HOLOCARBOXYLASE SYNTHETASE DEFICIENCY: a second report with neonatal cholestatic liver disease

Murray C (1), Lynch M (1), Minto T (1), Choo K (2), Bursle C (1), Lipke M (1), McGill J (3), Inwood I (1), Coman D (1, 4-5)

BACKGROUND

• Holocarboxylase Synthetase (HCLS) catalyses the binding of Biotin to carboxylases (1,2)
• Inherited deficiency of HCLS caused by pathogenic variants in the HCLS gene (OMIM #609018) results in decreased carboxylase activity (2)
• Holocarboxylase Synthetase Deficiency (HCLS, OMIM #253270) is a rare autosomal recessive condition characterised by life threatening metabolic acidosis, ketoadiposis and hyperammonemia (4)
• Increased incidence of HCLS in Polynesian populations is seen due to a founder mutation L216R in the HCLS gene which is associated with severe forms of disease (5,6)
• Individuals homozygous for this mutation are largely unresponsive to Biotin treatment and show increased mortality (7)

HISTORY

• A term female infant was born in poor condition to non consanguineous parents of Cook island and Samoan backgrounds
• A foetal MRI brain had shown subependymal cysts and a menatal microarray showed long contiguous stretches of homozygosity
• A complex urinary organic acid pattern, plasma acylcarnitine profile and newborn screening test were consistent with a diagnosis of HCLS and a HCLS genetic panel later revealed a homozygous pathogenic variant in HCLS c.647T=G (L216R) (Figure 1)
• Haemofiltration was commenced with peak lactate levels of 25mmol/L (0.5-2.2), Biotin and IV Carnitine were commenced
• On day 2 the patient developed Necrotising Enterocolitis
• Lactate normalized by day 4 of life and haemofiltration was ceased
• On day 16 the patient presented with cholestatic liver function derangement with a conjugated hyperbilirubinemia (Figure 2)
• A laparotomy revealed a stricture at the junction of the descending and sigmoid colon and a laparotomy was formed
• An intraoperative cholangiogram was normal. A liver biopsy showed features of a mild cholestatic pattern of injury which persisted and the patient was commenced on Ursodeoxycholic acid
• Investigations for G6PD, Alpha 1 anti-trypsin deficiency, thyroid dysfunction and TORCH infections were negative. There was no impairment to hepatic synthetic function
• The stoma was reversed at three months of age, by which time the liver function abnormalities had also resolved
• At six months the patient continued on regular Biotin and was growing well on regular infant formula with no ongoing liver function derangement

DISCUSSION

• Our patient developed persistent cholestatic liver dysfunction in the context of HCLS secondary to L216R mutation, despite resolution of other biochemical abnormalities
• Extensive investigation including liver biopsy did not reveal an underlying aetiology
• Cholestatic jaundice with liver function derangement has previously been reported in a Polynesian infant presenting with HCLS secondary to homozygous L216R mutation (7). In this instance the cholestatic picture was thought secondary to giant cell hepatitis
• Our patient did not have significant findings on liver biopsy and with no other aetiology liver dysfunction was thought related to her underlying HCLS.
• This is the second report of cholestatic liver dysfunction secondary to HCLS in the literature.

CONCLUSION

We describe the presentation of a Polynesian neonate presenting with HCLS and associated cholestatic liver disease. Cholestasis relating to giant cell hepatitis has been reported only once in HCLS on the literature.