Ethyl Malonic Aciduria Encephalopathy with Respiratory Failure and Nephrotic Syndrome Rare Presentation

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ABSTRACT

Ethyl malonic aciduria encephalopathy is a syndrome characterised by relapsing petechiae and progressive neurodegenerative symptoms and signs. The defining metabolic abnormality is the excretion of large amounts of ethyl malonic acid in the urine. EMA encephalopathy has been reported in fewer than 30 cases worldwide, the majority of them being in Europe, Israel and Saudi Arabia. We report a patient with EMA presenting with nephrotic syndrome and respiratory failure.

INTRODUCTION

Ethyl malonic encephalopathy (EE) first described by Burlina ed al [1991] is a syndrome characterised by relapsing petechiae, progressive neurodegenerative symptoms and signs, acrocyanosis and in some cases with chronic diarrhoea. There has been no case report with this syndrome presenting with nephrotic syndrome and respiratory failure.

Marked persistent ethyl malonic and methylsuccinic aciduria with abnormal excretion of C4-C5 (n-butyrl-; isobutyryl -, isovaleryl -, and 2 methyl butyryl -) acylglycines and acylcarnitines are typical biochemical findings. Excretion of adipic acid is not increased in contrast to multiple acylcoenzyme-A dehydrogenase deficiency. Ethyl malonic aciduria is also found in short-chair acyl-coenzyme dehydrogenase deficiency. Symmetric lesions in the basal ganglia (caudate and putamen), periventricular white matter and cerebellar dentate nuclei are detected on MRI (Ozano et al 1994; Burlina et al 1994).

The vascular manifestation of EE are unusual and characteristic features. Acrocyanosis appears to be its mildest manifestation. The development of showers of petechiae, ecchymosis in response to intercurrent illness has lead to investigation and treatment for presumptive meningococcaemia. Biopsy of the skin lesion has shown only haemorrhage.

Further evidence of a bleeding abnormality is microscopic haematuria and haemoperitoneum. Dilated tortuous retinal vessels are seen. Cerebral abnormality is manifest in infancy as hypotonia and delayed development. Neurologic deterioration accelerates following intercurrent infections, illness, and most patients have died in the early years of life. Brain imaging has shown infarcts of basal ganglia.

CLINICAL REPORT AND RESULTS

A 10 months old male infant was admitted to the paediatric intensive care unit with acute respiratory failure and generalised oedema. He was the sixth child of healthy Kuwaiti parents who were first cousins. His four other siblings were all healthy. He was born full term, appropriate for gestational age by spontaneous vaginal delivery and had a normal neonatal period. He appeared to develop normally in the initial few months and at six months evaluation he was noted to have neurodevelopmental delay. At this time he was admitted to a regional hospital for evaluation, investigations, and assessment.

On physical examination, growth was as follows: Weight was 5th percentile, height 10th percentile and head circumference 5th percentile. He had dysmorphic features with depressed nasal bridge, epicanthal folds and posteriorly rotated ears. A characteristic petechial rash was evident on the face and limbs (Fig.1). He had generalised oedema, ascites and pleural effusion. Neurologically he had a Glasgow coma scale of 7/15, generalised hypotonia with increased deep tendon reflexes and bilateral sustained ankle clonus.

INVESTIGATIONS

Haemoglobin 10 gms/L, haematocrit 0.306 units, bicarbonate 17 mmol/L, sodium, potassium and chloride 131 mmol/L, 4.7 mmol/L and 110.8 mmol/L respectively, a normal prothrombin time, partial thromboplastin time, bleeding time and platelet count (248).

His serum lactate was high (7.0), his plasma lactate to pyruvate-ratio was elevated (68.3) (N <25), blood ammonia, and amino acids were normal. His ANA, CANCA Ab, pANCA Ab and Antids-DNA (8A U/ml (NR < 26, AU ml) were normal. Lysosomal enzymes, very long chain fatty acids were normal.

Urine examination showed proteinuria +++, and 24 hour urine protein was >10g/ 24 hours, spot urine protein/creatinine ratio was raised (360 mgmmol), S.albumin 17 g/L, S.Cholesterol was raised.

Urine for organic acids showed markedly raised ethyl malonic acid. Blood spot acylcarnitine showed an elevated concentration of butyrylcarnitine (C4) and

ratio of butylcarnitine to propionylcarnitine, C4/C3 were substantially above normal.

MRI brain revealed disseminated white matter lesions, hypointense on T1W and hyperintense on T2W & PD (Fig.2 & Fig.3). The lesions involve cerebellum, medulla and cerebral white matter (Fig.4). The caudate nuclei are also hyperintense as T2 & PD (Fig.5).

EEG was abnormal with asymmetric background and active focus from left frontotemporal leads.

Blood spot acylcarnitine and urine organic acid analysis for parents and siblings were normal.

The analysis of the ETHE 1gene for the patient revealed the presence of a homozygous deletion of exon (4).

The parents and the healthy sibling showed the presence of exon (4). It has been fully sequenced and it was found to be homozygous normal, thus indicating that the other allele in the index case was deleted.

ETHE I protein analysis was confirmed by Western Blot analysis from skin fibroblast culture, which revealed complete absence of ETHE 1 protein .

Based on the above clinical, biochemical, MRI and urine findings a diagnosis of EMA with nephrotic syndrome was made. Management included initial ventilatory support from which he was successfully weaned off. The nephrotic state was managed with steroids. The response to steroids was noted over a period of four weeks. Dietary regulation included methionine free milk formula9, carnitine Vitamin E and ascorbic acid.

DISCUSSION

This 10 months old male infant is an unusual case of ethyl malonic encephalopathy presenting with nephrotic syndrome and in respiratory failure has evidenced from the typical clinical, biochemical, MRI findings, gene analysis, and urine examination. (1) Malgorzata JM et al reported EMA rises from abnormal isoleucine metabolism The observed high lactate/pyruvate ratio in EMA suggested the possible involvement of the mitochondrial electron transport chain (2) (Garavaglia et al 1994. (3) Hoffman et al reported fatal progressive pancytopenia with ethyl malonic acidurias in which were para crystalline inclusion bodies on electron microscopy findings and reduced activity of cytochrome C oxidase and reductase in muscle. The blood counts in the index case were normal. Progressive neurologic disease and partial deficiency of cytochrome oxidase were reported by Lehnert and (4) Ruitessbeck. (5)Burlina AB et al reported this syndrome with normal fatty acid oxidation in fibroblast. A relationship with this syndrome and the metabolism of sulphur aminoacid has been proposed by (6) Duran et al. We are reporting this case of EMA encephalopathy with the unusual association with nephrotic syndrome and has not been reported hitherto in the literature. It is proposed that the vasculitis of EMA or EMA in the urine can involve the glomerular basement membrane causing protein loss. Electron microscopic study of renal tissue may elucidate this process.

Figure 1

Figure 2

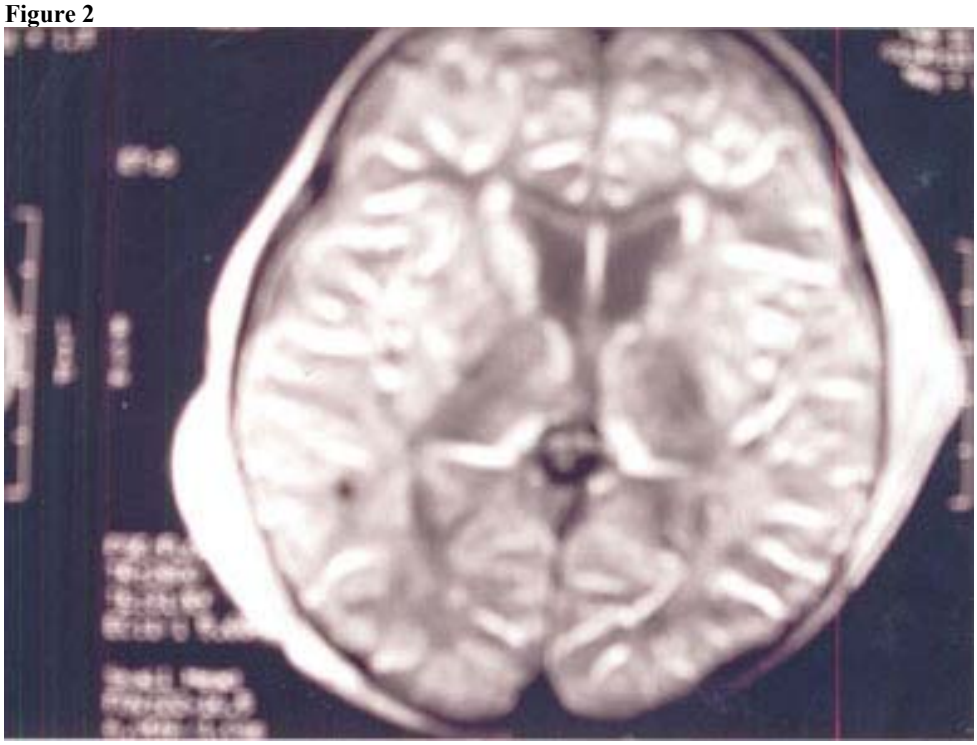
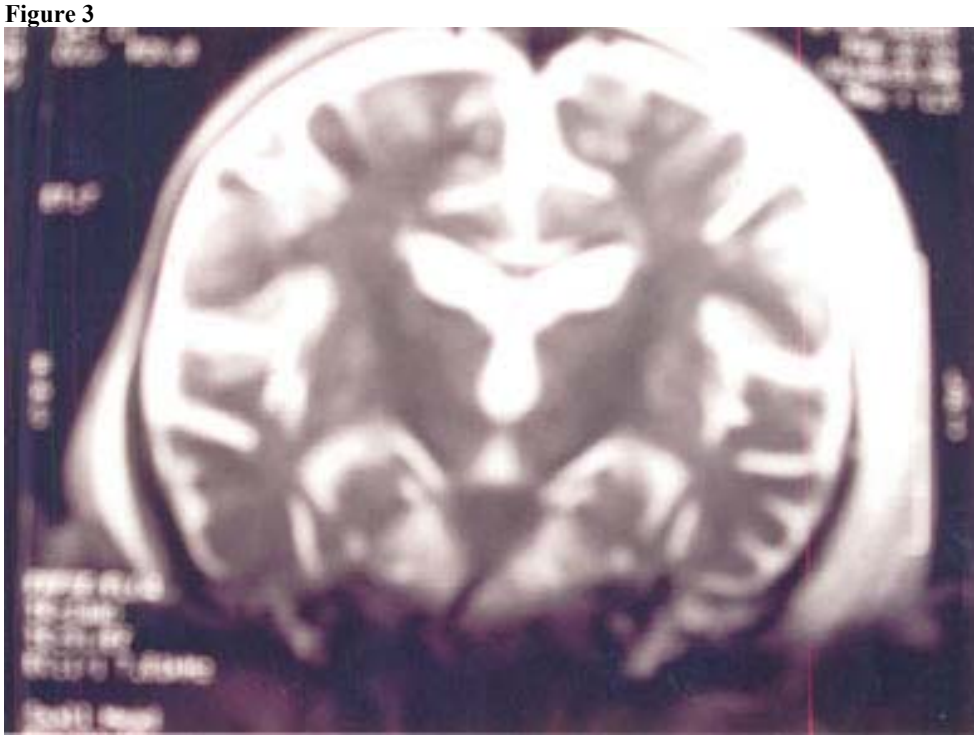


Figure 3



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