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Mitochondrial multiorgan disorder syndrome (MIMODS) due to a compound heterozygous mutation in the *ACAD9* gene

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Letter to the Editor

We read with interest the article by Fragaki et al. about a 1yo Algerian female with hypertrophic cardiomyopathy, developmental delay, growth retardation, hepatomegaly, failure-to-thrive, general hypotonia, and lactic acidosis, being attributed to the biallelic variants c.1204G > T and c.358delT in the *ACAD9*-gene encoding for acyl-CoA-dehydrogenase-9, an essential assembly-factor for respiratory-chain complex-I and component of fatty-acid oxidation [1,2]. We have the following comments and concerns.

Was hypotonia attributed to involvement of the skeletal muscles, the peripheral nerves, or the cerebrum? Did cerebral MRI show any abnormalities that could explain the CNS-abnormalities? Leigh-like features are well appreciated as cerebral manifestation of *ACAD9*-mutations (Table 1) [3].

Patients carrying *ACAD9*-mutations may develop myopathy (Table 1) [4]. Was there clinical, blood-chemical, electromyographic, or bioptic evidence for myopathy in the index case? Were nerve-conduction studies normal?

The parents carried one of the mutations each. Was either of them clinically affected? Did any of the other first degree relatives exhibit phenotypic features of *ACAD9*-mutations (Table 1)? Were other first degree relatives neurologically or genetically investigated?

Though liver failure and hepatopathy have been previously described in association with *ACAD9*-mutations (Table 1), hepatomegaly seems to be a unique feature. Since *ADAC9*-mutations may cause cardiac compromise [5], it is conceivable that hepatomegaly was due to systolic dysfunction. Did the patient ever develop clinical or instrumental evidence of heart failure? Were proBNP-values elevated? Was heart transplantation ever considered? Did the patient suffer from an infectious disease or did she carry a second mutation? Was a liver-biopsy taken? Was there deposition of lipids?

Complex-I deficiency is frequently associated with *ACAD9*-mutations [6] but is complex-II and complex-IV deficiency, not being previously described, truly attributable to a secondary effect? Did the patient carry a second mutation?

Overall, this interesting case could be more meaningful if more clinical and instrumental investigations would have been carried out in the index case and in her first degree family members.

Author contribution

JF: design, literature search, discussion, first draft, SZ-M: literature search, discussion, critical comments.

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Table 1
Phenotypic manifestations of ACAD9 mutations.

Phenotypic manifestation	Reference
Central nervous system	
Developmental delay	[Fragaki, 2017, Garone, 2013]
Failure to thrive	[Fragaki, 2017]
Microcephaly	[Aintablian, 2016]
Dystonia	[Aintablian, 2016]
Seizures	[Collet, 2016]
Cognitive impairment	[Collet, 2016]
Optic atrophy	[Collet, 2016]
Leigh-like features on MRI	[Aintablian, 2016]
Heart	
Hypertrophic cardiomyopathy	[Aintablian, 2016]
Mild ventricular hypertrophy	[Dewulf, 2016]
Dilated cardiomyopathy	[DEwulf, 2016]
Patent ductus arteriosus	[DEwulf, 2016]
Intestines	
Acute liver failure	[Valencia, 2016]
Vomiting	[Schrank, 2017]
Nausea	[Schrank, 2017]
Hepatomegaly	[Fragaki, 2017]
Hepatopathy	[Robinson, 1998]
Episodes of acute liver dysfunction	[He, 2007]
Kidneys	
Proximal tubulopathy	[Collet, 2016]
Renal failure	[Collet, 2016]
Endocrine organs	
Secondary ovarian failure	[Collet, 2016]
Muscles	
Myopathy	[Collet, 2016]
Muscle weakness	[Nouws, 2014]
Fatigue	[Schrank, 2017]
Exercise intolerance	[Schrank, 2017, Garone, 2013]
Others	
Fatal neonatal multiorgan failure	[Leslie, 2016]
Postnatal growth retardation	[Fragaki, 2017]
Lactic acidosis	[Aintablian, 2016, Fragaki, 2017]
Intrauterine growth retardation	[Lagoutte-Renosi, 2015]
Reye-like episode	[He, 2007]
Elevated serum alanine	[Fragaki, 2017]
Reduced serum ornithine and citrulline	[Fragaki, 2017]

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