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Case report

Mevalonate kinase deficiency masked by cytomegalovirus infection and obscure liver disease

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ABSTRACT

Background: Chronic liver disease with conjugated hyperbilirubinaemia and failure to thrive can have multifactorial aetiologies. Investigations can be complex and difficult especially when obscured by a viral infection affecting liver function.
Methods: A 5 month old male infant was referred for investigation of chronic liver disease and a history of jaundice with multiple febrile episodes. Liver function tests were performed followed by a liver biopsy and microbiological workup for infectious disease. In addition, urine analysis of organic acids was also performed.
Results: There was marked conjugated hyperbilirubinaemia with markedly elevated hepatocellular enzymes and normal ductal enzymes. Proteinuria and near normal renal function suggested early renal impairment. There was also leukocytosis and bicytopenia. An extensive bacteriological investigation including TB workup was negative. CMV infection was confirmed by viral load and antibody reactivity. There was prolonged PT and PTT and high INR.

The liver biopsy showed giant cell transformation of hepatocytes with mild cholestasis, portal and pericellular fibrosis with alpha-1-antitrypsin positive granules in the hepatocyte cytoplasm suggesting alpha-1-antitrypsin deficiency. Urine organic acids revealed significantly elevated mevalonolactone.
Conclusions: We confirmed the genetic diagnosis of mevalonic aciduria caused by MVK deficiency which had been masked by liver disease and the possible misdiagnosis of alpha-1-antitrypsin deficiency.

Genes

MVK
Mevalonate kinase

1. Introduction

Hepatic and hepatobiliary disease is a common cause of morbidity in infants and may arise from a number of causes including viral infection, inherited metabolic disorders, drugs, autoimmune hepatitis or may be of unknown aetiology. Chronic liver disease in a child requires complete clinical evaluation and biochemical investigation as well as biopsy of the liver to enable a histological diagnosis to be made. Liver tissue can also be used for enzyme analysis to determine the presence of an inborn error or a storage disease. Histological analysis can usually facilitate a diagnosis as well as determine the severity of the disease and exclude other causes such as Wilson's disease. There are a multitude of causes of chronic liver disease in children. Biliary atresia is the most common cause in infants and this is followed by inherited metabolic disease, genetic abnormalities and other biliary tract problems. In older children, autoimmune hepatitis; non-alcoholic fatty liver disease, chronic viral hepatitis and inherited metabolic diseases are the leading causes.

Abbreviations: PCR, Polymerase chain reaction; RR, reference interval; ALT, Alanine transaminase; AST, Aspartate transaminase; GGT, Gamma glutamyl transferase; ALP, Alkaline phosphatase; CMV, cytomegalovirus; CRP, C-reactive protein; PT, Prothrombin time; PTT, Partial thromboplastin time; INR, International normalised ratio; PAS, periodic acid Schiff; MVK, Mevalonate kinase; IL1, Interleukin 1

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2. Materials and methods

2.1. Case description

A 5 month old male toddler, from a nonconsanguineous marriage, was referred for investigation of chronic liver disease of unclear aetiology. Following delivery by caesarean section and normal birth weight (3.54 kg), the history was of jaundice with multiple febrile episodes since birth. Neonatal phototherapy had no effect on the jaundice. He subsequently developed a distended abdomen and bleeding diathesis. The mother had been diagnosed with HIV during antenatal screening and received antiretroviral treatment. HIV PCR was negative but positive for cytomegalovirus infection with a remarkable viral load of 1600 copies/ml.

On examination, he was significantly below the third percentile for weight, height and head circumference. He was pyrexial with profound jaundice and had petechiae on the torso and back. There were no dysmorphic features but he had significant neurodevelopmental delay as well as prominent head lag and spastic limbs. There was significant hepatosplenomegaly, ascites and caput medusae.

3. Results

The liver function tests showed marked conjugated hyperbilirubinemia with markedly elevated hepatocellular enzymes and normal ductal enzymes: Total bilirubin 27 mg/dL [456 μmol/L; reference interval (RI) 0.4–1.2 mg/dL (6–20 μmol/L)]; direct bilirubin 13.86 mg/dL [237 umol/L; RI 0.1–0.3 mg/dL (1.7–5.1 μmol/L]; ALT 155 U/L (RI 2–25 U/L); AST 361 (RI 0–49 U/L); GGT 114 U/L (RI 15–132); ALP 118 U/L (RI 82–383 U/L). The spot proteinuria and near normal renal function suggested early renal impairment with probable damage to the glomerular basement membrane; urea 3.6 mg/dL [1.3 mmol/L; RI 0.39–1.78 mg/dL (1.1–5 mmol/L);] Creatinine 0.21 mg/dL [19 umol/L; RI 0.08–0.19 mg/dL(7–17 umol/L)]. Lipid profile showed significantly low values: Total Cholesterol 82 mg/dL (2.13 mmol/L) [RI 1.71–5.91 mmol/L] while CRP was persistently elevated. Leukocytosis and remarkable bicytopenia were revealed by the complete blood count (haemoglobin 7.3 g/L [RI 10.7-13 g/L] and platelets 49 × 10^9L [RI 180-440 × 10^9L]; White cell count 16.99 × 10^9/L. [RI 6–10 × 10^9/L]). An extensive microbiological investigation including that for tuberculosis was negative. Bleeding diathesis was confirmed by prolonged PT, (17.4 s; RI, 11.4 -16 s)and PTT (45.9 s; RI 23.4–31.8 s) and high INR (1.47).

The liver biopsy histology showed giant cell transformation of hepatocytes with mild cholestasis, portal and peri-cellular fibrosis (Fig. 1) with the striking presence of alpha-1-antitrypsin positive granules in the hepatocyte cytoplasm. However, alpha-1-antitrypsin deficiency was excluded by genetic testing.

The overall picture was of recurrent febrile episodes and conjugated hyperbilirubinemia, features of chronic liver disease and portal hypertension, complicated by prominent neurodevelopmental delay. This clinical presentation was initially attributed to congenital CMV infection diagnosed by detection of IgG and IgM antibodies as well as a remarkably elevated viral load. CMV infection is the commonest viral intrauterine infection associated with significant morbidity particularly coming in immunocompromised mothers. Infected offspring may present with low birth weight, petechial rash, hepatosplenomegaly with jaundice as well as microcephaly and neurodevelopmental delay which were reported in this patient [1]. He was subsequently treated with a two week course of intravenous Ganciclovir and the viral load became undetectable. However, astonishingly after completion of treatment completion and resultant viral suppression, there was no improvement but rather deterioration.

3.1. Alpha-1-antitrypsin deficiency

The liver biopsy findings suggested the diagnosis of an atypical alpha-1-antitrypsin deficiency without pulmonary manifestations. The presence of periodic acid-Schiff (PAS) positive alpha-1-antitrypsin granules is nonspecific and has also been noted in other causes of liver diseases such as haemochromatosis, alcoholic liver disease and in rare cases of normal liver function [2]. In this instance, it may have arisen as a result of CMV infection or mevalonic aciduria. Although serum alpha-1-anti-trypsin level was not measured in this patient, the condition was excluded through genotype analysis. It was at this point that an inborn error of metabolism was sought as possible culprit for the non-improving clinical manifestations.

3.2. Mevalonic aciduria

The case was eventually solved by analysis of urine organic acids which revealed significantly elevated mevalonolactone on two occasions (Fig. 2). The diagnosis of mevalonic aciduria was confirmed by *MVK* gene sequencing which detected compound heterozygous missense mutations *i.e. Tyr116His and Arg277Cys.* The significantly elevated mevalonolactone detected with urine organic acid analysis on the gas chromatography mass spectrometry is the dehydrated form of mevalonic acid, an essential intermediate in the common step in the cholesterol and non-sterol isoprenoid biosynthesis.

4. Discussion

Mevalonate kinase deficiency is a metabolic autoinflammatory disorder that is recessively inherited and presents with a spectrum of manifestations and with a continuum of well-defined clinical phenotypes including mevalonic aciduria; hyperimmunoglobulinaemia D and periodic fever syndrome [3]. Patients present with recurrent attacks of severe inflammation with fever, lymphadenopathy, abdominal pain, arthralgia and mucocutaneous lesions. With the more severe phenotype of mevalonic aciduria, there may be dysmorphic features, perinatal growth retardation and neurological and ocular involvement [3–5].

Mevalonate kinase is one of the tightly regulated enzymes in the common mevalonate pathway of cholesterol biosynthesis in the hepatocyte cytoplasm. The pathway begins with formation of 3-hydroxy-3-methylglutaryl-Co (HMG-CoA) from three molecules of acetyl CoA by condensation reactions catalysed by acetoacetyl-CoA thiolase followed by HMG-CoA synthase. HMG-CoA is further reduced to mevalonate acid by HMG-CoA reductase, an important rate limiting step. The next step is catalysed by mevalonate kinase which converts mevalonate acid to mevalonate-5-phosphate; this further undergoes phosphorylation by phosphomevalonate kinase to produce mevalonate-5-pyrophosphate. The final step of the mevalonate pathway is a decarboxylation which yields isopentenyl-5-pyrophosphate; this is an essential product for the subsequent biochemical steps resulting in the formation of cholesterol and non-sterol isoprenoids [6].

It is the lack of isoprenoids that have the greatest impact in the pathophysiology of this inflammatory disorder. The numerous isopentenyl-5-pyrophosphate structures are complexed together to form larger molecules of geranylgeranyl pyrophosphate and farnesyl pyrophosphate which are responsible for protein prenylation [7]. The hallmark of mevalonate kinase deficiency is the systemic auto-inflammatory processes discovered to be mediated by Interleukin 1β. Reduced production of isoprenoids leads to activation of caspase 1, the enzyme responsible for conversion of pro-IL-1 β to the active IL-1 β. Excessive production of IL-1 β amongst other cytokines contribute to inflammasome compilation leading to the inflammatory hyperresponsiveness and recurrent febrile attacks [7,8].

The patient was reported to have some recurrent unprovoked cyclical inflammatory attacks. Except for the dolichocephalic microcephaly present in the patient, other described dysmorphic craniofacial

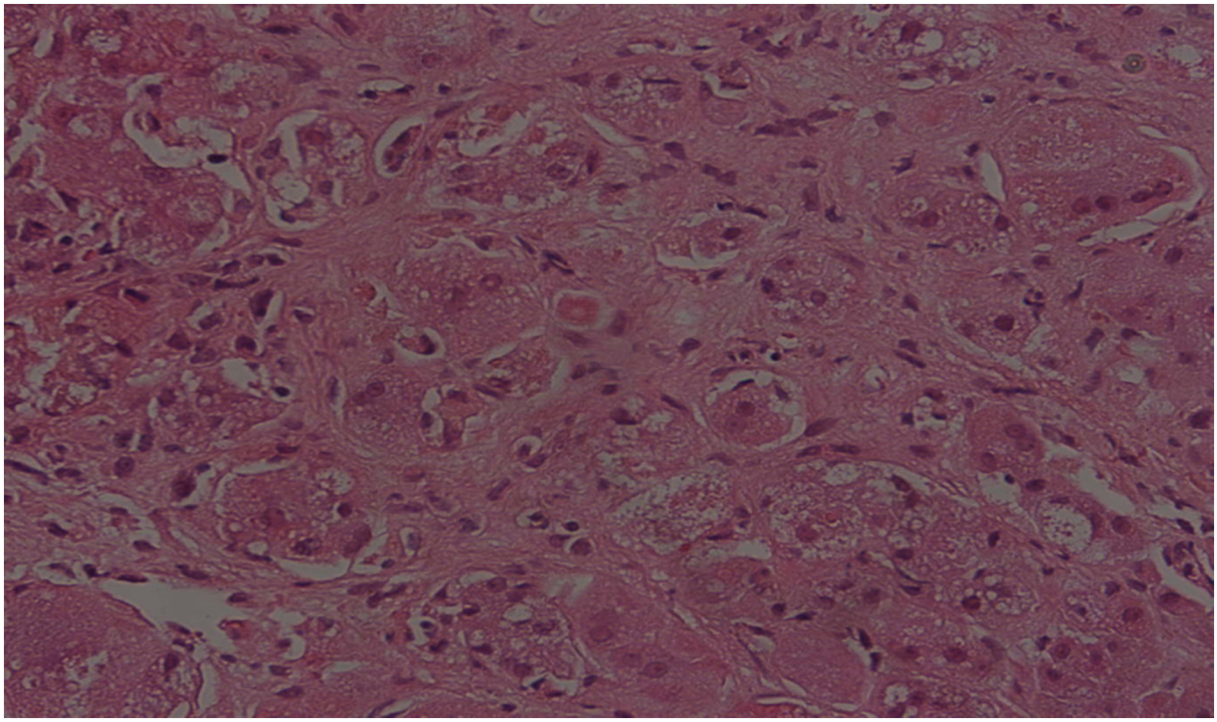

Fig. 1. Photomicrograph of liver biopsy, X20 magnification, Haematoxylin and Eosin. There is prominent giant cell transformation of hepatocytes, obvious disarray of liver cell plates, associated with portal and pericellular fibrosis. Note the round to oval cytoplasmic eosinophilic globular inclusions in some of the hepatocytes.

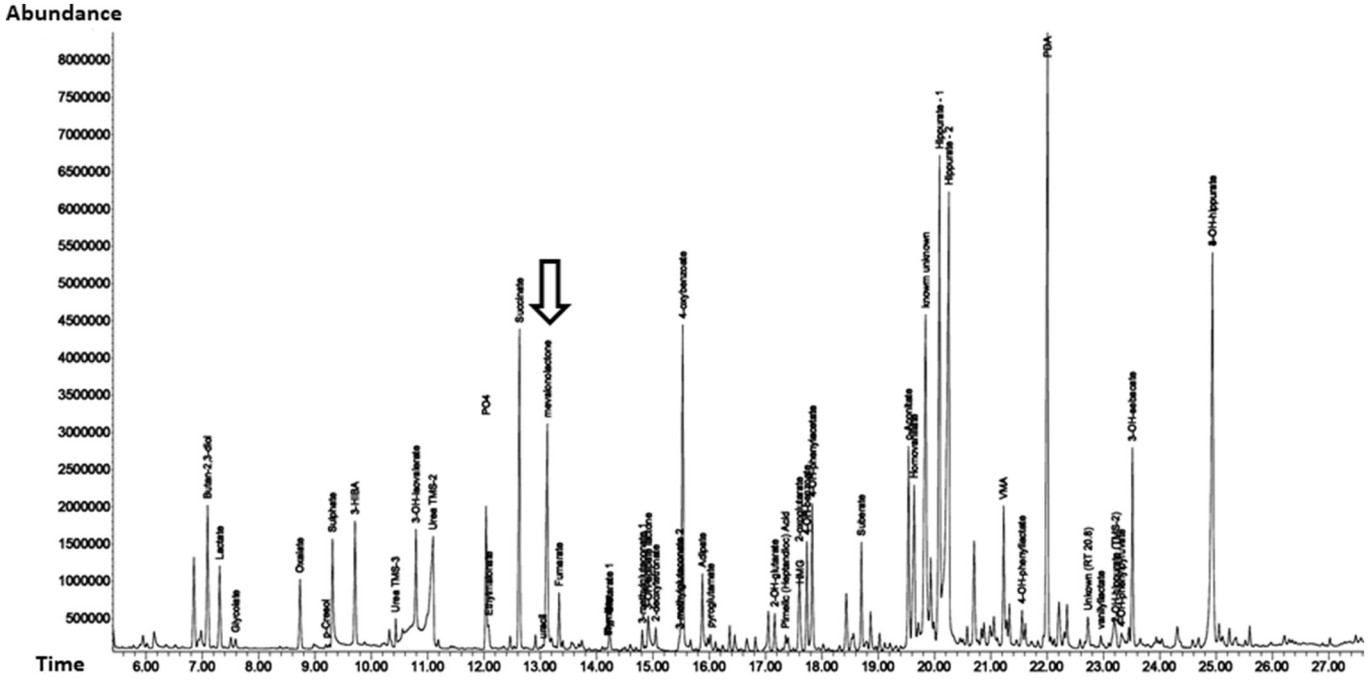

Fig. 2. Urine GCMS chromatograph demonstrating significantly elevated mevalonolactone (indicated by arrow).

features such as frontal bossing, low set dysplastic ears, down slanting eye brows, lengthy eye lashes and cataracts were not discernible. Chronic active cholestatic or non-cholestatic hepatitis and portal fibrosis are the usual reported liver manifestations. [9] However, this patient has been interesting in the severity of liver disease to the extent of sustaining portal hypertension with massive splenomegaly. One patient has been reported with end stage liver disease as a result of mevalonic aciduria requiring liver transplantation as lifesaving definitive treatment [10]. The profound bicytopenia (anaemia and thrombocytopenia) could be explained by sequestration from hypersplenism. Lack of isopentenyl adenine has also been implicated in defective proliferation of cell lines in the bone marrow [11]. The white cell count was spared in this instance because of the recurrent inflammation resulting in persistent leucocytosis.

Mevalonic aciduria is a very rare condition with the incidence reported to be 1.3–6.2 in 1,000,000. It is for this reason and the non-specific symptomatology of the condition that lead to misdiagnosis or late diagnosis. This is supported by the report that the median age of

diagnosis is 8 to 10 years while the onset of most clinical presentations is in the first year of life [5]. The delay in diagnosis was clearly highlighted in this case, attributable to masking by congenital CMV infection and the possible diagnosis of alpha-1-antitrypsin deficiency. The misdiagnosis often leads to extensive microbiological investigations and unwarranted long courses of antibiotics.

Essentially, investigation of suspected mevalonate kinase deficiency should be undertaken in individuals with persistent febrile and inflammatory episodes accompanied by raised inflammatory markers not responding to conventional treatment modalities. A fair number of affected patient will have normal IgD levels. As a result IgA is used as adjunct marker to further delineate the disease. Both the IgD and IgA were within reference intervals in the index patient, illustrating their non-specificity and insensitivity for diagnosis of mevalonate kinase deficiency. Both the urine and plasma mevalonic acid concentrations demonstrate a good correlation with the severity of the clinical disease in addition to the metabolite being a reliable screening biomarker [5]. However, a normal mevalonic acid level does not exclude the disease [12].

The commonest cause of mevalonate kinase deficiency is due to missense mutations in the *MVK* gene inherited in compound heterozygote fashion. V377I is the common founder mutation discovered in the Dutch population. Mutations detected in the index patient have been reported in the literature to have moderately low allele frequency [13]. Most of the mutations described are hypothesized to adversely affect the protein product's stability and function. The degree of MK protein instability and inactivity is likely the reason for the poor correlation between the genotype and phenotypic severity [13].

Unfortunately, the confirmatory genome sequencing result for mevalonic aciduria was obtained post-mortem, after he had succumbed to the disease as a result of multiorgan failure most likely from macrophage activation syndrome and/or septic shock. This case illustrates how a common intrauterine infection masked the diagnosis of a rare metabolic disorder with detrimental consequences. Furthermore, the alpha-1-antitrypsin granules detected on liver histology may have contributed to the delay in obtaining the final diagnosis. The need for high index of suspicion and early newborn screening particularly for inborn errors of metabolism were highlighted in this case. In summary, a number of lessons were learnt from this case: Inborn errors of metabolism should always be considered, in infants, even in clear diagnoses of congenital infections and other common disorders; PAS positive alpha-1-antitrypsin granules are not specific for alpha-1-antitrypsin deficiency; mevalonate kinase is a critical enzyme in the common pathway of cholesterol and non-sterol isoprenoid biosynthesis; febrile and inflammatory episodes accompanied by raised inflammatory markers not responding to conventional treatment modalities should be investigated for mevalonate kinase deficiency; mevalonic aciduria is at the severe end of the spectrum of mevalonate kinase deficiency presenting with multiple organ inflammation with devastating sequelae.

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