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Case Report

Megalencephalic leukoencephalopathy with subcortical cysts without macrocephaly: A case study of comorbid Turner's syndrome

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ABSTRACT

We present a case of megalencephalic leukoencephalopathy with subcortical cysts without macrocephaly and who initially presented with severe psychiatric symptoms. The patient presented with presented with late-onset secondary generalized focal motor seizures, gait ataxia and mild spasticity with hyperreflexia. MRI showed diffuse white matter hyperintensities and bilateral anterotemporal cysts. Genetic analysis confirmed the causal MLC1 mutation and Turner's syndrome. Surprisingly, our patient had no macrocephaly, which is a typical finding in MCL1 mutations; we emphasize that comorbid unrelated Turner's syndrome could explain the absence of macrocephaly: although short stature is typical, microcephaly is not associated with Turner's syndrome. Our observation thus argues for detailed investigations in cases presenting with an atypical clinical picture.

1. Introduction

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) (OMIM 604004) is an autosomal recessive disorder, with macrocephaly developing within the first year of life, normal or mildly delayed early psychomotor development; cerebellar ataxia and mild spasticity occur later in childhood, wheelchair dependency is common in the second decade. Typical MRI criteria include megalencephaly, diffuse signal abnormality, cerebral white matter swelling without grey matter abnormalities, and subcortical cysts or near-cysts in the anterior temporal and other regions [1].

Turner syndrome (TS) is a congenital disorder with loss of the entire or critical parts of the X chromosome and mosaicism in which two or more cell lines may be present. Common features are gonadal dysgenesis, typical facial dysmorphy, and growth retardation, resulting in short stature in almost 100% of cases [2].

The main cognitive and behavioral features of TS result from decrease in occipital white matter and impaired social and spatial networks (i.e., left superior temporal sulcus, orbitofrontal cortex, right intraparietal sulcus); and manifest as visuo-spatial and executive dysfunction and impaired emotion processing [3].

2. Case report

A 30-year-old female with previously recognized mosaic TS (i.e., 46 × 0/46XX), with growth hormone substitution during childhood, and recurrent depression since age 10 years, presented with secondary generalized focal motor seizures. She complained of gait instability and progressive fatigue over several months before the onset of seizures. MRI found leukodystrophy and she was referred to our center.

On admission, she had psychomotor slowing, dysarthria, gait ataxia and mild spasticity with hyperreflexia. Her head circumference was 55.5 cm (60th percentile of adult female norms) and her body height was 148.5 cm (−2.96 SD, i.e., median height of 11-year-old girls). She was being treated for hypogonadism but had no facial dysmorphism typical for TS. EEG showed slow background activity without epileptiform discharges. Neuropsychological assessment detected delayed memory recall, construction apraxia, and executive dysfunction with perseverative behavior and attention deficits.

The patient's mother reported no accelerated head growth during infancy nor macrocephaly; psychomotor development was normal and cognitive impairment was absent until the second decade of life.

MRI (Fig. 1) showed diffuse white matter hyperintensities on T2 with edematous changes and bilateral anterotemporal cysts on T1 and FLAIR sequences. Genetic analysis detected (1) two causal mutations c.250C > T, p.Arg84Cys (the same mutation was found in the mother) and (2) a frameshift mutation c.908_918delinsGCA, *both in* the *MLC1* gene.

Gait, ataxia, and dysexecutive syndrome progressively worsened; depressive manifestations increased despite treatment and at age 36 she

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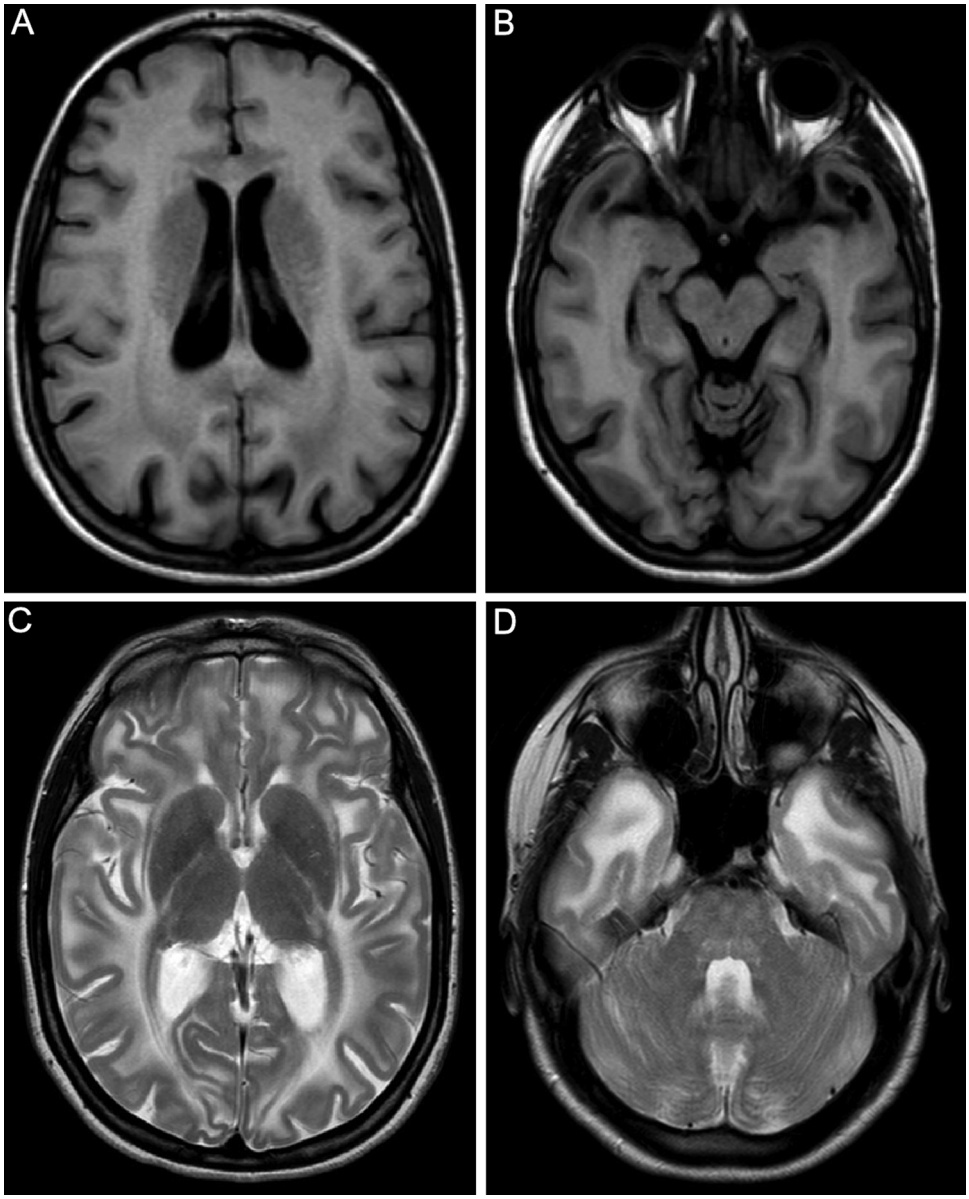

Fig. 1. Brain magnetic resonance imaging findings: axial view of fluid-attenuated inversion-recovery (FLAIR) sequence shows diffusely abnormal and mildly edematous white matter (A) and bilateral anterior temporal cysts (B); axial T2 weighted images demonstrate a double-line-shaped abnormal signal in the posterior limb of the internal capsule (C) and a mildly increased signal from the cerebellar white matter (D).

attempted suicide resulting in severe polytrauma with prolonged intensive care. Six months later, she returned home, able to stand without support, but motor symptoms continued to progress and the patient became wheelchair bound at age 37.

3. Discussion

We present a genetically confirmed MLC1 case with a typical MRI presentation, predominant neuropsychiatric features in childhood with recurrent depression, but absent macrocephaly, and late onset motor involvement. Our patient also had unrelated comorbid Turner's syndrome.

Surprisingly, even though genetic comorbidity should be an aggravating condition due to the increased metabolic burden (e.g., comorbid TS appears to increase morbidity in Cornelia de Lange's syndrome) [4], our patient did not develop a severe MLC phenotype.

Patients with MCL1 mutations usually have macrocephaly over the 98th percentile (MLC without macrocephaly involve another mutations) [5]. The absence of MLC related macrocephaly in our patient could be explained by the comorbid TS (i.e., growth retardation in TS with its typical short stature [2] could also inhibit macrocephaly development due to MLC). The delay in the onset of motor symptoms, which was probably unrelated to TS, is not uncommon in MLC [5].

Suicidal rates are usually low in TS (2.8% in one study); on the other hand, psychiatric manifestations, can occur in up to 12% of MLC patients. This comorbidity could have impacted the severity of our patient's depression [2,5].

In conclusion, to our knowledge this is the first report of comorbid MCL and Turner's syndrome and should help alert those in daily clinical practice to atypical presentations of rare diseases.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

The patient agreed with the publication of this case report and signed an informed written consent.

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