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SHORT COMMUNICATION

Turkish case of ethylmalonic encephalopathy misdiagnosed as short chain acyl-CoA dehydrogenase deficiency

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Abstract Ethylmalonic encephalopathy is a very rare autosomal recessively inherited inborn error of metabolism; characterized by encephalopathy, recurrent petechiae without bleeding diathesis, chronic diarrhea, and orthostatic acrocyanosis. Here, we describe a case of ethylmalonic encephalopathy with late onset neurologic symptoms and a confusing family history of two deceased brothers with the wrong suspicion of short chain acyl-CoA dehydrogenase deficiency.

Keywords Ethylmalonic encephalopathy · Acrocyanosis · Short chain acyl-CoA dehydrogenase deficiency · C4 and C5 acylcarnitines

Introduction

Ethylmalonic encephalopathy (EE) is a rare devastating; autosomal recessively inherited neurometabolic disorder characterized by chronic diarrhea, encephalopathy, recurrent petechiae and orthostatic acrocyanosis, which usually leads to death in the first 2 year of life. Approximately 50 reports have been published describing this disease, most involving patients from Mediterranean or Arab origin (Burlina et al. 1991).

The disease was first described by Burlina et al. (1991) and *ETHE1* gene which is responsible for the disease was discovered by Tiranti et al. in 2004. *ETHE1* gene mutations lead to dysfunction of a mitochondrial deoxygenase involved in hydrogen sulfide (H2S) detoxification. H2S toxicity affects brain, endothelium and intestines, but the exact pathogenetic mechanisms are not yet clear (Barth et al. 2010).

Clinical features usually arise before the age of 7 months, and neonatal forms are observed in 25% of the cases. Half of the patients die within the first 2 years of life from metabolic decompensation (Burlina et al. 1991). Persistent lactic acidosis with elevated levels of plasma C4 and C5 acylcarnitines, and ethylmalonic aciduria, isobutyrlglycinuria, and 2-methylbutyrlglycinuria are the common metabolic indicators of EE (Barth et al. 2010; Burlina et al. 1991). Typical cerebral magnetic resonance imaging (MRI) findings are symmetric patchy/necrotic signals in basal ganglia, periventricular white matter, and dentate nuclei along with brain and spinal cord malformations (Nowaczyk et al. 1998).

Although there is not a known specific therapy, it is reported that combined treatment with metronidazole and N-acetylcysteine has been provided some clinical, biochemical and MRI improvements in 5 EE patients (Viscomi et al. 2010). Also, some reports mentioned that EE patients may benefit from riboflavin and coenzyme Q10 treatments (Yoon et al. 2001). Liver transplant has been related with amelioration of developmental parameters and biochemical abnormalities (Dionisi-Vici et al. 2016). In mice with ethylmalonic encephalopathy, liver-targeted adeno-associated virus-mediated *ETHE1* gene transfer is reported to have dramatical improvement in both the clinical status and metabolic abnormalities (Di Meo et al. 2012).

In differential diagnosis of EE, short chain acyl-CoA dehydrogenase deficiency (SCAD) must be in mind, as both of them share the common metabolic abnormalities of elevated levels of plasma C4 acylcarnitine and urine ethylmalonic acid (EMA). However, the clinical course somewhat differs in SCAD, the main symptoms and signs are developmental delay, hypotonia, epilepsy, behavioral disorders, and hypoglycemia. Elevated levels of EMA, C4-C5 acylcarnitines and the other acylglycines in EE indicate a functional deficiency of short chain acyl-CoA (SCAD) and branched acyl-CoA dehydrogenases (Barth et al. 2010; Burlina et al. 1991).

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Case report

A 2-months-old Turkish male infant was admitted to our outpatient clinic with the complaints of restlessness and history of death of two brothers at the ages of 5 and 6 years with the similar symptoms. His parents are first degree cousins and have two healthy daughters. The deceased brothers both had normal growth and development parameters for their age until the end of 10 months. Then, they eventually developed hypotonia, convulsions, and neurologic deterioration. Only one of the affected brothers had a metabolic investigation showing an elevation of C4 acylcarnitine, compatible with short chain Acyl-CoA dehydrogenase deficiency. But, as this result was obtained after the death of the child, a molecular analysis was not available within the index case. Then the parents were evaluated for the carrier status and the mutation analysis of the *ACADS* gene (short chain Acyl-CoA dehydrogenase deficiency) put forward a known heterozygous mutation for the father, although the mother had no mutation for the same gene. The patient was referred to our clinic to rule out short chain Acyl-CoA dehydrogenase deficiency.

On initial physical examination; weight was 4830 g (25–50 percentiles), height was 55,7 cm (25–50 percentiles), and head circumference was 37 cm (3–10 percentiles). Any pathological finding was not observed from the systemic and neurological evaluation. He had head control, gave reaction to the sounds, and smiled to the mother. The routine hematological and biochemical parameters, thyroid function tests, and metabolic profile including amino acids, acylcarnitines, and urine organic acid analysis were normal. Echocardiography and abdominal ultrasonography revealed no abnormality. However, based on the family history, the patient was followed frequently for any clinical or laboratory finding indicating an inborn error of metabolism. The developmental milestones and growth parameters were completely normal until the age of 6 months, when convulsions, persistent crying and recurrent petechiae observed after a mild upper respiratory tract infection (Fig. 1). Coagulation defects and central nervous system infections were excluded. Metabolic re-evaluation of the patient demonstrated an elevation in the levels of C4 and C5 acylcarnitines with persistent lactic acidosis, and significant ethylmalonic aciduria. The cerebral MRI showed symmetrical hyperintense signals on T-2 weighted images in basal ganglia. Fundoscopic examination revealed vessel tortuosity. Ethylmalonic encephalopathy was suspected and molecular analysis confirmed the diagnosis with a known homozygous mutation of p.R163W (c.487C > T) on *ETHE1* gene. Father, mother and two healthy sisters were carriers for the same mutation.

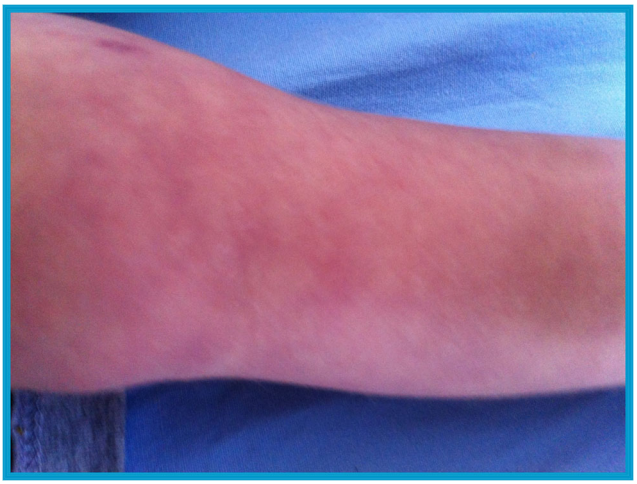

Fig. 1 Acrocyanosis of lower extremity

Discussion

Ethylmalonic encephalopathy is mainly a mono-ethnic, autosomal recessive inborn error of metabolism. Approximately, 85 patients are reported worldwide. Ethylmalonic encephalopathy is almost always fatal and treatment efforts are generally failed.

Neurodevelopmental delay and regression, pyramidal and extrapyramidal signs, episodes of acrocyanosis, recurrent petechiae and chronic diarrhea are the major symptoms and signs which finally results with early death (Burlina et al. 1991). Although recurrent petechiae, acrocyanosis, and chronic diarrhea are the most striking features of ethylmalonic encephalopathy, we neither detected these findings in index case in the beginning of our follow-up nor revealed from the history and the records of two brothers.

It is a confusing disease; its rarity and subtle symptoms frequently leads to delayed diagnosis or laboratory findings may cause misdiagnosis (Dionisi-Vici et al. 2016). Our patient's deceased brother has elevated C4-acylcarnitine and patient's father has heterozygous mutation on *ACADS* gene. This led to misdiagnosis of the elder brother. Our patient had a p.R163W (c.487C > T) mutation on *ETHE1* gene. Tiranti et al. (2004) originally reported the same mutation in 3 patients from unrelated families. Clinical course of these patients were not stated in that report, but several reports postulated that symptoms of EE start between the first weeks and 6 months of life (Mineri et al. 2008). Di Rocco described an atypical EE case with the same mutation, who differently had connective tissue disorders; vascular fragility, articular hyperlaxity and delayed motor milestones with normal cognitive development (Di Rocco et al. 2006). Papetti et al. (2015) reported an infant with early onset West syndrome due to a novel *ETHE1* mutation, she also presented acrocyanosis and petechiae later, similar to our case.

The clinical picture of EE may differ even in monochorionic twins, so it is postulated that there is not a clear phenotype-genotype correlation (Pigeon et al. 2009). Age of death was between 8 months and 3 years (Mineri et al. 2008; Di Rocco et al. 2006). The oldest patient in the literature was 13 years old, who had a compound heterozygous mutation like the other milder EE cases (Mineri et al. 2008; Pigeon et al. 2009).

Also, cerebral MRI findings including frontotemporal atrophy, increased densities in the caudate nuclei, putamina, and posterior fossa are not pathognomonic (Nowaczyk et al. 1998). Symmetrical hyperintense signals on T-2 weighted images in basal ganglia were defined in the cerebral MRI of our patient.

Differential diagnosis of ethylmalonic aciduria includes glutaric aciduria type 2/multiple acyl-CoA deficiency (GA2/MAD), SCAD, branched-chain acyl-CoA dehydrogenase deficiency and Jamaican vomiting sickness. Also, psychomotor retardation, cerebral MRI findings, and lactic acidosis suggest Leigh syndrome and some other mitochondrial respiratory chain deficiencies. Acylcarnitine analysis is required in order to demonstrate the elevation of C4 and C5 acylcarnitines for exact diagnosis.

We report this case, as ethylmalonic encephalopathy is a very rare and a severe inherited metabolic disease, and the patient had a confusing history mimicking a short chain Acyl-CoA dehydrogenase deficiency with laboratory and genetic findings of the family. Another interesting point of this case is the carrier status of the father for both short chain acyl-CoA dehydrogenase deficiency (SCAD) and ethylmalonic encephalopathy. Two different and rare metabolic diseases that cause the elevated levels of C4 acylcarnitine affected this family and easily led to misdiagnosis. High rates of consanguineous marriages, complex and inadequately known genetic background in Turkey may explain this extraordinary genetic status of the family. This case also put forward the importance of the suspicion of two separate inherited metabolic diseases for a valid prenatal diagnosis.

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Compliance with ethical standards

Human and animal rights Because the patient is a minor, informed consent from the parents are taken. Also, ethical approval was taken on 07.07.2017. The ethical committee members were Selim Kadıoğlu, Davut Alptekin, Dinçer Yıldızdaş, Mehmet Kanadaşı, Gülşah Şeydaoğlu and Murat Gündüz.

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

Informed consent Informed consent was obtained from the patient's parents.

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