White Matter Disease in a Young Adult Presenting as Rapidly Progressive Parkinsonism

A 36-year-old Chinese lady presented with bilateral hand tremors and difficulty in performing simple tasks such as typing and handling of utensils. She also reported short-term memory loss over the last 3 months. On initial examination, bradykinesia was observed in her upper limbs which was slightly more pronounced on the left. This was associated with postural and intention tremors as well as left upper limb dystonia, posturing and apraxia. Brisk tendon reflexes were also elicited. Her sensory and motor power and coordination examinations were unremarkable. Her gait and speech were normal.

Within 1 year of her initial presentation, her symptoms progressed rapidly. Her speech became impaired with hypokinetic dysarthria. She had difficulty initiating speech and features such as festination and reduced volume were observed. Emotional lability was also noted. Additionally, she developed postural instability and was unable to stand independently. There was progression of bilateral upper limb dystonia with increased rigidity and spasticity. Two years after symptom onset, she required assistance in most of her activities of daily living.

Notably, her mother passed away at the age of 55 in another country and was suspected to be suffering from an undetermined neurodegenerative disease. No definite family history of Parkinsonism was otherwise present. There was no history of consanguinity. Her father and 3 siblings were healthy.

What do her serial magnetic resonance imaging (MRI) show?

A. Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP)
B. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
C. Multiple sclerosis (MS)
D. Central nervous system (CNS) vasculitis
E. Adult-onset Krabbe disease

Workup and Findings

The initial clinical diagnosis was asymmetrical Parkinsonism syndrome. Cerebrospinal fluid (CSF) and serum workups for MS, vasculitis, infective and other immune-mediated causes (both paraneoplastic and non-paraneoplastic) were negative. Initial MRI done in a private hospital showed bilateral white matter hyperintensities on T2-weighted axial images and fluid-attenuated inversion recovery (FLAIR) coronal images, predominantly in the frontoparietal lobes, and included the corticospinal tracts at the posterior limbs of the internal capsules (Fig. 1). Additionally, multiple foci of restricted diffusion were present in the bilateral centrum semiovale (Fig. 1), corona radiata and splenium of the corpus callosum. There was also frontal atrophy which is rare in someone of her age (Fig. 1). No abnormal parenchymal or leptomeningeal enhancement was identified. The basal ganglia, brainstem and cerebellum were not involved. Computed tomography (CT) of the brain and angiogram study showed confluent white matter changes that were similar in appearance and distribution to that seen on MRI. A calcific focus was seen in the right frontal lobe periventricular white matter. There was normal contrast opacification and calibre of the anterior and posterior circulations. No stenosis or beading was seen that would otherwise suggest vasculitis.

At follow-up 1.5 years later, MRI showed increased confluent white matter FLAIR signal abnormalities that still predominantly involved the frontoparietal lobes (Fig. 2). There was increased prominence and new foci of raised diffusion-weighted image (DWI) signal in the bilateral centrum semiovale, corona radiata and splenium of the corpus callosum. Some of these showed apparent diffusion coefficient (ADC) signal dropout that was consistent with new and persistent foci of restricted diffusion (Fig. 2). New foci of restricted diffusion were also seen in the left genu of the corpus callosum. There was generalised cerebral atrophy with frontal predominance that had progressed since the previous examination (Fig. 2).

Answer: A

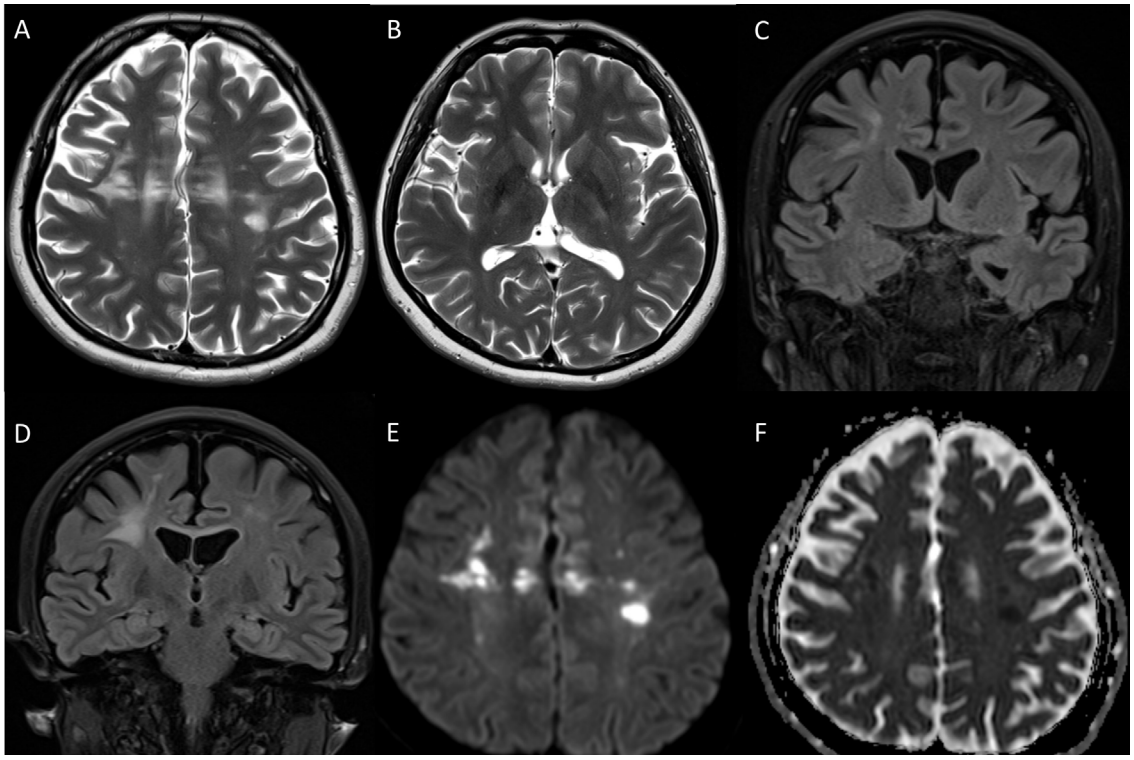

Fig. 1. Initial brain MRI. A and B: T2-weighted axial images showed signal changes in bilateral frontoparietal deep and subcortical white matter and corticospinal tracts in the posterior limb of internal capsules associated with generalised cerebral volume loss that exhibited frontal lobe predominance. C and D: Fluid-attenuated inversion recovery coronal images corroborated findings of T2-weighted images but also showed involvement of body of the corpus callosum. E and F: Diffusion-weighted and apparent diffusion coefficient axial images showed multiple areas of restricted diffusion in bilateral centrum semiovale. MRI: Magnetic resonance imaging

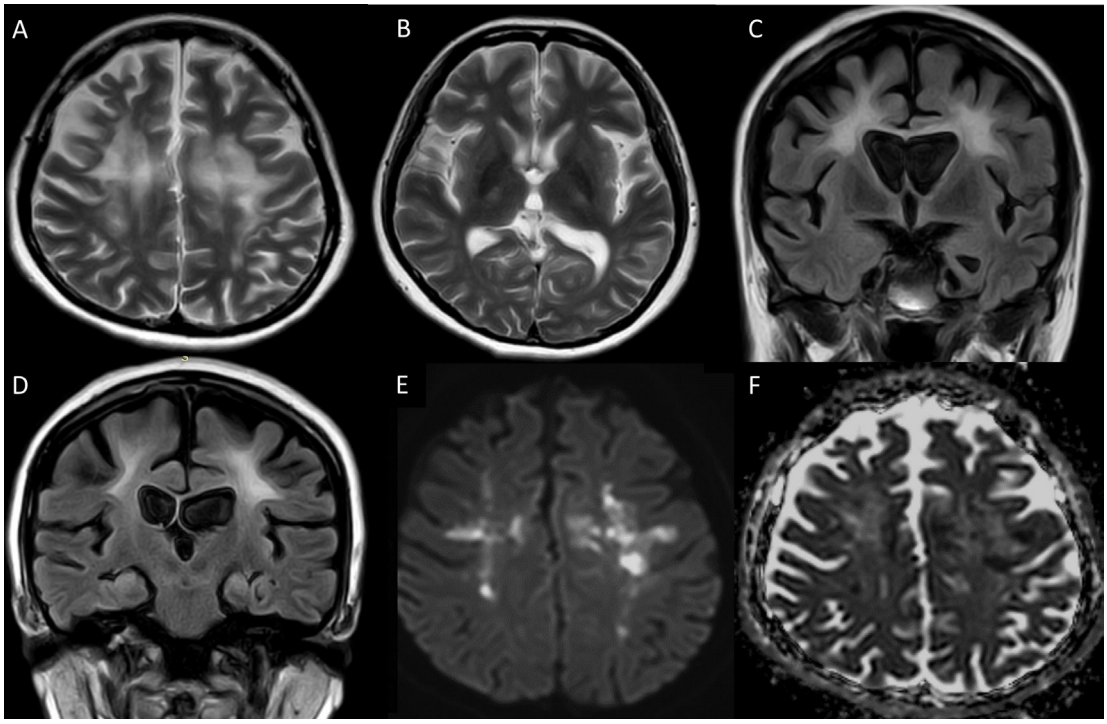

Fig. 2. Follow-up brain MRI. A and B: T2-weighted axial images showed interval progression of confluent white matter signal changes and generalised cerebral volume loss with frontal lobe predominance. C and D: Fluid-attenuated inversion recovery coronal images corroborated findings of T2-weighted images but also showed prominence of lateral ventricles from volume loss. E and F: DWI and ADC axial images showed new and increased prominence of DWI signal abnormalities, some of which showed corresponding ADC signal change that was consistent with new and persistent foci of restricted diffusion. ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted image; MRI: Magnetic resonance imaging

In view of her suspected family history of neurodegenerative disease and unexplained white matter changes seen on her imaging studies, a few differential diagnoses were considered and she underwent a genetic test. Whole-genome sequencing (WGS) revealed a variant of the colony-stimulating factor-1 receptor (*CSF1R*) gene, *T567M*, that was predicted in silico to be pathogenic with a rare exome variant ensemble learner score of >0.5.[1] No other pathogenic variants or mutations were found on WGS, including in the alanyl-tRNA synthetase 2 (*AARS2*) gene that could suggest another cause of adult-onset leukoencephalopathy such as *AARS2*-related leukoencephalopathy. Her clinical syndrome and characteristic findings on imaging studies, such as bilateral frontoparietal involvement and persistent restricted diffusion, as well as the finding of the *CSF1R* gene variant on WGS and absence of other potential pathogenic variants made ALSP the likeliest diagnosis.[1]

Discussion

The term "leukoencephalopathy" encompasses an extensive group of white matter diseases that may be acquired or are congenital in origin. They may be broadly divided into demyelinating conditions that involve secondary destruction of normal myelin or dysmyelinating conditions which occur as a result of disordered myelin production.[2] The onset of presentation may range from as early as the neonatal period to adulthood. The primary focus of our discussion will be on adult-onset leukoencephalopathies. The increased use of MRI has greatly helped clinicians and radiologists to gain a better understanding of this rare subgroup of conditions.

ALSP is a rare, autosomal dominant, adult-onset leukodystrophy with a mean age of onset at 43 years old. Although it is an autosomal dominant trait, sporadic cases are common due to incomplete penetrance, genetic mosaicism and de novo mutations.[3-6] The typical imaging features include frontoparietal predominant white matter signal abnormalities that are bilateral but are not always symmetrical, corpus callosum involvement, multifocal persistent restricted diffusion on DWI, progressive volume loss and presence of calcifications that have been described in periventricular frontal and parietal subcortical white matter.[3-6] Patients usually present with early-onset cognitive dysfunction, personality changes and movement disorders including tremours, bradykinesia and rigidity that mirror features of Parkinsonism.[3-6] The neuropathological hallmark involves destruction and volume loss of cerebral white matter with a marked loss in myelin, large numbers of axonal spheroids and pigmented glia. Mutations in the *CSF1R* gene have been implicated in ALSP; most mutations were found on the tyrosine kinase domain of the protein.[3-6] Taking into account our patient's demographics, clinical presentation, preliminary genetic findings and characteristic imaging results, ALSP was suspected.

Another adult-onset inherited white matter disease is CADASIL. It may also present with confluent white matter signal abnormality, positive lesions on DWI and progressive volume loss. Although the characteristic involvement of the anterior temporal lobes and external capsules were absent in our patient, studies have shown that these manifestations may not be seen in the Asian population, particularly those with *R544C* mutations.[2,7,8] Nonetheless, CADASIL was considered as less likely given the persistent foci of restricted diffusion (atypical for infarcts) and absence of cerebral microbleeds, intracranial haemorrhage and involvement of the brainstem, which are reportedly more common in the Asian variant.[7,8]

An imaging differential of primary progressive MS was briefly considered. Demyelinating plaques are typically T1-weighted hypointense and T2-weighted hyperintense, and may show contrast enhancement in the active phase. Both high and low ADC values have been described in the active phase and are typically found in the periventricular, juxtacortical, infratentorial and spinal cord.[9,10] Additionally, compared to the Western population, Asian patients with MS tend to have optic-spinal involvement.[11] Although our patient had progressive disability and periventricular lesions on MRI, she did not respond to a trial of corticosteroids therapy. The absence of optic-spinal involvement and oligoclonal bands in CSF also rendered the diagnosis of MS as less likely.[9,11]

CNS vasculitis comprises a wide spectrum of diseases that include systemic vasculitides, connective tissue diseases, malignancies, drug- and radiation-induced infections.[12] Primary CNS vasculitis or primary angiitis of the CNS is a rare idiopathic entity that is confined to the CNS and typically presents as encephalopathy and headache in the 5th and 6th decades of life.[2,12] Imaging findings of CNS vasculitis may show microvascular ischaemic changes, infarcts, haemorrhages, white matter oedema and contrast enhancement. The cerebral arteries may have a beaded appearance that show varying degrees of stenosis, occlusion and vessel wall contrast enhancement.[12] In our patient, the clinical presentation was limited to neurological symptoms and there were no evidence of other organ involvement. Additionally, she was not on any long-term medications or radiation treatment. Serum and CSF workups did not reveal any findings that would suggest autoimmune, infective, inflammatory or malignant processes. The imaging results revealed multiple foci of restricted diffusion which could also be seen in infarcts. However, many of the foci of restricted diffusion persist over time and these are atypical

for infarcts. Other findings such as haemorrhages, contrast enhancement and vascular stenosis were also absent in our patient.

Inborn errors of metabolism (IEM) remain an important differential diagnosis in patients who present with leukoencephalopathy. IEM is a diverse group of genetic defects that result in enzyme deficiency in the metabolic pathway and in the case of leukodystrophies, it can lead to myelin disorders. These tend to produce symmetrical white matter changes in the brain.[5,6] Specifically, the more common disorders such as Krabbe disease, X-linked adrenoleukodystrophy (X-ALD) and metachromatic leukodystrophy may be considered.

Krabbe disease is an autosomal recessive lysosomal storage disease caused by beta-galactocerebrosidase enzyme deficiency. Adults with this condition present with pyramidal tract signs accompanied by spastic paraparesis or tetraparesis. Peripheral demyelinating polyneuropathy may also occur in up to 60% of patients. The clinical course is slowly progressive. MRI features include bilateral parieto-occipital white matter changes and involvement of the splenium of the corpus callosum, corticospinal tracts and optic radiation. Periventricular white matter involvement is less commonly seen. Intracranial calcifications may be seen on CT.[5,6]

X-ALD is one of the most common adult leukodystrophies that is due to mutations in the adenosine triphosphate-binding cassette subfamily D member 1 gene. On MRI, there are typically abnormalities in the parieto-occipital white matter, splenium of the corpus callosum, audio-visual pathways and occasionally the frontal lobes and corticospinal tracts. Enhancement of the lesions may be seen. Thoracic cord involvement is often seen in the adrenomyeloneuropathy form, which is the most common type of X-ALD.[5,6]

Metachromatic leukodystrophy is an autosomal recessive lysosomal disease related to arylsulfatase A gene mutations. Patients with this condition present with central and peripheral demyelination. MRI shows symmetrical and confluent frontal or periventricular white matter signal changes with sparing of subcortical U-fibres. A tigroid pattern caused by sparing of perivascular white matter may be seen.[5,6]

Our patient presented with rapidly progressive cognitive and Parkinsonian symptoms. No distal axonopathy was present. MRI showed non-enhancing frontoparietal deep and subcortical white matter signal changes, involvement of corticospinal tracts and frontal predominance cerebral volume loss. Her gender, clinical presentation, rapid clinical course and pattern of white matter involvement rendered IEM disorders such as adult-onset Krabbe disease, X-ALD and metachromatic leukodystrophy unlikely.

Currently, there is no cure for ALSP and the prognosis remains dismal. The mean disease duration is 6.8 years. Management is primarily targeted at controlling symptoms that include depression, seizures and spasticity. Additionally, conventional therapies such as levodopa and cholinesterase inhibitors have not proven beneficial for manifestations of Parkinsonism and cognitive impairment, respectively. Limited research has hinted at the potential of haematopoietic stem cell transplantation to halt disease progression in 1 patient for at least 15 years.[4] However, studies that involve large populations are required to evaluate its efficacy. Some authors have advocated early screening of *CSF1R* mutations in patients with possible CNS vasculitis or adult-onset leukodystrophy to circumvent the need for a brain biopsy with its associated risks.[3]

Conclusion

Though rare, awareness of ALSP is important as it can mimic other conditions and has a poor prognosis. In adults presenting with progressive leukoencephalopathy, more common conditions such as MS, CADASIL and CNS vasculitis should first be considered. The possibility of other adult-onset hereditary leukodystrophy, such as Krabbe disease, should also be explored. However, when characteristic imaging features such as typical frontoparietal distribution, presence of white matter calcification, temporal progression of white matter changes and cerebral atrophy are present, ALSP should be entertained. The presence of persistent foci of restricted diffusion and absence of other findings, such as contrast enhancement and vasculopathy, are important to differentiate ALSP from other disease entities. Together with biochemical, clinical and genetic findings, these characteristic imaging features can prevent a delay in diagnosis.

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