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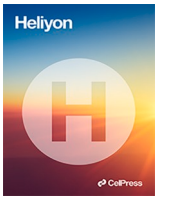

Case report

An early diagnosed cerebral small vessel disease in a 12-year-old girl

Xiaojuan Tian, Jiuwei Li *

Department of Neurology, Neurological Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, 100045, China

A B S T R A C T

Cerebral small vessel disease (CSVD) is a leading cause of ischaemic and haemorrhagic stroke and a major contributor to dementia. It occurs mostly in adult patients, rarely in children. COL4A1 is a candidate gene in monogenic CSVD with a wide clinical and neuroimaing spectrum. Here we presented a 12-year-old girl with recurrent dizziness, mild learning difficulties and inability to concentrate, the brain MRI showed diffuse periventricular leukoencephalopathy, lacunes in bilateral centrum semiovale, periventricles and basal ganglia, dilated perivascular spaces in bilateral basal ganglia with brain MRA and MRV were normal, highly mimicked the neuroimaging of CSVD regardless of the young age and no episodes of cerebrovascular events for now. We found no vascular risk factors and excluded other diseases such as primary angitis of central nervous system (PACNS). Then a trio-whole exome sequencing was performed. We found a de novo variant of COL4A1 gene c.2662G>A (p.Gly888Arg). She was finally diagnosed as a MRI-defined covert CSVD case. Though there are no specific treatments, with the very early diagnosis in our patient, excessive physical activity, trauma, anticoagulant therapy should be avoided for possible strokes in her future life. Therefore, genetic screening should be considered in familial cases and also in sporadic cases even in pediatric patients when the brain MRI showed diffuse periventricular leukoencephalopathy, dilated perivascular spaces, as well as microhemorrhage, and deep intracerebral hemorrhages, associated with early onset ischemic strokes or not.

1. Introduction

Cerebral small vessel disease (CSVD) is a heterogeneous group of pathological conditions affecting small arteries, arterioles, venules, and/or brain capillaries, which is the main cause of stroke, cognitive impairment, and vascular dementia in late adults [1]. Hereditary CSVD is rare, and mainly occurs in young adults, characterized by early-age stroke, and also by migraine, mood disturbances, vascular dementia and often gait disturbances. Several monogenic CSVD genes have been reported including *NOTCH3*, *HTRA1*, *COL4A1*, *COL4A2*, *GLA*, *TREX1*, *APP*, *CTSA*, and *FOXC1* [1–6]. Neuroimaging of CSVD primarily involves visualizing recent small subcortical infarcts, lacunar infarct, white matter hyperintensities(WMH), microbleeds, enlarged perivascular spaces, and brain atrophy [6–8]. Covert CSVD, which is detectable with brain MRI but does not manifest as clinical stroke, is highly prevalent in the general population but rarely found in children.

A previously healthy 12-year-old Han-Chinese female presented to our institution with a major complaint of intermittent dizziness for 5 months. The dizziness lasted for a few minutes without headache, vomiting, weakness, flash, visual rotation, tinnitus or hearing loss. The symptoms recurred recently. She has mild learning difficulties and inability to concentrate. She was born at term following a normal pregnancy and had no significant past medical history. Her father had intermittent headaches without any examinations. There is no other family history of migraine, strokes, or similar symptoms. Neurological physical examination was normal. The count of blood

* Corresponding author.
E-mail address: ljw981229@163.com (J. Li).

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cells, serum chemistries, coagulation, homocysteine, plasma lactate, ammonia and thyroid function were unremarkable. The head CT showed multiple patchy low-density areas in the left basal ganglia, corona radiata, and near the precornu of the right lateral ventricle, and punctate calcification in bilateral basal ganglia (Fig. 1A–D). Further examination of the brain MRI showed diffuse periventricular leukoencephalopathy, lacunes in bilateral centrum semiovale, periventricles, and basal ganglia, and dilated perivascular spaces in bilateral basal ganglia (Fig. 2A–L). The extensive evaluations of the patient including erythrocyte sedimentation rate (ESR), Anti-neutrophil cytoplasmic antibodies (ANCA), the brain MRA and MRV, were unremarkable. As the brain MRI abnormality of our patient highly mimicked the neuroimaging of CSVD regardless of the young age and the absence of episodes of cerebrovascular events so far, and she had no high-risk factors, such as hypertension, diabetes mellitus, and hyperlipemia, a genetic cause was suspected. Then a trio-whole exome sequencing was performed. Interestingly, we found a *de novo* variant of *COL4A1* gene(NM_001845.6 exon33) c.2662G > A (p.Gly888Arg), which had been reported as a pathogenic variant in a patient with porencephaly and leukoencephalopathy as well as cataract and myopathy [9]. Further examinations of other systems were performed on our patient. Ophthalmic examination was normal, and no abnormality was found in urinalysis, renal and renal arterial and venous ultrasound.

COL4A1 gene, which encodes collagen type IV alpha 1 chain, combined with *COL4A2* gene encoding collagen type IV alpha 2 chain, play an important role in the formation of Type IV collagen, which is a basement membrane protein expressed in blood vessels and organs throughout the body. *COL4A1* expression varies considerably in different tissues, with high levels of expression in small perforating cerebral arteries. *COL4A1* mutations have been reported with a broad spectrum of cerebrovascular, renal, ophthalmological, cardiac, and muscular abnormalities, indicated as "*COL4A1*-related disorders" [10]. *COL4A1* is a candidate gene in monogenic CSVD with a spectrum including perinatal intracerebral hemorrhage with consequent porencephaly, adult-onset intracerebral hemorrhage, lacunar infarcts, and leukoaraiosis, clinically manifesting as infantile hemiparesis, seizures, single or recurrent hemorrhagic stroke, ischemic stroke, and isolated migraine with aura. High susceptibility to hemorrhagic strokes frequently triggered by birth trauma, brain trauma, or anticoagulant treatment [10]. Here we reported a teenage girl with recurrent dizziness, mild learning difficulties and inability to concentrate, without any cerebrovascular events ever described when administered. She was diagnosed after a genetic founding of the *COL4A1 de novo* variant when the very likely neuroimaging of CSVD was present. The examinations of her eyes and kidneys were normal. So it was a case of MRI-defined covert CSVD. We presumed the high-intensity areas of the head CT indicated previously microbleeds without clinical symptoms. As there are no effective treatments, with the very early diagnosis of hereditary CSVD before cerebrovascular events in our patient, excessive physical activity, trauma, anticoagulant therapy and risk factors for hypertension, obesity, diabetes and bad habits like smoking should be avoided in her future life. As the father did not carry the COL4A1 variant which was detected in our patient, his intermittent headaches may be caused by other reasons.

Therefore, genetic screening should be considered in familial cases and also in sporadic cases even in pediatric patients [11], when the MRI showed diffuse periventricular leukoencephalopathy, dilated perivascular spaces, as well as microhemorrhage, and deep intracerebral hemorrhages, associated with early onset ischemic strokes or not, and when the extent of microvascular lesions on MRI contrasts with the paucity of vascular risk factors and exclusions of other diseases such as primary angitis of the central nervous system (PACNS). Then tailored preventive interventions could be proposed in advance to avoid the potential cerebrovascular events, and genetic counseling could be performed for a better life management.

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Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

CRediT authorship contribution statement

Xiaojuan Tian: Writing – original draft. **Jiuwei Li:** Writing – review & editing.

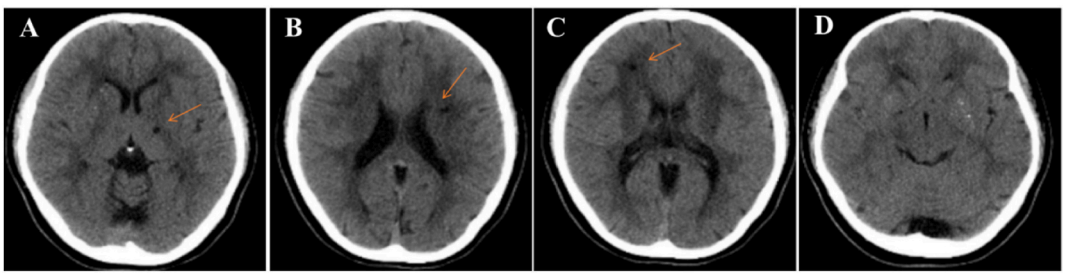

Fig. 1. The brain CT of our patient at 12 years old showed multiple patchy low density areas (arrows) in left basal ganglia (A), corona radiata (B), and near the precornu of the right lateral ventricle (C), and punctate calcification can be seen in bilateral basal ganglia (D).

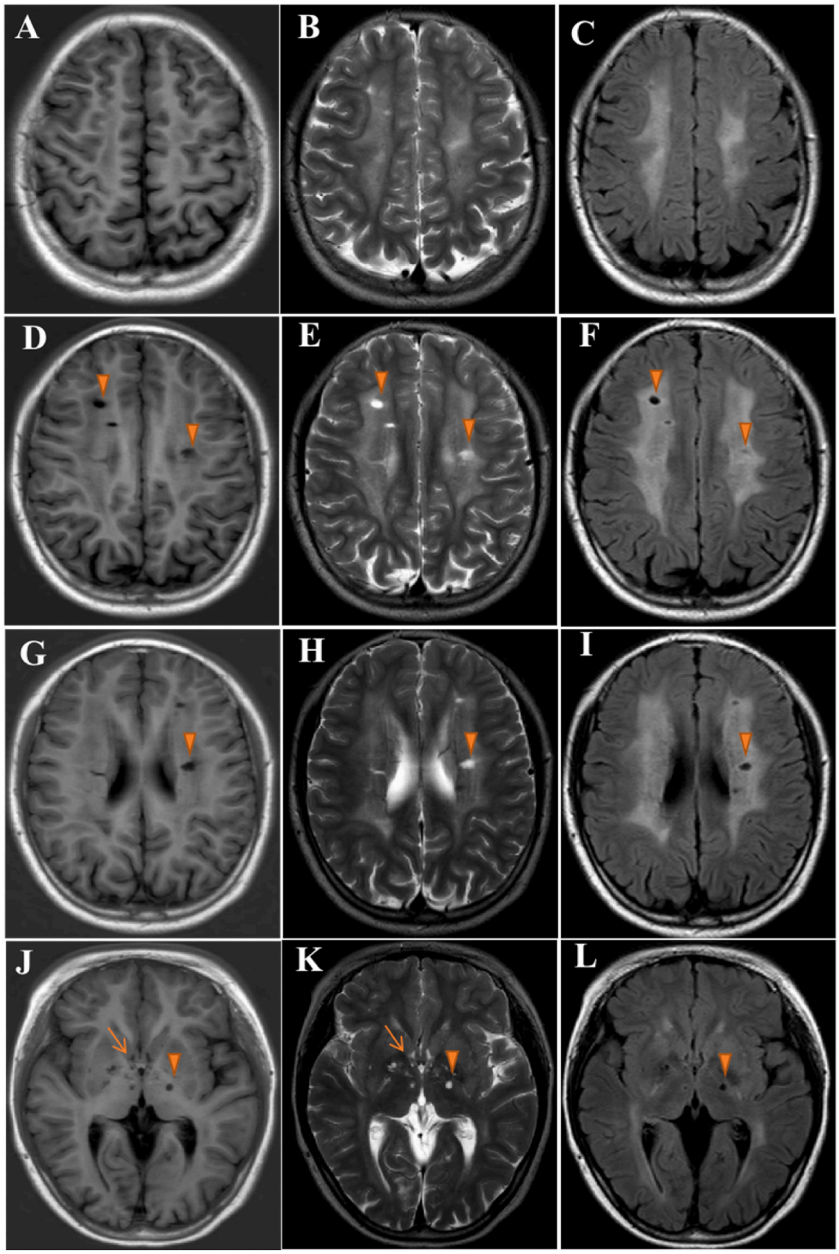

Fig. 2. The brain MRI of the patient at 12 years old showed diffuse periventricular leukoencephalopathy (A–I), lacunes (arrowheads) in bilateral centrum semiovale (D–F), periventricles (G–I) and bilateral basal ganglia (J–L), dilated perivascular spaces (arrows) in bilateral ganglia(J–K).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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