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Case report

Leigh syndrome with atypical cerebellar lesions

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ABSTRACT

Leigh Syndrome is a neurodegenerative disorder caused by mitochondrial dysfunction, with significant phenotypic and genetic heterogeneity. It usually presents in early life, with a severe prognosis. It can be caused by more than 75 different gene mutations, of nuclear and mitochondrial origin, involving all respiratory chain complexes, with less than 25% of Leigh syndrome having mitochondrial DNA mutations. The typical pathologic hallmarks are focal, bilateral, and symmetric lesions in the basal ganglia, thalamus, cerebellum, cerebral white matter and spinal cord gray matter, usually with T2WI and FLAIR hyperintensity. The basal ganglia and thalami frequently present with a pattern of cytotoxic edema. We present one case with clinical and analytical features consistent with Leigh Syndrome, with peculiar imaging features, showing dominant cerebellar edematous changes with unexpected petechial component suggestive of microangiopathy. To our knowledge, these features are unreported and suggest the existence of microvascular lesions. Based on the reported imaging findings, we propose that Leigh Syndrome should be added to the differential diagnosis of acute cerebellitis.

1. Background

Leigh Syndrome (or subacute necrotizing encephalomyelopathy) is a mitochondrial neurodegenerative disorder, with a significant phenotypic and genetic heterogeneity. Usually presenting in infancy or early childhood, it has a severe prognosis [1], being relatively common, with an incidence of 1 in 40,000 births and no known predilection for sex or race [2].

Leigh syndrome can be caused by more than 75 different gene mutations, of both nuclear and mitochondrial origin, involving all respiratory chain complexes [2,3]. With current genetic diagnostic technology, both nuclear and mitochondrial gene mutations are being identified at an increasing rate [1]. Less than 25% of affected individuals have mitochondrial DNA (mtDNA) mutations [1].

Signs and symptoms usually appear between 3 and 12 months of age, but the age of onset is variable, with evidence of connatal disease in some patients and adult-onset presentation in others [4,5]. Once the clinical signs appear, the disease often results in regression of both mental and motor skills, leading to disability and progression to death [1,5]. There is a wide range of possible initial manifestations of the disease. Gait disturbance, hypotonia, dystonia, dysarthria, intellectual regression, dysphagia and gastrointestinal distress are some of the most common signs and symptoms at presentation [1,5]. Refractory seizures, dystonic posturing, encephalopathy, and ataxia are usually seen later in the disease evolution [1]. The most frequent cause of death is respiratory failure [1].

The symptoms may have variable progression, but early-onset patients generally have a worse prognosis. Most patients die within a few years of diagnosis, being 2.4 years the median age of death after first symptoms [4]. This variability can be related to the genetic mutation effect and the frequency of stressors, such as intercurrent illnesses.

The typical pathologic hallmarks are focal, bilateral, and symmetric spongiform lesions in the thalamus, putamen, periaqueductal gray matter, pons, medulla oblongata, inferior olives, and posterior columns of the spinal cord [6].

On MRI, T2WI and FLAIR usually show bilateral and symmetrical hyperintensities in basal ganglia, thalami, cerebellum, cerebral white matter and spinal cord gray matter [6]. Although basal ganglia lesions are most typical, their magnitude and extent are quite variable [7]. Cerebellar white matter lesions are less prominent and usually occur when supratentorial white matter lesions are already visible [8]. Although rare, there are reported cases with notable cerebellar affection

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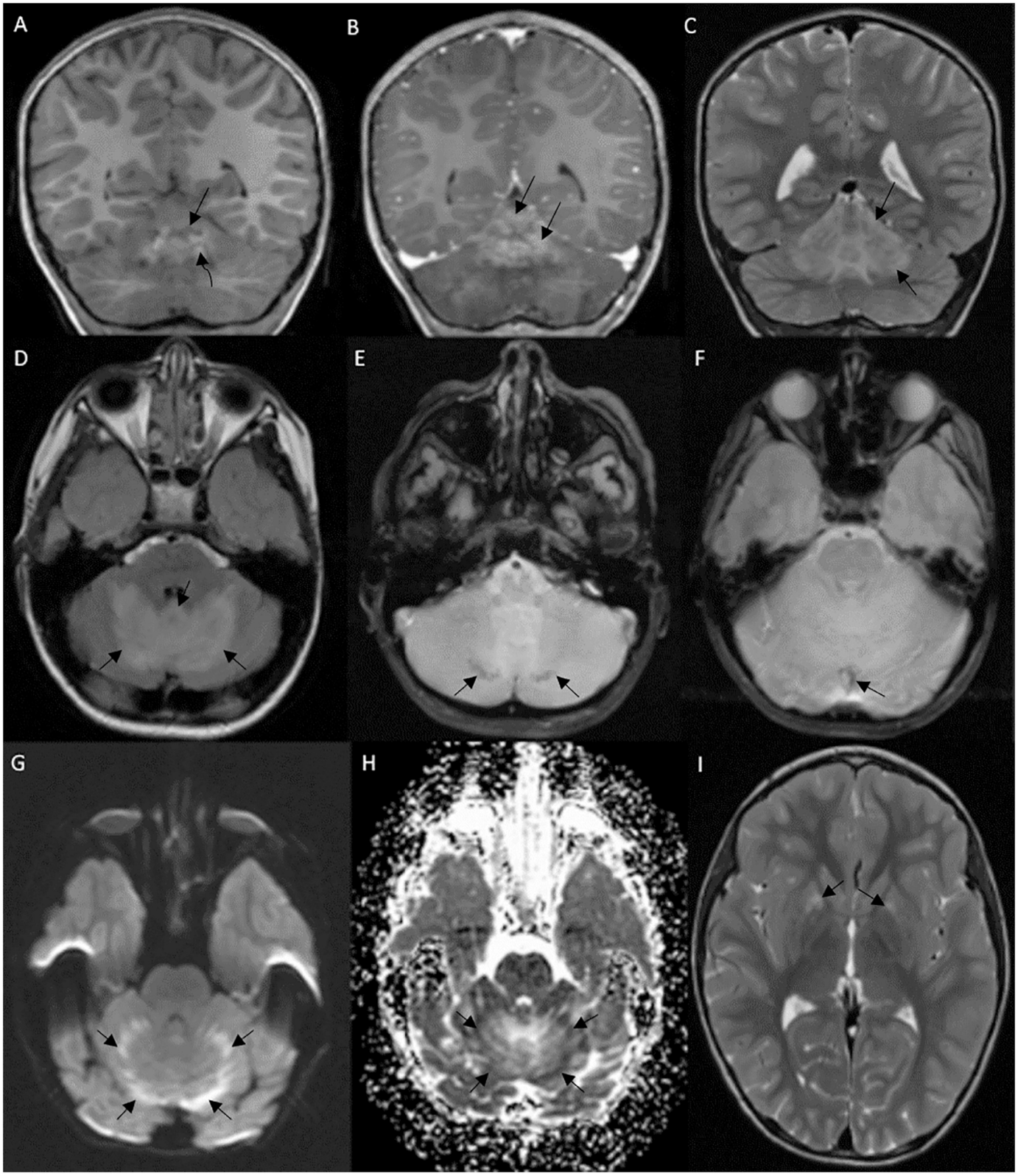

Fig. 1. Symmetric partial superior vermis and cerebellum hemispheric affection, including cortex and white matter. Displayed images show central areas of T1 hypo and hyperintensity (A), and gadolinium enhancement (B); T2 (C) and T2 FLAIR (D) wider hyperintensity; T2* (E,F) shows peripheric hypointensity foci related to blood degradation products; (G,H) DWI and ADC map show features of peripheric restricted diffusion; (I) Symmetric lenticular anterior-inferior T2 hyperintensity (similar findings on follow-up exam). There was no evidence of the typical restricted diffusion on the basal ganglia (DWI and ADC map not shown).

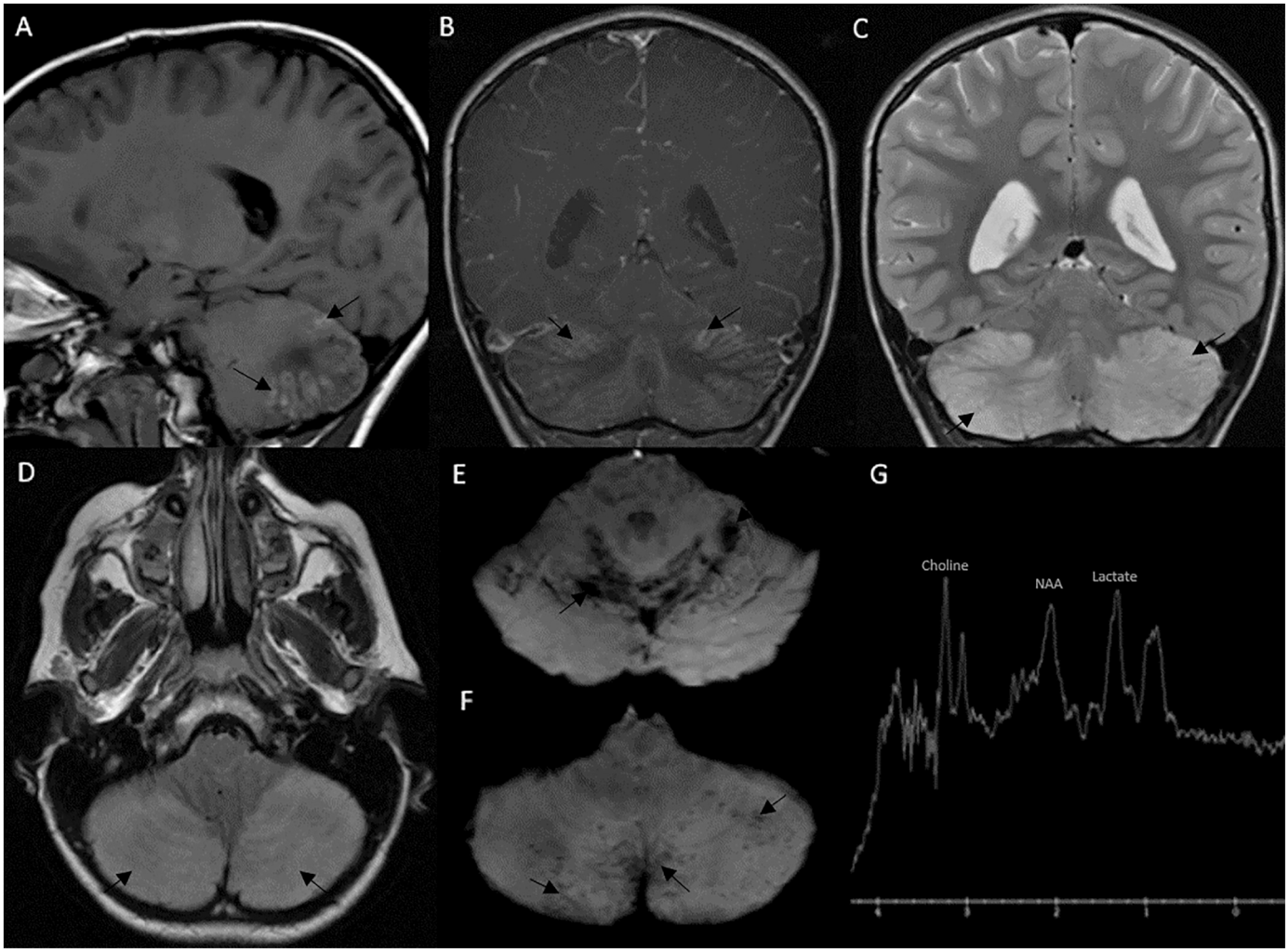

Fig. 2. On the second MRI, the previously non-affected part of the cerebellum showed (A) cortical T1 spontaneous hyperintensity and (B) gadolinium enhancement; as well as cortical and subcortical edematous changes, with (C) T2 and (D) T2 FLAIR hyperintensity. SWI shows hypointense foci on the previous (E) and currently affected regions (F). (G) Short TE Spectroscopy with left cerebellar hemisphere voxel, shows evident NAA reduction, as well as choline, lactate peaks.

[9]. Evidence of cytotoxic edema, with a pattern of restricted diffusion, is frequently present in basal ganglia and thalami [10]. Spectroscopy usually shows a lactate peak and a decrease in NAA [10].

2. Case presentation

Our patient was born to nonconsanguineous parents, with an uneventful personal and family medical history. Manifestations of neurological illness were first recognized at two years of age, when poor language skills, motor incoordination and frequent falls were noticed. The boy was evaluated in our neurology clinic 2 years later, with developmental regression and additional neurological signs, including muscular hypotrophy, orofacial dyskinesia, dysarthria and bilateral Babinski sign. Muscle tone and strength were normal. At this point, serum lactate and alanine were slightly elevated. Organic acid chromatography and MRI were normal. During the following year, there was a progressive worsening of motor function with chorea, ataxia and kinetic tremor.

At the age of 8, neurologic symptoms aggravated in the context of febrile illness and he was admitted for additional investigation and treatment. CSF lactate was abnormal (3,6 mmol/L; reference value: 1,1–2,4 mmol/L) and lactate blood levels varied between slightly elevated and normal (0,8–2,9 mmol/L). CSF cell count, glucose and protein were within reference values. Multiplex PCR in CSF for viral agents (Enterovirus, Coxsackievirus, Poliovirus, Herpes simplex 1 and 2, Herpes hominis 6 and 7, Cytomegalovirus, Epstein Barr virus, Varicella zoster virus) was negative. Brain MRI revealed cerebellar edema with peripheral petechial hemorrhages, gadolinium enhancement and restricted diffusion (Fig. 1 A-H). A bilateral T2 hyperintensity (Fig. 1 I) was seen in the lenticular nuclei and tectum. A muscle biopsy was performed, and genetic testing revealed an m.8993 T > C missense mutation on the MT-ATP6 gene, with heteroplasmy of 98%, consistent with Leigh Syndrome.

Pyruvate, blood glucose, hepatic and renal function, creatine kinase, ammonia, repeated amino acids, organic acids, homocysteine, biotinidase activity, chitotriosidase activity and pyruvate dehydrogenase complex activity were all normal.

Six months later, in the context of a febrile illness, there was an acute and severe neurologic deterioration. A new brain MRI (Fig. 2) showed a symmetric hyperintense signal in the cerebellar cortex and white matter with hemorrhagic cortical component and intense gadolinium enhancement. Hypointense foci on SWI remained on the previously affected regions and developed on the currently edematous area. Spectroscopy showed a prominent lactate peak. The lenticular T2 hyperintensities were similar to the previous MRI and there was, in addition, a loss of supratentorial white matter volume.

3. Discussion

Lax *et al* described ischemic-like lesions in the cerebellar cortex in 8/16 patients with mitochondrial disease, although none had Leigh Syndrome [11]. These lesions were suggestive of dysfunction of vascular smooth muscle cells and blood–brain barrier breakdown [11]. Other reports provide further evidence in favor of cerebral microangiopathy in mitochondrial diseases, mainly in MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), MERRF (myoclonic epilepsy with ragged-red fibers) and LHON (Leber hereditary optic neuropathy) [12–14].

Our patient had progressive ataxia, extrapyramidal signs, variable serum lactate and high CSF lactate with genetic confirmation of Leigh syndrome. Two episodes of increasingly severe ataxia, fever and cerebellar lesion could be compatible with cerebellitis. However, the recurrent symptoms, normal CSF examination and negative multiplex PCR testing would argue against this diagnosis and are consistent with mitochondrial disease.

The relationship between cerebral microbleeds and vasculopathy is established in the literature [15,16]. The cerebellar lesions with contrast enhancement, T1 spontaneous hyperintensity and SWI hypointensity as petechial hemorrhages, were suggestive of microangiopathy. We propose that they may result from mitochondrial microangiopathy.

In the follow-up brain MRI, six months later, there were substantial changes within the cerebellum. The T2 hyperintense, edematous lesions showed similar features on both exams but topographically changed. The edematous area of the second MRI was almost a mirror-image of the previously affected area (compare Figs. 1C-D with 2 C-D).

Another unusual feature was the isolated involvement of cerebellar white matter without supratentorial white matter lesions. Nonetheless, a loss of supratentorial white matter volume was apparent. Cystic components or gliotic changes were absent, which is also atypical [17].

A prominent basal ganglia T2 hyperintensity, paradigmatic for Leigh syndrome, was not seen in this patient although this has been previously reported [6].

In conclusion, we present a Leigh syndrome-like patient with imaging features not previously published and eventually resulting from microangiopathy. Additionally, we propose that Leigh Syndrome should be added to the differential diagnosis of acute cerebellitis.

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