Is Stroke in Beta-Keto-Thiolase Deficiency Due To the ACAT1 Variant C.152T>C Ischemic or Metabolic In Nature?

Abstract:

Keywords: ischemic stroke, metabolic stroke, mitochondrial disorder, ketoacidosis, coma, encephalopathy.

LETTER TO THE EDITOR

With interest we read the article by Manawadu, T. V. et al., 2020 about a 4 years-old male with beta-keto-thiolase deficiency (BKTD) due to the novel, homozygous variant c.152C>T in ACAT1 (Manawadu, T. V. et al., 2020). The patient manifested phenotypically with a first episode of metabolic ketoacidosis, triggered by a febrile infection, multiple cerebral infarctions, and coma (Manawadu, T. V. et al., 2020). We have the following comments and concerns.

Ischemic stroke is a rare complication of BKTD and has been reported only in single patients with the disease so far (Wojcik, M. H. et al., 2018). To confirm that the hypodensities seen on cerebral computed tomography (CT) scan were truly ischemic in nature, multimodal, cerebral magnetic resonance imaging (MRI) is essential. Thus, we should be informed if cerebral MRI was carried out to confirm the ischemic nature of the cerebral lesions, to assess if the different lesions had a similar age or were of different age, and if arteries were involved in the pathogenesis of the stroke.

Additionally, we should be informed if stroke in the patient was classified as embolic, atherosclerotic, metabolic, or thrombophilic. Assuming that the patient had experienced multiple embolic strokes, we should know if endocarditis, heart failure, patent foramen ovale, thrombophilia, left ventricular hypertrabeculation (noncompaction), intraventricular thrombus formation, cerebral arteriopathy, or atrial fibrillation were excluded. In this respect echocardiographic or cardiac MRI investigations should be presented.

If stroke in the index patient was classified as metabolic, we should be informed about the presentation on diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC) maps, perfusion weighted imaging (PWI), and oxygen-extraction fraction MRI (OEF-MRI). Additionally, we should know the results of cerebral MR-spectroscopy (MRS). Metabolic stroke on multimodal MRI presents in the acute stage with hyperintensities on DWI, ADC, PWI, and hypointensities on OEF-MRI. MRS may show a lactate peak. Knowing the pathogenesis of the stroke is crucial as treatment may be different between the various types of stroke.

Since BKTD is a mitochondrial disorder (MID) and deficiency of the enzyme may cause oxidative stress, it is conceivable that not only ketone bodies but also serum and cerebro-spinal fluid (CSF) lactate were elevated. Thus, we should know serum and CSF lactate values.

Missing is an extensive family history. Since BKTD follows an autosomal recessive trait of inheritance, only few family members may be phenotypically affected. However, we should know if the family history was positive for stillbirth or early death in childhood or infancy in any of the first degree relatives of different generations of the index patient.
Since the patient was born out of a consanguineous marriage and since BKTD is transmitted via an autosomal recessive trait, it can be expected that both parents carried the culprit variant in the heterozygous form. We should be informed about the genetic test results of the index patient’s parents. In case either parent did not test positive for the ACAT1 variant, we should know if the mutation of the index case was assessed as sporadic. In this respect we should know if either parent manifested clinically or not.

Neurological manifestations of BKTD may develop after metabolic crises (Fukao, T. et al., 2019). Particularly extra-pyramidal manifestations have been reported (Fukao, T. et al., 2019). Single patients may even manifest with chorea (Buhaş, D. et al., 2013). We should know the neurological outcome of the index patient after the first metabolic crisis.

Overall, this interesting case report could profit from provision of additional data, particularly clarification of the nature of the cerebral lesion on multimodal MRI and clarification of the genetic status of the parents and other first degree relatives. Since BKTD is an ultra-rare disease, it is worthwhile to obtain as much information about these cases as possible.

REFERENCES