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LETTER TO THE EDITOR

Cerebellar atrophy with T2/FLAIR hyperintense cerebellar cortex: a new imaging phenotype of combined complex II/III deficiency

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Dear Editor:

There is a general lack of genotype-phenotype correlations in many mitochondrial disorders. Hence, a genetic diagnosis remains elusive for many patients. Although currently there is no effective therapeutic intervention for mitochondrial disorders, the establishment of a genetic diagnosis will provide additional information for prognostication and genetic counseling. Herein, we describe a case of combined complex II/III deficiency due to SDHA mutation with FLAIR hyperintense cerebellar cortex. To the best of our knowledge, this imaging finding has never been reported before in patients with complex II/III deficiency.

A 3-year and 6-month-old girl presented to our institution with global developmental delay. Antenatal and perinatal period was unremarkable and she was delivered via vaginal delivery at 42 weeks of gestation. She was first noted to have motor developmental delay at the age of one. She was otherwise well with no visual or hearing impairments. There was also no history of seizures or developmental regression. On physical examination, no dysmorphic or myopathic facies were noted. Subtle dystonia and abnormal eye movements were present.

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MRI of the brain was performed and showed bilateral signal abnormalities within the basal ganglia, cerebellar cortex, thalamus, and cerebellar tonsils. Mild cerebellar hypoplasia was also observed (Fig. 1). The vermis and pons are relatively preserved. Muscle and skin biopsy was performed under general anesthesia and samples were sent for histopathological examination, muscle respiratory chain enzymes, and skin fibroblast culture. Muscle biopsy showed low levels of complex II and III respiratory chain enzymes. Molecular genetic testing for common mitochondrial mutations did not yield any pathogenic mutations. Decision was made to proceed with whole exome sequencing, looking at genes known to be associated with mitochondrial disorders in children. Two variants in the SDHA gene (c.403G > C,p.(Asp135His) and c.1787A > G,p.(Asp596Gly) were identified.

Mitochondrial disorders are the most common inborn errors of metabolism affecting the oxidative phosphorylation system (OXPHOS). Until date, more than 250 gene mutations have been shown to cause mitochondrial disease [1]. The OXPHOS consists of four complexes (complex I–IV) of the electron transport chain (ETC) and ATP synthase (complex V), encoded by both the nuclear and the mitochondrial genomes. Two electron carriers (Coenzyme Q 10 and Ubiquinone) and cytochrome c facilitate the transfer of electrons through the complexes. Complex I deficiency is the most common biochemical phenotype for pediatric patients with respiratory chain deficiencies. Complex II deficiencies are rare [2–4], accounting for approximately 2% of respiratory chain deficiency cases; with less than 50 reported cases [4, 5]. To the best of our knowledge, less than 15 cases of combined complex II/III deficiency have been reported. Complex II consists of four exclusively nuclear-encoded subunits; succinate dehydrogenase (SDH) subunits A to D. All four SDH genes and one of its known assembly factors SDHAF2 have tumor suppressor function. Mutations in SDHA have also been found in hereditary paragangliomas (PGLs) and pheochromocytomas (PHEOs), a specific subtype of gastrointestinal stromal tumors (GISTs) and very rarely in pituitary adenoma. Until date,

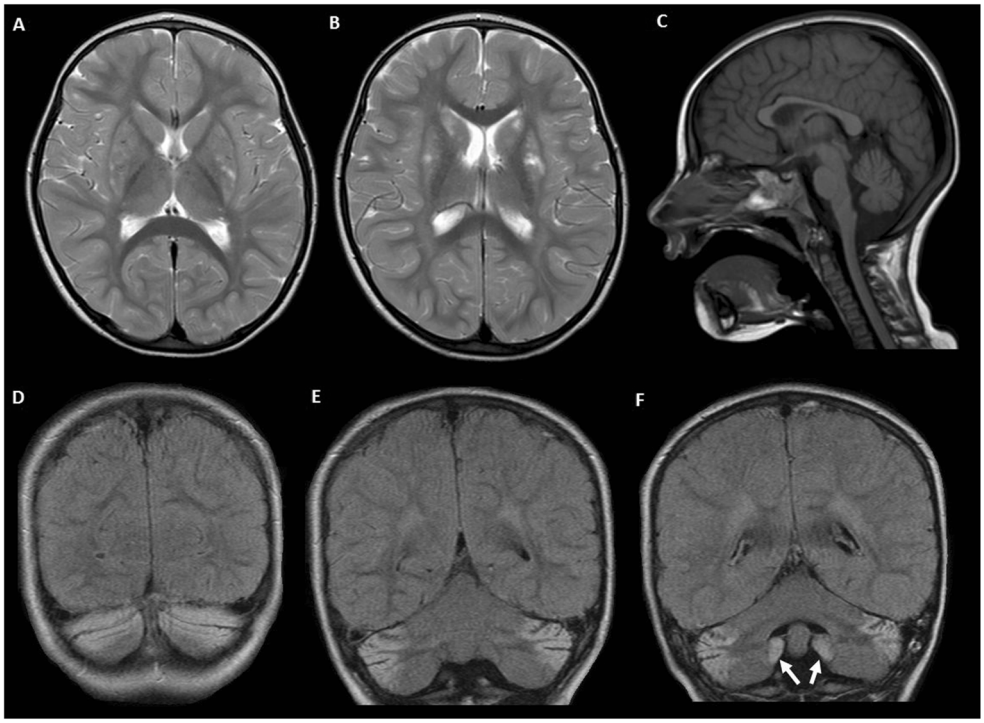

Fig. 1 **a**, **b** Axial T2-weighted images show signal abnormalities within the putamen, caudate head, and thalamus. **d**–**f** Abnormal FLAIR hyperintense signal is seen within the cerebellar cortex and cerebellar tonsils (white arrows in **f**). Of note is also mild prominence of the interfolial spaces, in keeping with mild cerebellar atrophy/hypoplasia. **c** The pons and vermis are relatively preserved

SDHA-related mitochondrial disease has not been reported in association with hereditary tumors.

Complex II/III deficiency has been associated with variable neuroimaging phenotypes, including Leigh syndrome, Kearns-Sayre syndrome, optic atrophy, leukodystrophy, and cerebellar atrophy. No FLAIR hyperintense cerebellar cortex is however described in these reported cases. Cerebellar atrophy (CA) with cerebellar cortex T2/FLAIR hyperintensity is one of the five subgroups of cerebellar atrophy described by Poretti et al. [6]. Known causes of CA with cerebellar cortex T2/FLAIR hyperintensity include infantile neuroaxonal dystrophy, Marinesco-Sjogren syndrome, congenital disorder of glycosylation type Ia (CDG-1a) due to PMM2 mutations, mitochondrial disorders such as complex I deficiency due to NUBPL mutations and coenzyme Q10 deficiency, Christianson syndrome, pontocerebellar hypoplasia type 7, advanced-stage late-onset GM2 gangliosidosis, and spinocerebellar ataxia. In some diseases with CA and T2-hyperintense signal of the cerebellar cortex, histopathology showed severe loss of Purkinje cells and reactive proliferation of microglial cells such as Bergmann glia [7]. The finding of CA with cerebellar cortex T2/FLAIR hyperintensity in patients with CDG-1a (a neurodegenerative disorder) was first described by Feraco et al. in five children [8]. In three patients, 1H-MRS (magnetic resonance spectroscopy) was performed and revealed reduced NAA/Cr ratios. The authors hence proposed that this peculiar finding of CA with cerebellar cortex T2/FLAIR hyperintensity to be related to a combination of astrogliosis and neuronal loss [8]. The optimal functioning of OXPHOS is crucial as it ensures that the energy requirements of neurons are met. Alterations in function of the OXPHOS are linked to energy failure and neuronal cell death [9]. Dysfunction of the OXPHOS is also associated with increased levels of reactive oxygen species (ROS) derived from the leakage of electrons from the electron transport chain [9]. Mitochondrial dysfunction and oxidative damage are major contributors to neuronal loss [10]. Hence, it is not a surprise that complex II/III deficiency could have resulted in neuronal loss and astrogliosis, giving rise to CA with cerebellar cortex T2/FLAIR hyperintensity, similar to that seen in CDG-1a.

Our reported case of expands the neuroimaging phenotype of complex II/III deficiency. This finding, although not specific to complex II/III deficiency secondary to SDHA mutation, may assist the reporting radiologist in narrowing the list of differential diagnoses as well as in assisting the clinician in the planning of additional investigations.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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