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redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

MELAS or Leigh syndrome, that's the question

Zespół MELAS czy Leigh, jak zróżnicować?

Josef Finsterer

Klinik Landstrasse, Messerli Institute, Vienna, Austria

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MELAS, Leigh syndrome, polyglandular syndrome, lactic acidosis, encephalopathy.

With interest we read the article by Baszyńska-Wilk *et al.* about a 12 years old female who was diagnosed with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome upon the clinical presentation, blood tests, and the cerebral magnetic resonance imaging (MRI) [1]. The diagnosis was neither confirmed by biochemical nor by genetic investigations [1]. The study is appealing but raises the following concerns.

The main limitation of the study is that the diagnosis MELAS was not biochemically or genetically confirmed. Missing are biochemical investigations of the muscle homogenate and missing is the sequencing of the mitochondrial DNA (mtDNA) respectively whole exome sequencing (WES) if mtDNA sequencing would have been negative. Though there are some indications for a mitochondrial disorder (MID) in the index patient, the suspicion needs to be supported by either biochemical investigations or documentation of a pathogenic, causative mutation in a gene involved in mitochondrial functions.

MELAS is usually diagnosed according to the Hirano criteria [2] or the Japanese criteria [3]. According to the Hirano criteria [2], stroke-like episodes (SLEs) before age 40 years, encephalopathy, manifesting with seizures or dementia, and lactic acidosis or ragged-red fibers on muscle biopsy are the criteria that need to be met for diagnosing MELAS. However, the index patient neither presented with seizures, cognitive decline, or dementia nor with SLEs. According to the Japanese criteria MELAS is diagnosed if there were SLEs manifesting as headache with vomiting, seizures, hemiplegia, cortical blindness or hemianopia, or an acute focal lesion on MRI (category A) together with lactic acidosis, mitochondrial abnormalities on muscle biopsy, or a mutation related to MELAS (category B) [3]. Thus, a hallmark of MELAS are SLEs, which were not reported in the index patient.

A second limitation of the study is that the MRI findings are rather suggestive of Leigh syndrome than MELAS. Bilaterally symmetric lesions in the brain stem are only rarely reported in MELAS patients but a hallmark of cerebral imaging in patients with Leigh syndrome [4]. Suspecting Leigh syndrome also suggests that the underlying genetic defect should be located rather in a gene of the nuclear DNA (nDNA) than an mtDNA gene as the vast majority of the mutations responsible for Leigh syndrome is located on the nDNA.

Missing is a morphological and comprehensive functional investigations of the pituitary gland. These investigations are crucial in a patient with polyglandular disease to assess if there was an empty sella syndrome or pituitary ademona, abnormalities which have been reported in association with a MID [5]. Functional studies of all hormones produced in the pituitary gland are warranted as there was polyglandular disease and as there may be also subclinical hypopituitarism.

A further limitation is that the cranial nerve VI lesion remained unexplained. We should be told if this was due to subclinical diabetes or cranial neuropathy due to other causes. Was diabetes detected after diagnosing the 6th cranial nerve palsy or before?

Unexplained remains the cause of headache during three years. We should be informed about the type, frequency, duration, associated manifestations, and location of headache. We also should be told if headache resolved spontaneously or upon treatment.

Overall, the interesting study has limitations which should be addressed to further strengthen the conclusions. Biochemical or genetic evidence should be provided that the clinical presentation was truly due a mitochondrial defect. According to the clinical presentation and imaging findings the patient rather had Leigh syndrome than MELAS.

We do not agree that the MRI lesions described in Figure 1 are located in the cerebellar pedunculus but rather in the tectum of the pons [rech].

We do not agree with the diagnosis PCB [1]. According to the Ropper criteria, absence of alternative diagnoses is warranted [2]. However, the patient did not undergo multimodal

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Josef Finsterer, MD, PhD
Postfach 20, 1180 Vienna
Austria
tel. +43-1-71165
fax +43-1-71165
e-mail: fipaps@yahoo.de

magnetic resonance imaging (MRI) of the cervical spine with contrast medium to exclude, vertebral stenosis, malignoma, spinal stroke, or myelitis of the cervical spine. Furthermore, the patient had peripheral facial palsy, which is usually not a feature of PCB [2]. Assuming that the index patient truly had GBS, acute motor axonal neuropathy (AMAN) with affection of cranial nerves VII, IX, and X rather than PCB should be diagnosed. Generally, GBS, is diagnosed according to the Brighton criteria, which require dissociation cyto-albuminique for establishing the diagnosis. Since neither the Ropper nor the Brighton criteria were entirely met, the diagnosis PCB in the index patients remains unconfirmed.

Assuming that the patient had truly GBS, it is crucial that nerve conduction studies (NCSs) were repeated. NCSs had been carried out only once 2 days after admission but might more informative if having been carried out again later in the course.

Missing is the exclusion of an infection with SARS-CoV-2 as the trigger of GBS. There was neither a search for virus RNA in the nasopharynx nor in the cerebro-spinal fluid (CSF) carried out [1]. From SARS-CoV-2 infections it is well-known that they can be complicated by GBS [3].

Overall, the elegant study has several limitations which challenge the results and their interpretation and should be addressed before diagnosing PCB. Since COVID-19 is also highly prevalent in Pakistan, a SARS-CoV-2 infection should be excluded as the cause of GBS.

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