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

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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. Neuroimaging of CSVD primarily involves visualizing recent small subcortical infarcts, lacunar infarct, white matter hyperintensities(WMH), microbleeds, enlarged perivascular spaces, and brain atrophy. 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. CSVD occurs mostly in adult patients, rarely in children. COL4A1 is a candidate gene in monogenic CSVD with a wide clinical and neuroimaing spectrum.

Case Presentation

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. 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. There is no other family history of migraine, strokes, or similar symptoms. Neurological physical examination was normal. The count of blood 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 (FIGURE 1 A-D). The brain MRI showed diffuse periventricular leukoencephalopathy, lacunes in bilateral centrum semiovale, periventricles, and basal ganglia, and dilated perivascular spaces in bilateral basal ganglia (FIGURE 2 A-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. Further examinations of other systems were performed. Ophthalmic examination was normal, and no abnormality was found in urinalysis, renal and renal arterial and venous ultrasound. 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.

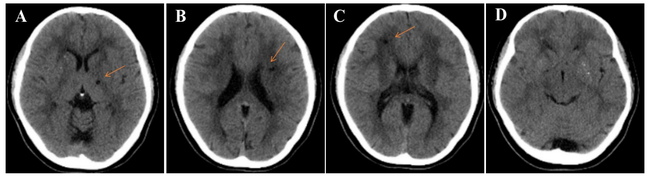

FIGURE 1. The brain CT of our patient at 12 years old showed multiple patchy low density areas (arrows) in left basal ganglia (A), corona radiata (B), and near the precornu of the right lateral ventricle (C), and punctate calcification can be seen in bilateral basal ganglia (D).

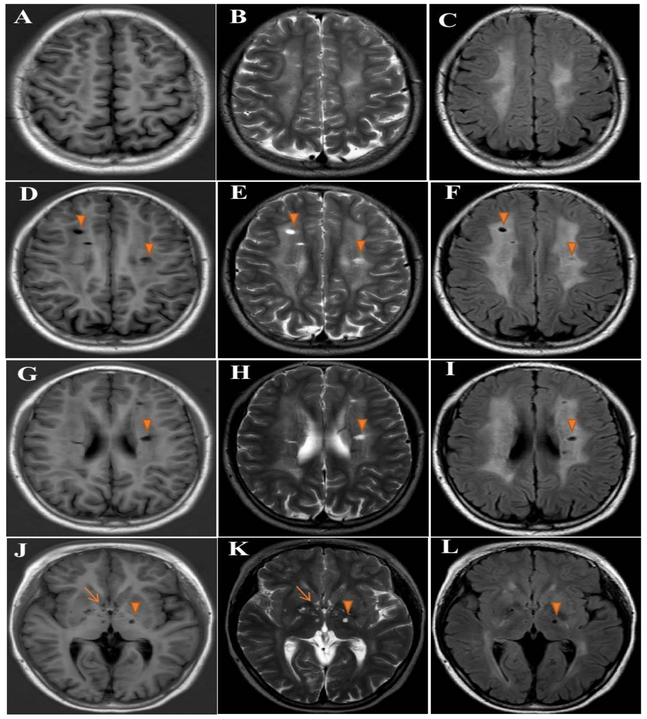

FIGURE 2. The brain MRI of the patient at 12 years old showed diffuse periventricular leukoencephalopathy (A-I), lacunes (arrowheads) in bilateral centrum semiovale (D-F), periventricles (G-I) and bilateral basal ganglia (J-L), dilated perivascular spaces (arrows) in bilateral ganglia(J-K).

CONCLUSIONS

Genetic screening should be considered in familial cases and also in sporadic cases even in pediatric patients, 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.

REFERENCES

1.Litak J, Mazurek M, Kulesza B, Szmygin P, Litak J, Kamieniak P, Grochowski C. Cerebral Small Vessel Disease. Int J Mol Sci. 2020 Dec 20;21(24):9729. doi: 10.3390/ijms21249729. PMID: 33419271.

2.Bordes C, Sargurupremraj M, Mishra A, Debette S. Genetics of common cerebral small vessel disease. Nat Rev Neurol. 2022 Feb;18(2):84-101. doi: 10.1038/s41582-021-00592-8. Epub 2022 Jan 5. PMID: 34987231.

3.Paraskevas GP. Hereditary causes of ischemic cerebral small vessel disease. Hell J Nucl Med. 2019 Jan-Apr;22 Suppl:95-101. PMID: 30877727.

4.Søndergaard CB, Nielsen JE, Hansen CK, Christensen H. Hereditary cerebral small vessel disease and stroke. Clin Neurol Neurosurg. 2017 Apr;155:45-57. doi: 10.1016/j.clineuro.2017.02.015. PMID: 28254515.

5.Marini S, Anderson CD, Rosand J. Genetics of Cerebral Small Vessel Disease. Stroke. 2020 Jan;51(1):12-20. doi: 10.1161/STROKEAHA.119.024151. Epub 2019 Nov 22. PMID: 31752611.

6.Zanon Zotin MC, Sveikata L, Viswanathan A, Yilmaz P. Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management. Curr Opin Neurol. 2021 Apr 1;34(2):246-257. doi: 10.1097/WCO.0000000000000913. PMID: 33630769.

7.Chen X, Wang J, Shan Y, Cai W, Liu S, Hu M, Liao S, Huang X, Zhang B, Wang Y, Lu Z. Cerebral small vessel disease: neuroimaging markers and clinical implication. J Neurol. 2019 Oct;266(10):2347-2362. doi: 10.1007/s00415-018-9077-3. PMID: 30291424.

8.Taylor-Bateman V, Gill D, Georgakis M, Malik R, Munroe P, Traylor M; International Consortium of Blood Pressure (ICBP). Cardiovascular Risk Factors and MRI Markers of Cerebral Small Vessel Disease: A Mendelian Randomization Study. Neurology. 2021 Nov 29:10.1212/WNL.0000000000013120. doi: 10.1212/WNL.0000000000013120. PMID: 34845052.

9.Meuwissen ME, Halley DJ, Smit LS, Lequin MH, Cobben JM, de Coo R, van Harssel J, Sallevelt S, Woldringh G, van der Knaap MS, de Vries LS, Mancini GM. The expanding phenotype of COL4A1 and COL4A2 mutations: clinical data on 13 newly identified families and a review of the literature. Genet Med. 2015 Nov;17(11):843-53. doi: 10.1038/gim.2014.210. Epub 2015 Feb 26. PMID: 25719457.

10.Plaisier E, Ronco P. COL4A1-Related Disorders. 2009 Jun 25 [Updated 2016 Jul 7]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK7046/

11.Jankovic M, Petrovic B, Novakovic I, Brankovic S, Radosavljevic N, Nikolic D. The Genetic Basis of Strokes in Pediatric Populations and Insight into New Therapeutic Options. Int J Mol Sci. 2022 Jan 29;23(3):1601. doi: 10.3390/ijms23031601. PMID: 35163523.