Brain & Development 38 (2016) 768–771

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case Report

Diffusion restriction in ethylmalonic encephalopathy – An imaging evidence of the pathophysiology of the disease

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Received 5 January 2016; received in revised form 24 February 2016; accepted 28 February 2016

Abstract

Ethylmalonic encephalopathy is an inborn error of metabolism characterized by encephalopathy, petechiae chronic diarrhea and acrocyanosis. Imaging findings include patchy signal changes in the basal ganglia, periaqueductal region, subcortical white matter and cerebellum. We describe the novel finding of diffusion restriction in brain lesions, in a proven case of ethylmalonic encephalopathy.

Keywords: Ethylmalonic encephalopathy; Restricted diffusion; Basal ganglia; Middle cerebellar peduncles

Ethylmalonic encephalopathy (EE), is a rare autosomal recessive metabolic disorder caused by a mutation in the ETHE1 gene [1,2]. The disease affects the brain, gastrointestinal tract, and peripheral vessels. Characteristically, affected patients present with central hypotonia, pyramidal and extrapyramidal signs, delayed psychomotor development, chronic diarrhea, orthostatic acrocyanosis and petechiae in early infancy [2]. Since the earliest report, less than forty cases have been reported worldwide. Imaging features that have been described previously include increased T2 signal in the basal ganglia, subcortical white matter, brainstem and cerebellar white matter [3–5]. We herewith report the unusual finding of diffusion restricting lesions in a patient of ethylmalonic encephalopathy.

A 20 month-old girl was admitted with history of developmental delay, petechial rash, loose stools and frequent episodes of upper respiratory tract infections since birth. She was the second offspring, born of healthy parents who were second cousins. She was apparently normal during the postnatal period. Her motor and language milestones were subsequently delayed. She had multiple episodes of respiratory tract infections, which were followed by further regression of the milestones. On examination, the child had a reddish-blue lacy petechial rash all over the body and ecchymotic patches on the face and neck. There was bluish discoloration of the palms and plantar aspect of both the feet, suggestive of acrocyanosis (Fig. 1a and b). The child had partial head control and could sit with sup-

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http://dx.doi.org/10.1016/j.braindev.2016.02.014
0387-7604/

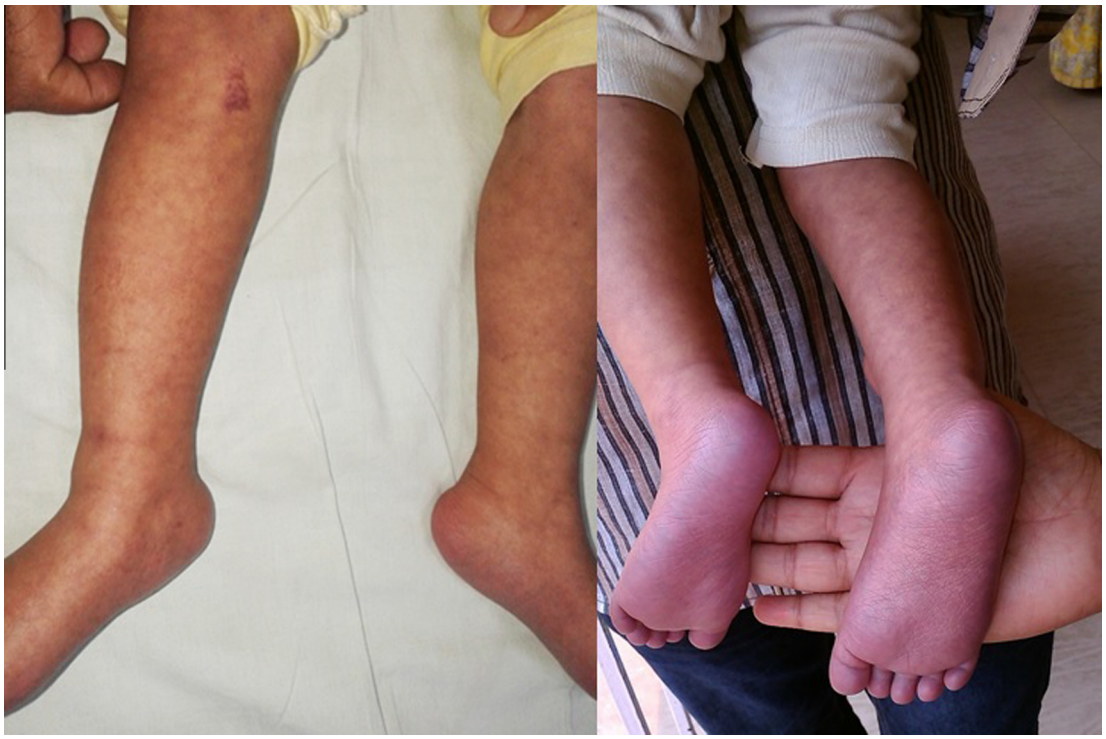

Fig. 1. (a and b) Clinical photograph of the patient revealing the lacy pattern of ecchymotic rash on the lower extremities and acrocyanosis.

port. Tone was increased in all four limbs with paucity of movement in both lower limbs. The deep tendon reflexes were brisk and bilateral plantar reflexes were extensor.

Laboratory investigations revealed a hemoglobin of 11.3 g/dL. The platelet count was 365,000/μl. The plasma ammonia and lactate were elevated at 64 μmol/L and 34.9 mg/dL respectively. Blood urea and serum creatinine were 11 mg/dL and 0.3 mg/dL respectively.

The patient was evaluated with an MRI performed on a 1.5T clinical MRI scanner (Intera, Philips Healthcare, Netherlands). T1WI (TR = 500, TE = 15), T2WI (TR = 4846, TE = 110), FLAIR (TR = 9000, TE = 140, TI = 2800), GRE (TR = 582, TE = 18,) and DWI (TR = 2907, TE = 84, $b = 0$ & 1000) images were obtained. On T2 and FLAIR images, patchy hyperintensities were observed involving the heads of both caudate nuclei and putamina. Similar hyperintensities were also observed in bilateral centrum semiovale, bilateral parieto-occipital white matter, splenium of corpus callosum, bilateral middle cerebellar peduncles (MCP) and cerebellar white matter. The lesions were hypointense on T1WI and did not demonstrate blooming on GRE images. Diffusion weighted images revealed hyperintensities in bilateral MCP's, cerebellar white matter, centrum semiovale and corpus callosum which were hypointense on ADC maps, indicating diffusion restriction (Fig. 2a–d). The basal ganglionic lesions were hyperintense on diffusion weighted images and ADC maps. In view of typical basal ganglionic lesions and characteristics clinical findings the possibility of ethylmalonic encephalopathy was considered. However, diffusion restriction in the brain lesions was unusual.

Blood tandem mass spectrometry (TMS) and urine organic acid estimation was performed to confirm the diagnosis. TMS revealed raised levels of butyrylcarnitine, C4 (1.9 μmol/L, reference range 0.06 – 1.14 μmol/L) and isovaleryl C5 (1.2 μmol/L, reference range 0.03 –0.65 μmol/L). Urine examination by gas chromatography–mass spectrometry revealed 11.22-fold increase in ethylmalonic acid levels and 3.72 and 3.48-fold elevation of isovalerylglycine and isobutyrylglycine respectively. These findings were considered typical of EE.

The patient was started on levocarnitine and Vitamin B1, B6, B12 supplements and put on protein restricted diet. Minimal improvement was observed. Subsequently, the patient was discharged and advised follow-up after 3 months.

EE was first described in 1991 by Burlina et al. [3]. The present case is the first report from India. EE is clinically characterized by the early onset of neurodegeneration, chronic diarrhea, recurrent petechial rash, and orthostatic acrocyanosis, usually leading to death in the first decade of life. EE is caused by mutations in ETHE1, a gene encoding a mitochondrial sulfur dioxygenase. Loss-of-function mutations of ETHE1 gene leads to accumulation of hydrogen sulfide [1]. Increased