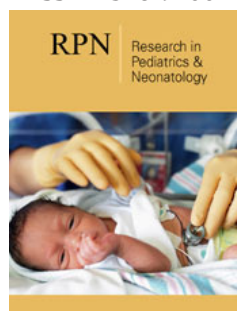


Clinical Case of a 7-Year-Old Child with Newly Diagnosed Intermittent form of Maple Syrup Urine Disease

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Abstract

Maple syrup urine disease (MSUD) is an autosomal recessive genetic disorder caused by a deficiency of branched-chain alpha-ketoacid dehydrogenase (BCKAD). This condition results in the accumulation of branched-chain amino acids (BCAAs): leucine, isoleucine and valine. With five recognized clinical variants, the disease varies in severity and the clinical spectrum is quite broad. The classic form of MSUD can be recognized by the characteristic odor of maple syrup in the cerumen at 12 to 24 hours and in the urine at 48 to 72 hours after birth. Following the introduction of extended neonatal screening, cases of the disease are being detected earlier and treatment is being initiated before the onset of symptoms. However, this clinical case presents an intermittent form of MSUD newly diagnosed in a 7-year-old child with signs of metabolic intoxication and encephalopathy. The diagnosis was difficult as other conditions were more likely due to the postnatal placement of the ventriculoperitoneal shunt and the lack of detection of maple syrup smell in the urine. Treatment with diuretics and a protein-free diet significantly improved the child's condition. Further management includes restriction of branched-chain amino acid intake and regular metabolic monitoring.

Keywords: Maple syrup urine disease (MSUD); Branched-chain amino acids (BCAAs); Branched-chain alpha-ketoacid dehydrogenase (BCKAD); Intermittent form of MSUD

Abbreviations: MSUD: Maple Syrup Urine Disease; BCAAs: Branched-Chain Amino Acids; BCKAD: Branched-Chain Alpha-Ketoacid Dehydrogenase; CT: Computed Tomography; TMA: Territorial Medical Association; EEG: Electroencephalography; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; MRI: Magnetic Resonance Imaging; ECG: Electrocardiogram

Introduction

Maple syrup urine disease (MSUD) is a rare genetic disorder with an average incidence of approximately 1 case per 185,000 live births worldwide. It is caused by abnormal activity of the BCKAD complex, which is responsible for breaking down BCAA, in particular isoleucine, valine, and leucine. When this process is disrupted, excessive amounts of BCAA accumulate in the brain, plasma, urine and other tissues, causing psychomotor delays, failure to thrive, nutritional problems and the smell of maple syrup in the urine. Early diagnosis and correct treatment are essential to avoid serious complications, such as brain damage or central respiratory failure, and to maintain a good quality of life. A timely diagnosis could be made by using prenatal diagnosis or neonatal screening. In the management of MSUD, medical nutrition therapy aims to maintain plasma BCAA concentrations within therapeutic ranges by carefully limiting dietary intake. Treatment also involves regulating multiple factors that affect endogenous protein turnover, including anabolism and catabolism, as well as maintaining stable plasma amino acid levels [1-3].

Case Presentation

A 7-year-old male patient V. was admitted to the regional children's hospital in ternopil with vomiting, headache, nausea and profound lethargy. After birth, intracranial hydrocephalus

was diagnosed and a ventriculoperitoneal shunt was placed to treat this condition. The patient also underwent balloon angioplasty and surgical correction of aortic coarctation at 2 months of age. From an early age, the child had suffered frequent episodes of elevated ketones followed by convergent strabismus, facial asymmetry and acetone in the urine. The child's condition usually improved with a lactose-free diet.

Given this history, shunt dysfunction was suspected. A head CT was performed shortly after admission and showed moderate dilatation of the ventricular system with dimensions at the level of the bodies: right ventricle -9.9mm, left ventricle -9.06mm, III ventricle -2.5mm. The IV ventricle was located along the midline and measures 3 mm. At the border of the parietal and occipital bones on the left, a hole was traced through which the shunt was inserted, the distal end of which was visualized in the lumen of the ventricular system (posterior horn of the left ventricle).

Over the next 3 days, the patient developed seizures, remained lethargic and continued to have headaches. A second head CT showed a correct shunt position. There was no reliable CT data on focal brain changes or periventricular edema at the time of the examination. Compared to the previous CT scan, a slight enlargement (within 1-2mm) of the lateral ventricles was noted.

Since conservative treatment had no positive effect, it was decided to transfer the patient to a more specialized center for pediatric neurosurgery at "Saint Nicholas Hospital" of TMA No. 1 in Lviv. After transfer and examination, complaints were noted of recurrent convulsions in the form of fixation of the gaze and tonus of the upper and lower extremities for up to 5 minutes, headache with head tossing, photophobia, psychomotor agitation and confusion, muscle weakness, convergent strabismus, double vision, dysphagia and abdominal pain. The psycho-emotional state was hyperexcitable, mental development was in line with age. Eye movements were limited without signs of nystagmus. Active movements of the extremities were preserved, but the strength and tone of the muscles were reduced on both sides. Tendon reflexes were not evoked bilaterally, but foot reflexes bilaterally and abdominal reflexes were present. There were also positive meningeal symptoms, especially Kernig's symptom. The patient did not perform coordination tests, sensitivity was preserved and pelvic function was not impaired. He was treated with omeprazole and drotaverine for abdominal pain, phenobarbital and acetazolamide for seizures.

Video-EEG monitoring was started because of the seizures. In the first hours, a pattern of diffuse encephalopathy was recorded, with a renewed attack of tonic convulsions lasting up to 3 minutes, which occurred while falling asleep. In the postictal period increased disorientation, echolalia and lethargy were noticed. Encephalitis with acute symptomatic seizures was suspected, and long-term EEG monitoring was recommended because of the high risk of subclinical seizures.

Long-term EEG monitoring revealed a pathological record in a state of impaired consciousness, as well as during sleep and

wakefulness, with an episode of generalized tonic seizures and bilateral synchronous frontal-dominant fast and slow waves. There was also a diffuse slowing of background activity according to age, with alternating patterns of frontal-dominant generalized delta waves and frontal-dominant rhythmic delta activity. There was an intermittent polymorphic slowing of activity over the frontal areas and the absence of a clearly differentiated posterior dominant rhythm. Sleep signs differentiation was also disturbed.

Because of a suspected viral etiology an antiviral therapy with acyclovir was started. But as no viral cause was found, including CMV, EBV, herpes virus type 1-2, herpes virus type 6, acyclovir was discontinued. The patient was given an infusion of a 5% glucose solution with 25% magnesium sulphate and Vitamin C 5%. Paracetamol and metamizole were prescribed symptomatically. He was also given mannitol and furosemide.

In the next 2 days the patient underwent an MRI of the brain, which showed a post-ventriculoperitoneal shunt, with the distal end of the shunt at the level of the dorsal parts of the left lateral ventricular body. The ventricular system was not dilated, and the lateral ventricles were slightly asymmetrical. The subarachnoid spaces were not dilated. There was no evidence of cortical dysplasia or hydrocephalus.

The patient was also consulted by a gastroenterologist due to recurrent abdominal pain not related to food intake. Moderate hydroperitoneum and fine particulate content of the bladder were noted on abdominal ultrasound. The ECG showed sinus tachycardia, signs of right atrial overload and signs of incomplete right bundle branch block. The echocardiogram of the heart showed no signs of recoarctation or hypertrophy of the left ventricular myocardium. The aortic valve showed no signs of dysfunction.

Electroneuromyography showed a decrease in the speed of conduction of an electrical impulse along the motor fibers of the peripheral nerves, which was 80% of the norm for the right tibial nerve, 84% of the norm for the left tibial nerve, 62% of the norm for the right peroneal nerve and 84% of the norm for the left peroneal nerve. The amplitude of all M responses was slightly reduced. The lesions of the peripheral nerves of the lower extremities were of the polyneuritic type, with a predominance of myelinopathy.

Vitamin B1 and acetyl carnitine were added to the therapy. The patient was put on a protein-free diet-Anamix infant formula. After the prescribed treatment, the patient's condition improved and maple syrup disease was suspected. A blood test for organic amino acids was performed, which was positive for the amino acids leucine, valine and isoleucine and therefore confirmed the diagnosis. The blood tests showed no other changes.

As a result of the therapy, the seizures and headaches disappeared, the volume of active limb movements was restored, the child walked independently, his consciousness was clear, and strabismus and double vision decreased. The patient was discharged with recommendations to follow up with a geneticist and a neurologist, to continue a protein-free diet, and to take vitamin B1 and acetyl carnitine.

Conclusion

The diagnosis of MSUD can be challenging for several reasons. Non-classical variants, particularly the intermittent form, may present with normal psychomotor development and normal levels of BCKD enzyme activity over a prolonged period. The manifestation of clinical symptoms may occur at any age, and laboratory tests may be normal during asymptomatic intervals. MSUD should be considered in the differential diagnosis when a child presents with ketoacidosis, seizures, lethargy, or other neurological symptoms. In the case described, the absence of the characteristic maple syrup odor, the patient's age (7 years), and a history of intracranial hydrocephalus led to other diagnostic options and thus delayed appropriate treatment.

The lack of expanded neonatal screening for MSUD in Ukraine until August 2022 was another complicating factor in the timely diagnosis of MSUD. As the patient was born in 2017, no screening was performed at birth.

It is essential to ensure early identification and prompt initiation of therapy, as the most favorable outcomes are observed in patients treated before or immediately after symptom onset. Initial management involves the implementation of a protein-restricted diet, with the aim of preventing the accumulation of neurotoxic metabolites. A multidisciplinary approach involving pediatricians,

neurologists, and geneticists is needed to provide comprehensive care for individuals with MSUD. A further crucial element is the education of parents and caregivers to ensure adherence to dietary and therapeutic interventions [1-7].

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