Ethylmalonic encephalopathy

Another patient from Kuwait

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Ethylmalonic encephalopathy (EE), also known as ethylmalonic encephalopathy, petechiae, and ethylmalonic aciduria (EPEMA) syndrome, is a rare autosomal recessive disorder of unknown underlying metabolic defect (OMIM #602473). The disease was shown to be due to a mutation in the ETHE1 gene, located at chromosome 19q13.1 Typically patients present in infancy with central hypotonia, pyramidal, and extrapyramidal signs, delayed psychomotor development, chronic mucoid diarrhea, orthostatic acrocyanosis, petechiae, and neuroimaging changes. Biochemically the disease is characterized by lactic acidemia, elevated concentration of plasma C4 and C5 acylcarnitine species, reduced activity of cytochrome c oxidase in skeletal muscles and markedly increased excretion of ethylmalonic acid, and to a lesser extent methylsuccinic acid in the urine. Ethylmalonic aciduria is also seen in short-chain Acyl-CoA dehydrogenase deficiency (SCAD), glutaric acidemia type 2, and Jamaican vomiting sickness. Nearly 30 patients, most of Arabic or Mediterranean origin, have been previously reported. Two of them were from Kuwait. Although rare, it is still thought to be underdiagnosed or misdiagnosed; the ethylmalonic aciduria being attributed to other reasons. We add one more patient with the typical features of EE and ETHE1 gene mutation to the list of previously reported patients, to alert our colleagues to the presence of such a
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rare disease in our community. In addition, we stress the importance of screening families with an index patient, for the abnormal gene especially in a community with high consanguineous marriage rates.6

Case Report. This girl was born at term to double first-cousin parents after an uneventful pregnancy and delivery (Figure 1). Birth weight was 2.6 Kg. Her 2 elder brothers looked healthy. She was first seen at the age of 4 months for chronic mucoid smelly diarrhea since birth. She was fed infant milk formula since birth. She did not appear to be interested in her surroundings with severe central hypotonia, brisk deep tendon reflexes, and sustained clonus. Her weight and length were 4.7 kg and 57 cm (both just below the 5th percentile) while her head circumference was 39 cm (below the 3rd percentile). She was admitted to the hospital at the age of 6 months with 2 weeks history of recurrent myoclonic seizures and upper respiratory symptoms. She was observed to be apathetic and to have petechiae at both upper and lower limbs, forehead, and orthostatic acrocyanosis. Optic discs appeared pale, while visual evoked potentials revealed low amplitude and delayed latency bilaterally. Initial blood gases were unremarkable; while serum lactate was borderline high at 2.26 mmol/L (normal 0.5-2.2) that rose a few days later to 3.55 mmol/L. Serum pyruvate level was 25 umol/L (normal 30-80). The acylcarnitine profile of blood spots showed moderately elevated butyryl carnitine (C4-carnitine) at 1.65 uM (normal ≤0.1). A further examination of urine by MS/MS indicated a very high concentration of C4-carnitine at 15 uM (normal ≤0.3). Examination of urine by GC/MS indicated the presence of moderately high ethylmalonic acid. Normal investigations included thyroid, renal, liver and coagulation profiles, complete blood count, serum creatine kinase, and blood amino acids level. Cerebral CT scan revealed the presence of hypodense lesions in the area of caudate nucleus. Cerebral MRI at the age of 7 months showed widened subarachnoid space, increased signal intensity in the area of basal ganglia (caudate nucleus), left thalamus and white matter on T2 images (Figure 2). She did not show significant improvement on phenobarbitone and pyridoxine so clonazepam was added to her regimen on her sixth day of admission with partial control of her fits. She developed apnea on her tenth day and needed mechanical ventilation for 5 days. Her state of consciousness improved gradually and she was able to suck from a bottle and was discharged after 4 weeks. Screening the ETHE1 gene revealed that the patient had a homozygous deletion of exon 4, while her parents were heterozygous for the same deletion and the brothers were homozygous wild-type. Seizures were poorly controlled, and she had repeated chest infection. At the age of 14 months, she developed extensive bronchopneumonia and died in respiratory failure.

Discussion. The ETHE1 gene encodes a protein product that is targeted to the mitochondrial matrix after energy-dependent cleavage of a short leader peptide.1 Among 29 unrelated patients from different parts of the world, 22 types of mutations were reported.2 Three patients had homozygous deletion of exon 4 as in our patient.2 Their origin was not reported, but it was the same type of mutation found in 1 of 2 patients, for whom the test was carried out, from Kuwait.3 More patients have been recently reported with nearly a total of 30 different types of gene mutations identified.1,2,5,9 However, the clinical features observed are homogenous in the vast majority of patients.2 In addition, there is no obvious correlation between the clinical features including age of onset, severity of symptoms, time of progression, and the position or type of mutation.2

Figure 1 - The family pedigree. The filled symbol indicates our deceased patient and the numbers inside the symbols indicate the number of brothers and sisters.

Figure 2 - Brain MRI of the patient at the age of 7 months, axial T2 weighted image showing increased signal intensity in the caudate nucleus (thick arrow), left thalamus (thin arrow) and white matter.
Ethylmalonic encephalopathy is characterized by an unusual combination of biochemical findings including lactic acidosis, elevated concentration of C4 and C5 plasma acylcarnitine species, markedly elevated urinary concentration of ethylmalonic acid and C4-6 acylglycines. Of note, lactic acidosis might be intermittent being more observed during intercurrent infections as observed in our patient, also other metabolites may rarely be within normal range between crises. The underlying metabolic defect is unknown. It appears to be due to a mitochondrial disorder, but it is not clear whether it is related to a defect in the metabolism of isoleucine, methionine, or others. It has been shown in animal models (young rats) that ethylmalonic acid inhibits the activity of mitochondrial creatine kinase in the brain but not in the skeletal or cardiac muscles. Considering the importance of creatine kinase for brain energy homeostasis, this might explain the neurological features observed in EE patients.

Neuroimaging studies reveal fairly constant findings with involvement of the basal ganglia, thalami, and white matter changes. These reflect necrotic lesions in the involved structures, which are thought to be due to the accumulation of metabolites or to the vascular changes commonly observed in this disorder. Microscopically, at autopsy, there was marked capillary proliferation in the substantia nigra, periaqueductal area, putamen, caudate, and medial thalamus with increased number and size of the endothelial cells in one patient.

Different forms of treatment were tried including vitamins B1, B2, B6, B12, C, E, Biotin, coenzyme Q10, low protein diet, and carnitine, but none of them showed a consistent effect or long term benefit. The course of disease is a progressive one and most patients die in the first few years of life. Most patients die because of respiratory failure during intercurrent infection, apnea, metabolic decompensation or suddenly unexpectedly.

Our patient was no exception. Consanguineous marriage in the Arab community is high. Identification of the type of gene mutation in a family with an index patient might help prenatal diagnosis, which has not been reported yet in this devastating disease.

In summary EE, though rare, is more commonly reported in patients of Arabic or Mediterranean descent. It should be considered in patients with lactic acidosis and consistent clinical picture. Identification of the gene mutation will not only confirm the diagnosis, but may also help in the prenatal diagnosis of such a severe progressive disease.

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References