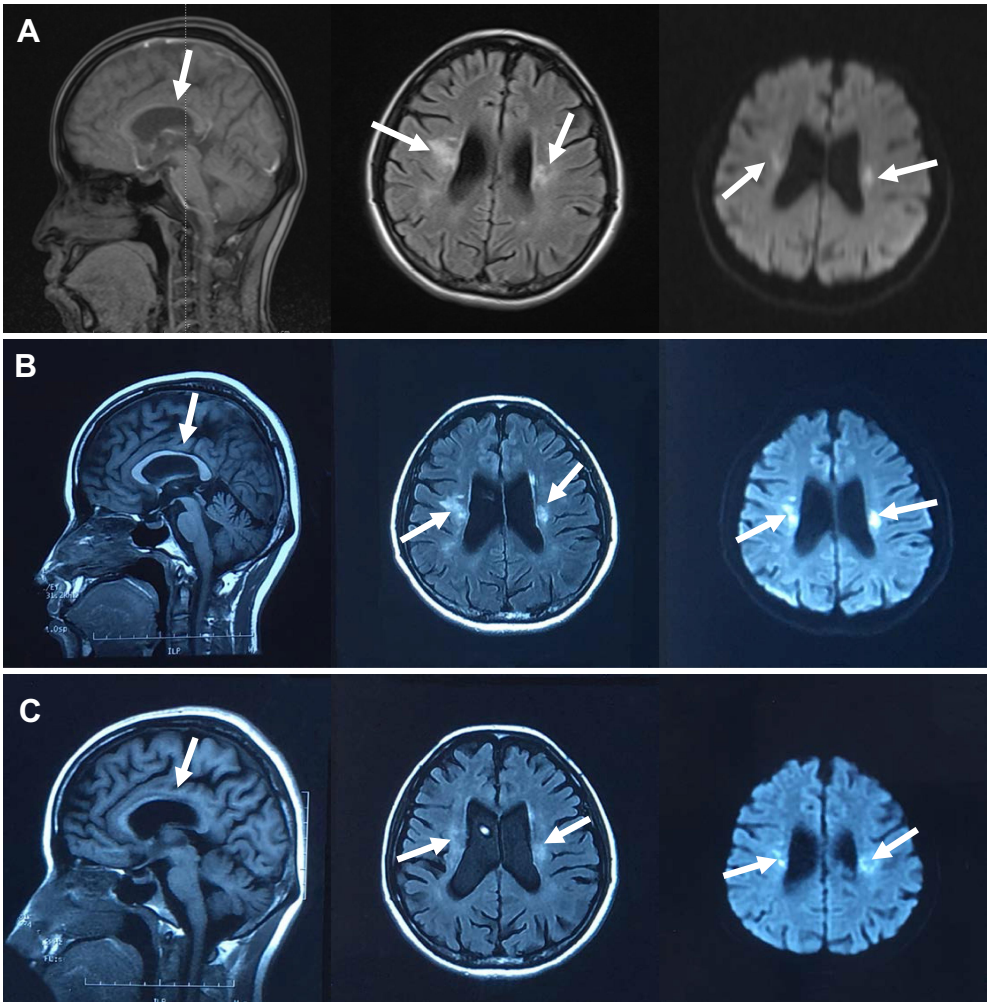


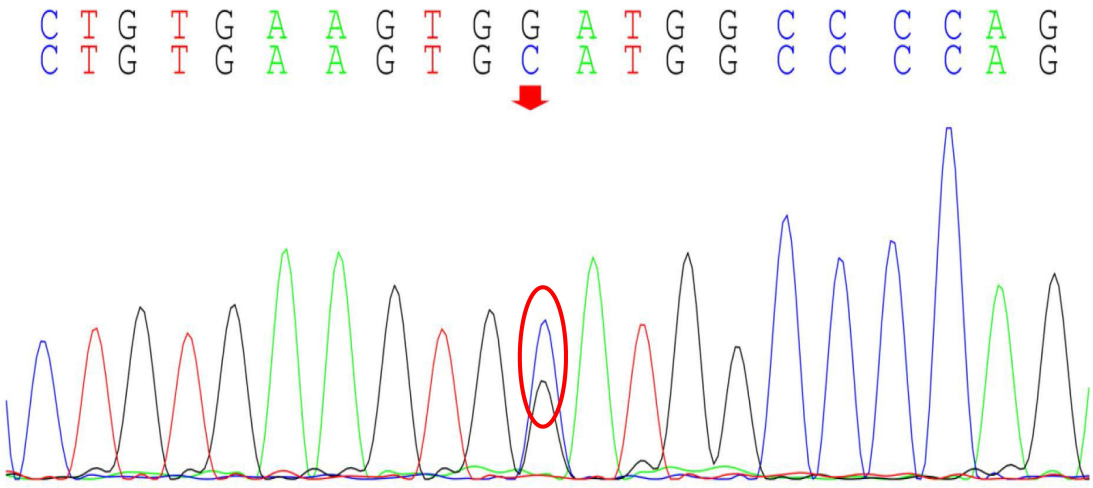
Figure 1 MRI features of *CSF1R*-related leukoencephalopathy. (**A**) T1-weighted sagittal images showed thinning of the corpus callosum (arrows). Fluid-attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) images showed periventricular white matter hyperintensities, abnormal signals on bilateral semi-oval centers (arrows). Global brain atrophy was noted. MRI was taken on 13th, June, 2019. (**B**) T1-weighted sagittal images showed that the corpus callosum is thinner than the last time (arrows). FLAIR images showed increased diffuse white matter lesions and the progression of global brain atrophy (arrows). DWI images revealed various isolated spots of hyperintense signals. MRI was taken on 08th, July, 2019. (**C**) Repeated MRI scans were taken on 10th, October, 2019. White arrows represent the brain lesions.

population, gender, age of onset, age of death, survival time, first symptoms, clinical features, neuroimaging findings, genetic testing, pathological results and family history.

A total of 120 patients with detailed MRI images were available. One of the most common imaging findings was brain white matter lesions (109/120, 90.8%). Specifically, they were mainly located in the periventricular areas (57/109, 52.3%), frontal lobes (43/109, 39.4%), corpus callosum (24/109, 22.0%) and parietal lobes (24/109, 22.0%). Brain lesions in some patients with *CSF1R*-related leukoencephalopathy can also be noted in the midbrain (3/109, 2.8%), temporal lobes (3/109, 2.8%), internal capsule hind limbs (2/109, 1.8%) and brain stem (2/109, 1.8%). Furthermore, atrophy (71/120, 59.2%, particularly frontal lobe atrophy) and thinning of the corpus callosum (48/120, 40.0%) were also frequently found (Figure 3A). In some patient, partial periventricular white matter lesions were oval in shape and perpendicular to the ventricles. Persistent limited diffusion on diffusion-weighted imaging (DWI) was also evident. In support of this, Onder et al recently proposed that the persistence of the diffusion restriction in deep white matter lesions may serves as a crucial sign for *CSF1R*-related leukoencephalopathy.[67]

A total of 147 patients with *CSF1R*-related leukoencephalopathy were included in our study. Specifically, 49 patients were sporadic and 98 individuals had a family history (from 46 families). The average age of onset was

A



B

Mutation	SIFT	Polyphen2	Mutation Taster	Mutation Assessor
c.2463G >C p.W821C	deleterious	probably damaging	disease causing	medium

Figure 2 Genetic test results of *CSF1R*-related leukoencephalopathy. (**A**) The *CSF1R* gene on chromosome 5 (exon 19) was c.2463G >C (p.W821C) with the missense mutation. The genetic code was mutated from GGA to GCA, leading to the changes of tryptophan number 821 to cysteine. The red arrow and red circle mean the base mutation site. (**B**) Results of insilico analysis for the W821C mutations by SIFT, Polyphen2, Mutation Taster and Mutation Assessor.

41.4 years (15 of them were not included due to unknown age of onset), among which males were 43.6 years old and females 39.7 years old. The average course of disease was 5.2 years. The duration of disease ranging from 3 weeks to 11 years. The first symptoms were mainly cognitive impairment (49/123, 39.8%), parkinsonism (22/123, 17.9%), abnormal behaviors (17/123, 13.8%), mental disorders (14/123, 11.4%), dysarthria (13/123, 10.6%) and gait disorder (11/123, 8.9%). Other potential symptoms included visual impairment (2/123, 1.6%), progressive weight loss (1/123, 0.8%) and nominalization (1/123, 0.8%) (Figure 3B). Furthermore, typical clinical manifestations of *CSF1R*-related leukoencephalopathy during the disease course included cognitive impairment (102/136, 75.0%), parkinsonism (57/136, 41.9%), gait disorder (28/136, 20.6%), personal and behavioral abnormalities (75/136, 55.1%), dysarthria (66/136, 48.5%), dysphagia (39/136, 28.7%), mental disorders (38/136, 27.9%), urinary incontinence (36/136, 26.5%), dementia (33/136, 24.3%), epilepsy (28/136, 20.6%), visual impairment (15/136, 11.0%) and apnea (13/136, 9.6%) (Figure 3C). Some rare manifestations such as drinking cough and orthostatic hypotension have also been reported.

The clinical spectrum of *CSF1R*-related leukoencephalopathy is expanding. For example, the involvement of spinal cord in *CSF1R*-related leukoencephalopathy has been reported.[68] Apart from typical *CSF1R*-related leukoencephalopathy clinical symptoms such as progressive motor impairment, hyperintense signals on DWI of this patient were noted from the subcortex white matter to the medulla, then extending to cervical and thoracic spinal cord.[68] Some researchers proposed that brain and spinal cord microglia may differ regarding their development, phenotypes and even functions.[69] Potential underlying mechanisms of microglial regional specificity in the condition of *CSF1R*-related leukoencephalopathy need to be further investigated. Furthermore, visual impairment had also been reported in a Chinese patient with *CSF1R*-related leukoencephalopathy.[25] Bilateral optic nerves lesions were evident on optic nerve MRI scans, causing difficulties to differentiate from MS.

A total of 114 patients with detailed genetic information were included for analysis, including 93 with

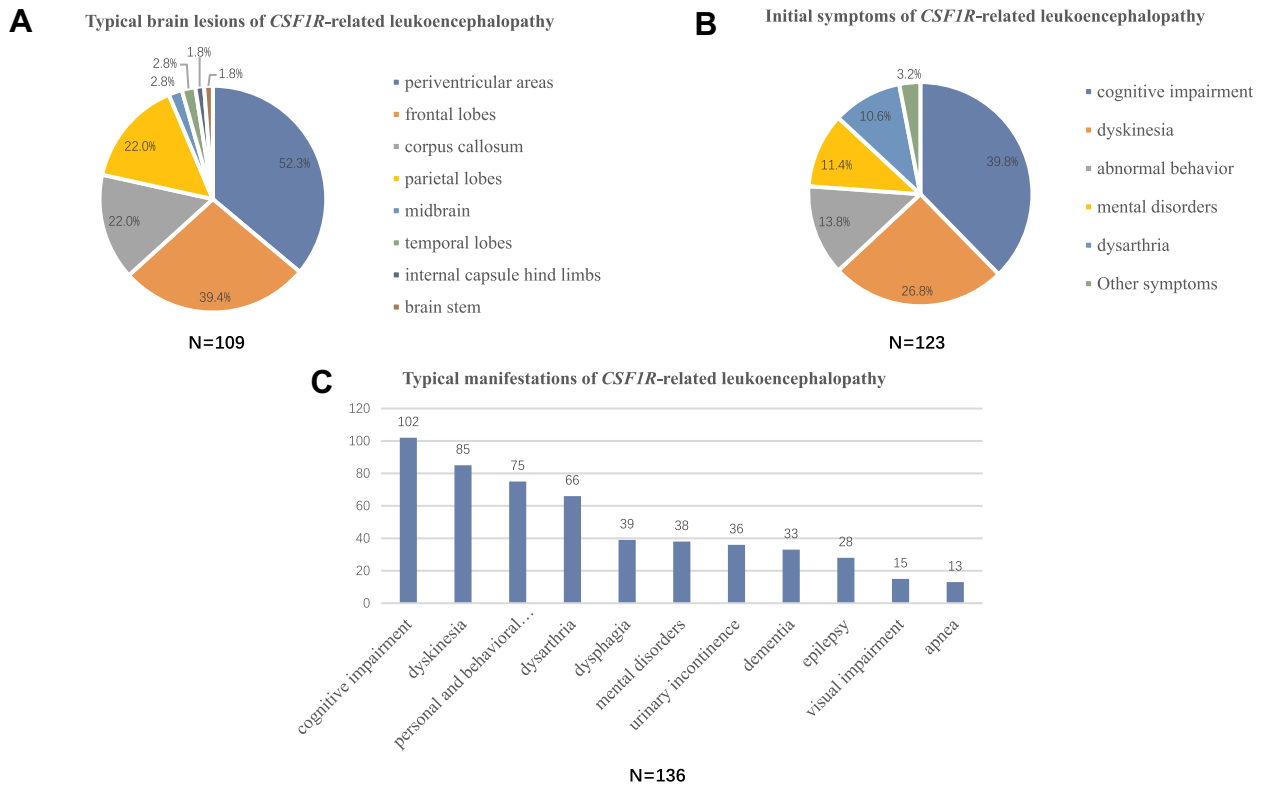


Figure 3 Clinical spectrum of *CSF1R*-related leukoencephalopathy. (**A**) Typical brain lesions of *CSF1R*-related leukoencephalopathy. White matter lesions were the most common lesions, which mainly located in the periventricular areas, frontal lobes, corpus callosum and parietal lobes. Atrophy and thinning of the corpus callosum were also noted. (**B**) Initial symptoms of *CSF1R*-related leukoencephalopathy. Cognitive impairment, parkinsonism, abnormal behaviors and mental disorders are the most common initial symptoms. (**C**) Typical manifestations of *CSF1R*-related leukoencephalopathy during the disease course. Cognitive impairment, parkinsonism, gait disorder, personal and behavioral abnormalities, and dysarthria are the most common typical manifestations during the disease course.

missense mutation, 13 with splicing mutation, 6 with deletion/insertion mutation, 1 with code shift mutation and 1 with nonsense mutation. The mutation site of one patient was located on exon 2, while the rest were located on exon 12–22 with exon 18 being the most common one. We summarized that 15 patients with *CSF1R*-related leukoencephalopathy from 11 unrelated families in 4 different countries had the same gene mutation: p.I794T, while their clinical manifestations were different. Furthermore, some family members who carried the mutations of *CSF1R* gene might not present obvious clinical symptoms. We suppose that it may be attributed to the changes of penetrance, making the mutation causing different degrees of disease severity. Meanwhile, this phenomenon also indicates that the dominant transmission pattern has familial phenotypic variation or incomplete penetrance.

Among 147 patients with *CSF1R*-related leukoencephalopathy, the brain biopsy was conducted in a total of 60 patients. Typical pathological features of *CSF1R*-related leukoencephalopathy are white matter pathologies with an enlargement of the frontal horn in the lateral ventricle. Microscopically, white matter damage presents as increased mitochondrial vacuolation and disorganized neurofilaments in ballooned axons or myelin loss.[14] Histopathologic studies showed that axonal spheroids were positive for phosphorylated neurofilament, amyloid precursor protein (APP) and variably for ubiquitin.[70] Macrophages with lipid-laden vacuoles and lipofuscin-like pigment of glial cells were visible. The formation of axonal spheroid is considered as a pathological manifestation of *CSF1R*-related leukoencephalopathy.[71,72] Tada et al indicated that in layers 3 and 4 of the frontal cortex in *CSF1R*-related leukoencephalopathy fewer numbers of Iba1 positive microglia were recorded than healthy control brains. A high proliferation of microglia was noted in selective brain regions.[73] Oosterhof et al also noted decreased microglial cell density and numbers in patients with *CSF1R*-related leukoencephalopathy.[74] Deep cortical layers could be more vulnerable than superficial cortical layers in patients with *CSF1R*-related leukoencephalopathy.[75]

CSF1R-related leukoencephalopathy is a rare but rapidly progressive neurodegenerative disease. A clinical diagnosis of *CSF1R*-related leukoencephalopathy should be considered

when the patients present cognitive impairment, movement disorders and personality changes. A combination of genetic testing and MRI imaging is needed for early accurate diagnosis and therapeutic decision making due to the complexity of *CSF1R*-related leukoencephalopathy. *CSF1R*-related leukoencephalopathy disease is relatively rare with unclear pathophysiological mechanisms and complex genetic mutation mechanisms. It is worth noting that with the popularization of genetic diagnostic methods, more and more mutations have been discovered. *CSF1R* gene mutation type has a dominant-negative effect,[13] haploinsufficiency,[74] biallelic variants[76] and homozygous mutations.[77] Hematopoietic stem cell transplantation (HSCT) is relatively effective in some patients,[78] however, some patients did not show any improvements after HSCT,[79] indicating that HSCT may not a specific treatment for *CSF1R*-related leukoencephalopathy. *CSF1R*-related leukoencephalopathy is considered as a primary CNS microgliopathy. Therefore, development of a potential microglia-based treatment is warranted.[80] Only when we are sufficiently knowledgeable can we find potential translational cues and clinical interventions to combat *CSF1R*-related leukoencephalopathy.

Ethics and Consent

As this typical case was not involved in any experimental interventions, no formal research ethics approval was required. The relatives of this patient provided written informed consent to the publication of the information and images related to this manuscript.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest and report no conflicts of interest for this work.

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