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SHORT COMMUNICATION

Ethylmalonic encephalopathy associated with crescentic glomerulonephritis

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Abstract Ethylmalonic encephalopathy (EE) is a rare autosomal recessive disorder caused by mutations in the *ETHE1* gene and characterized by chronic diarrhea, encephalopathy, relapsing petechiae and acrocyanosis. Nephrotic syndrome has been described in an infant with EE but the renal histology findings were not described in previous reports. We report a Palestinian girl with EE who presented with chronic diarrhea, encephalopathy, petechial rash and acrocyanosis. Subsequently, she developed progressive deterioration of renal function caused by rapidly progressive glomerulonephritis resulting in death within few days. This is, to our knowledge, the first reported occurrence of rapidly progressive glomerulonephritis in a child with ethylmalonic encephalopathy. Its presence is a serious complication associated with poor prognosis and may be explained by the diffuse vascular damage

Keywords Encephalopathy · Nephrotic syndrome · Glomerulonephritis · Chronic diarrhea · Petechial rash · Acrocyanosis · Hypoalbuminemia

Abbreviations

EE	Ethylmalonic encephalopathy
EMA	Ethylmalonic acid
H2S	Hydrogen sulfide
CsGN	Crescentic glomerulonephritis
NAC	N-acetylcysteine

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Introduction

Ethylmalonic encephalopathy (EE) is clinically characterized by the early onset of neurological deterioration, chronic diarrhea, recurrent petechiae and orthostatic acrocyanosis leading to death in the first years of life (Giordano et al. 2011). The main consequence of *ETHE1* loss is the accumulation of hydrogen sulfide (H2S) which, in addition to many effects, blocks short-chain fatty acids causing accumulation of ethylmalonic acid (EMA) and also has vasoactive and vasotoxic effects which explains the vascular lesions in the skin and possibly other organs (Giordano et al. 2011). Symmetrical necrotic lesions in the deep gray matter structures are the main neuropathological features of the disease (Tiranti et al. 2004). Clinical heterogeneity has been described in EE even in monochorionic twins (Pigeon et al. 2009). Biochemically it is characterized by lactic acidemia, elevated concentrations of C4 and C5 plasma acylcarnitine species, markedly elevated urinary excretion of ethylmalonic acid (EMA) and elevated methylsuccinic acid and acylglycines, notably isobutyrylglycine and 2-methylbutyrylglycine (Giordano et al. 2011; Tiranti et al. 2004). Combined treatment with oral metronidazole, N-acetylcysteine and coenzyme Q10 resulted in marked neurological improvement, disappearance of diarrhea, petechial showers and acrocyanosis (Viscomi et al. 2010). We report a case of EE who developed nephrotic-range proteinuria progressing to end-stage renal failure and death resulting from rapidly progressive crescentic glomerulonephritis.

Case report

An 8-month old girl was born to consanguineous Palestinian parents (i.e., first cousins) at term by normal vaginal delivery after uneventful pregnancy. At age 1 month, she developed the first episode of watery diarrhea with mucous and

streaks of blood. The diarrhea persisted despite trying various dietary formulas including soy-based, protein hydrolysate and lactose-free formulas.

At age 6 months, she required hospitalization due to intractable diarrhea, severe dehydration and metabolic acidosis. She had diaper dermatitis that was not responsive to various combinations of local treatments. She had poor weight gain and delay in acquiring developmental milestones. Also she had waxing and waning petechiae and ecchymoses mainly at pressure sites.

She was re-hospitalized at age 8 months due to chronic diarrhea, poor weight gain and pitting edema of the face and lower extremities. There was a positive family history of death (two cousins), one had metabolic acidosis and the other had, in addition, renal impairment (Fig. 1). Her growth parameters were as follows: Weight 5,160 g (−1.75 SD), length 64 cm (−1.5 SD) and occipitofrontal circumference 40 cm (−2.5 SD). Physical examination showed facial and lower extremities edema, petechiae, acrocyanosis and severe diaper dermatitis. Neurologically, she had axial hypotonia, spasticity of upper and lower extremities, exaggerated deep tendon reflexes and clonus. Investigations included the following: Initial serum creatinine 0.38 mg/dl (normal 0.2–0.4 mg/dl), blood urea nitrogen 26 mg/dl (normal 5–18 mg/dl), total proteins 3.2 g/dl (normal 5.5–7.5 g/dl), albumin 1.9 g/dl (normal 3.4–4.2 g/dl), ammonia 29 μmol/L (normal 21–50 μmol/L), lactic acid 2.5 mmol/L (normal 1.1–2.4 mmol/L). Immunoglobulin G 180 mg/dl (normal 217–904 mg/dl), immunoglobulin A 5.7 mg/dl(11–90 mg/dl) and immunoglobulin M 223 mg/dl (normal 34–126 mg/dl). Serum complement 3 (C3) was 80 mg/dl (normal 75–166 mg/dl) but unfortunately serum complement 4 (C4), anti-neutrophil cytoplasmic antibody (ANCA) and other immunological screening tests were not performed. She also had normal liver enzymes, electrolytes, calcium, phosphorous and coagulation tests. Stool analysis was normal with negative tests for fat and reducing substances. Sweat chloride test and plasma lipids were also normal.

The 24-h urinary protein excretion was 160 mg/m²/h and creatinine clearance was 72 ml/min per 1.73 m². Percutaneous renal biopsy showed diffuse glomerulonephritis with crescents (Fig. 2).

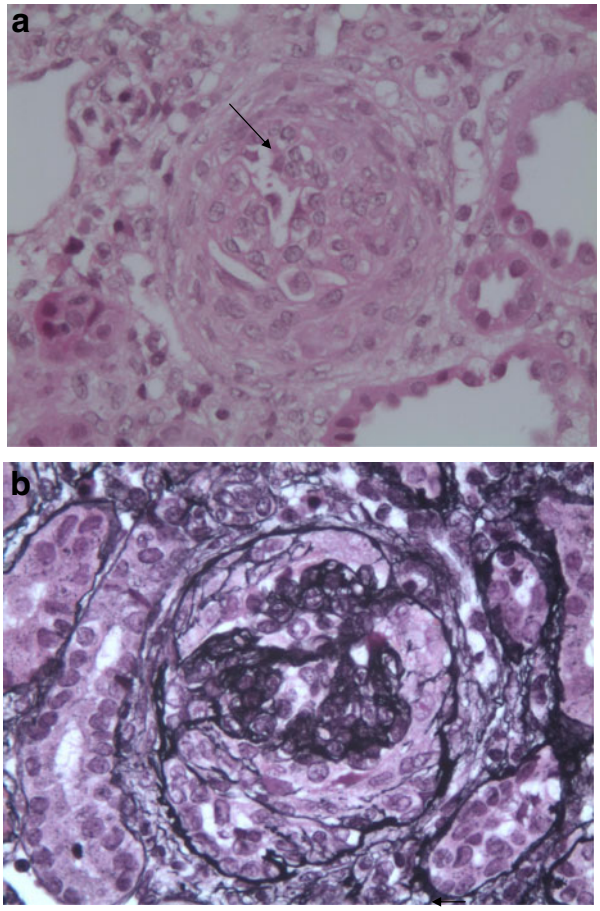

Fig. 2 Photomicrographs of the renal biopsy **a** Light microscopy (hematoxylin and eosin stain; original magnification ×400) Glomerulonephritis, crescentic: The normal renal architecture is lost, the glomerulus (*arrow*) is solid and hypercellular. **b** Light microscopy (*methenamine-silver stain*; *original magnification ×400*) *epithelial crescents*; *the proliferating cells are not accompanied by fibrous or collagen tissue. The stain emphasizes the compressed tuft*

Urine organic acids showed increased lactic, EMA, methylsuccinic, adipic and suberic acids and acylglycines (butyryl-,

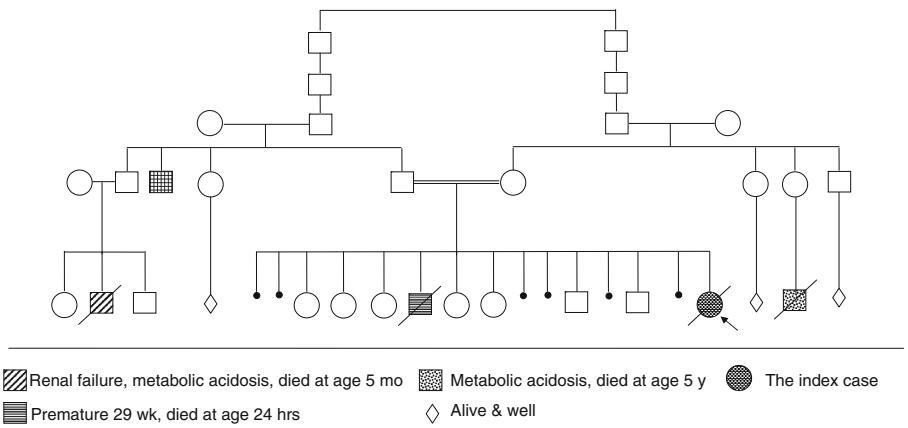

Fig. 1 Family pedigree showing two cousins who died with metabolic acidosis, one also had renal failure

isobutyryl-, 2-methylbutyryl and hexanoyl-glycines). Genetic analysis for the ETHE1 gene extracted from the patient blood confirmed that she was homozygous for the mutation at the splicing site 505+1 G>T.

Combination therapy with metronidazole, N-acetylcysteine and Co-enzyme Q10 resulted in disappearance of the diarrhea but there was no effect on the acrocyanosis and petechial rash. The patient showed progressive deterioration of renal function in form of progressive oliguria, edema, rising plasma creatinine and severe metabolic acidosis. Subsequently, she developed persistent hypotension unresponsive to intravenous fluids, dopamine and dobutamine infusin and intravenous diuretic therapy with metolazone and furosemide and ultimately she died 9 days after hospitalization.

Discussion

EE is a monogenic disorder exclusively caused by mutations in *ETHE1* gene and the clinical phenotype is quite homogeneous and characterized by psychomotor regression and hypotonia, later evolving into spastic tetraparesis, dystonia and eventually global neurologic failure (Tiranti et al. 2006). The encephalopathy is typically accompanied by chronic diarrhea and widespread lesions of the small blood vessels causing showers of petechiae, easy bruising and orthostatic acrocyanosis (Tiranti et al. 2006). This phenotype was shown to be the consequences of loss of ETHE1 gene which resulted in impaired catabolism of inorganic sulfar leading to accumulation of hydrogen sulfide in key tissues which has toxic effects that account for ethylmalonic acidurias, microangiopathy, acrocyanosis and chronic diarrhea (Tiranti et al. 2009). However, there were rare case reports of atypical presentation or with initially typical phenotype but later in the course of the disease developed additional features expanding the spectrum of the disease manifestations. Di Rocco et al. described a child who presented with vascular fragility, articular hyperlaxity, delayed motor development and normal cognitive development. His urine organic acids, plasma amino acids and plasma lactic acid levels were normal in a single random collection leading to erroneous suspicion of Ehlers-Danlos syndrome (Di Rocco et al. 2006). Hack et al. described a 12-month old child who developed, in the course of the disease, a drug-resistant nephrotic syndrome which led to anasarca, pulmonary edema and eventually cardiac and respiratory failure (Hack et al. 2008) resembling the course of the disease in our patient. However, histopathology examination of renal tissue samples was not performed. Campeau et al. reported monochorionic twins who presented a pyramidal syndrome which has been described for most other patients but both of them never displayed petechiae, orthostatic acrocyanosis or chronic diarrhea (Pigeon et al. 2009). One Italian and four Palestinian patients received combination therapy with oral metronidazole, N-acetylcysteine and Co-enzyme Q10. They showed marked neurological improvement, disappearance of diarrhea, petechial showers and acrocyanosis (Viscomi et al. 2010).

Our patient presented with the typical phenotype described in the Introduction. However, a distinctive feature was the presence of predominat renal manifestations as edema, nephrotic-range proteinuria and edema. Despite the combination therapy with NAC, metronidazole and Co-enzyme Q10, the clinical course was characterized by rapid deterioration of renal function, anuria and end-stage renal disease. Findings on renal biopsy were consistent with crescentic glomerulonephritis. This is the first report of histologically-proven CrGN developing during the course of EE and it explains the rapidly progressive course associated with rapid decrease in glomerular filtration rate over a short period. Since crescent formation appears to represent a nonspecific response to severe injury to the glomerular capillary wall and may be associated with various systemic diseases (Miller et al. 1984; Dewan et al. 2008), we hypothesize that the CsGN in our patient is the result of severe vasculitis causing damage of the renal vessels as part of systemic vasculitis. Our finding is in keeping with the hypothesis that probably the accumulation of hydrogen sulfide resulting from ETHE1deficiency is responsible for the diffuse vascular damage of target critical organs (Giordano et al. 2011) and the renal vessels are not an exception. However detailed immunological screening tests were not done to exclude a possible association between EE and immune- mediated glomerulonephritis

In conclusion, we think that severe renal disease represents one end of the spectrum of EE. Milder forms of renal involvement may be under recognized and should be investigated further in future studies. Nephropathy may be explained by the same pathogenic mechanisms underlying the involvement of skin, brain and colonic mucosa.

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