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Case Report

Treatable cause of leukodystrophy: Galactosaemia

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ABSTRACT

Galactosaemia is a group of autosomal recessive metabolic disorders characterised by increased blood levels of galactose. It is characterised by cataracts, organomegaly, sepsis and developmental delay. We are reporting a case of galactosaemia presenting as a neurodegenerative disease with a leukodystrophy-like presentation. An 11-month-old boy born to a second-degree consanguineously married couple presented with developmental delay, vomiting, lethargy and refusal of feeds. Examination showed normocephaly, cataract, hepatomegaly and spasticity in all limbs with exaggerated deep tendon reflexes. Magnetic resonance imaging (MRI) of the brain was suggestive of diffuse hyperintensities in periventricular, subcortical and deep white matter on T2WI. Plasma galactose levels were high (3784.0 u M/L) and the RBC Galactose 1-Phosphate uridylyltransferase (GALT) enzyme was low (<0.04). Genetic testing showed homozygous missense mutation c.428C>T (p.Ser143Leu) in exon 5 of the GALT gene. For any child who presents with cataracts, hepatomegaly, developmental delay and leukodystrophy picture on an MRI of the brain, a treatable cause of galactosaemia should be considered.

Keywords: Galactosaemia, Treatable leukodystrophy, Magnetic resonance imaging, Cataract, Hepatomegaly

INTRODUCTION

Galactosaemia is an inborn error of metabolism characterised by increased levels of galactose, due to one of the four enzymes deficient in the galactose metabolism pathway.[1,2] Galactose 1-Phosphate uridylyltransferase (GALT) deficiency (Classic galactosaemia) is characterised by acute neonatal toxicity that results in jaundice, hepatosplenomegaly, food intolerance, hypoglycaemia, renal tubular dysfunction, muscle hypotonia, sepsis and cataract.[3] Neuroimaging generally shows cerebral atrophy, cerebellar atrophy and non-specific white matter signal changes.[4] We are reporting a case of classical galactosaemia with neuroimaging suggesting a hypomyelinating leukodystrophy which is a rare association.

CASE REPORT

An 11-month-old boy, born of a second-degree consanguineously married couple, presented with developmental delay, decreased feeding and vomiting for 3 days. Developmentally, the child had attained partial neck control at 5 months, cooing at 6 months but not attained a social smile and does not follow the light. Birth history was uneventful, the child developed jaundice on day 3 of life and was treated with phototherapy. The child was exclusively breastfed till 7-month then complementary feeds with ragi were started. The child was admitted for vomiting and lethargy at 1, 4 and 7 months of age at some other hospital. On examination, there was normocephaly (45 cm), cataract and no neurocutaneous markers. There was hepatomegaly, spasticity of all four limbs, exaggerated deep tendon reflexes and bilateral upgoing plantar. The following differential

diagnosis was considered, hereditary fructose intolerance, Tyrosinemia Type 1, Niemann-Pick disease Type C, hypomyelination and congenital cataract (HCC), Congenital cytomegalovirus infections (CMV), and rubella hereditary fructose intolerance usually presents in infancy with growth failure, liver disease and renal tubular dysfunction. Tyrosinemia Type 1 usually presents either in young infants with severe liver involvement or later in the 1st year with liver dysfunction and renal tubular dysfunction associated with growth failure and rickets. The Niemann-Pick disease Type C manifests in the perinatal period and infancy with visceral symptoms of hepatosplenomegaly, jaundice and pulmonary infiltrates. Congenital CMV infection is characterised by a maternal infection in pregnancy, low birth weight, neonatal hepatitis, chorioretinitis, microcephaly, malformation of the brain, periventricular calcifications and hearing impairment. Congenital rubella infection is by a maternal infection in pregnancy, low birth weight, neonatal hepatitis, chorioretinitis, hearing impairment, congenital heart disease, microcephaly and intracranial calcifications.

Complete blood counts and liver and renal function tests were normal. Magnetic resonance imaging (MRI) of the brain showed, diffuse hyperintensities in periventricular, subcortical and deep white matter on T2WI and hypointensities on T1WI [Figure 1]. Plasma galactose levels were high (3784.0 u M/L)

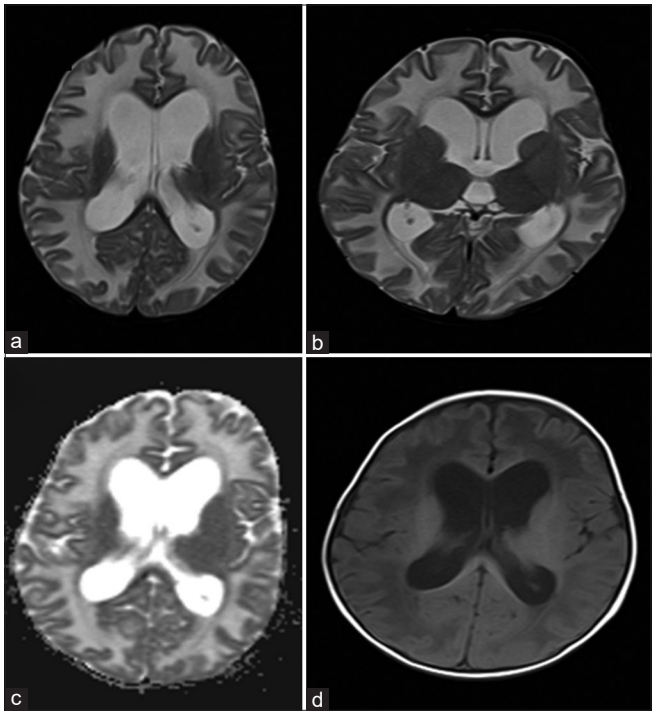

Figure 1: Axial T2 WI (a) showing hyperintensity involving lobar, subcortical and periventricular white matter with the presence of ventriculomegaly. Axial T2 WI (b) shows normal basal ganglia. ADC map (c) does not show any diffusion restriction. Axial T1WI (d) shows the hypointensity of involved white matter.

and RBC Galactose 1-Phosphate uridylyl transferase enzyme was low (<0.04). Genetic testing showed homozygous missense mutation c.428C>T (p.Ser143Leu) in exon 5 of the GALT gene. Sanger sequencing showed homozygous status in the index child and heterozygous status in both parents suggesting both parents are carriers of the same gene. The patient was put on a lactose-free diet. The patient has shown signs of significant improvement in development and the cataract becomes reversed.

DISCUSSION

This child is a classic case of Galactose 1-Phosphate uridylyl transferase deficiency with unusual findings of hypomyelinating leukodystrophy. The manifestations in galactosaemia are because of two metabolites mainly galactitol responsible for cataracts and Galactose 1 phosphate responsible for acute manifestations such as damage to the kidney, liver and brain.[4] The interference in normal galactocerebroside formation may be responsible for the features of neuroimaging.[5]

Otaduy *et al*. reported a case of galactosaemia with MRI showing, diffuse symmetrical involvement of frontal, temporal, parietal and occipital white matter characterised by hypointensity in T1 and T2 hyperintensities. FLAIR images suggested hyperintensities in temporal, frontal and parietal areas with no gadolinium enhancement The DWI showed hypointensity in the areas corresponding to white matter involvement with increased ADC[6] similar to the current case. In mild variants of galactosaemia, the neuroimaging can be normal.[4] We considered the possibility of HCC, we ruled it out based on acute presentation, hepatomegaly and galactosaemia were confirmed with high plasma galactose levels, low RBC GALT enzyme and positive mutations. HCC is characterised by bilateral congenital cataracts and mild initial developmental delay, followed by slowly progressive neurological impairment. Cerebellar signs and peripheral neuropathy are present in the majority of affected individuals. A cataract may be absent in some individuals. The diagnosis of HCC can be established with typical clinical findings, characteristic hypomyelination on the brain MRI and biallelic pathogenic variants in FAM126A identified by molecular genetic testing.[7]

The identified homozygous missense substitution (p.Ser143Leu) alters a conserved residue in the protein. The variant is predicted to be damaged by 6 (SIFT, Mutation Taster, PolyPhen-2, Mutation Assessor, FATHMM and M-CAP) out of seven *in silico* missense prediction tools. The identified variant has been reported in the Exome Aggregation Consortium database as a rare variant (allele frequency: <0.01%) in the South Asian population; however, no homozygosity (for this variant) has been reported. In the ClinVar database, the clinical significance of this variant has been reported as pathogenic concerning galactosaemia. The

identified variant has been previously reported in a patient affected with galactosaemia.[8] The identified missense variant alters a conserved residue and is predicted to be damaging to the protein function. Correlation with the clinical and laboratory values suggests that the mutation identified can be labeled as disease-causing in the current scenario.

CONCLUSION

In the background of a hypomyelinating leukodystrophy on MRI of the brain and the presence of cataracts and hepatomegaly, a treatable cause such as galactosemia should be considered.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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