CASE REPORT

Isoleucine Deficiency in a Neonate Treated for Maple Syrup Urine Disease Masquerading as Acrodermatitis Enteropathica

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Background: Special diet with restricted branched-chain-amino-acids used for treating maple syrup urine disease can lead to specific amino acid deficiencies. **Case characteristics**: We report a neonate who developed skin lesions due to isoleucine deficiency while using specialised formula. **Intervention/Outcome**: Feeds were supplemented with expressed breast milk. This caused biochemical and clinical improvement with resolution of skin lesions. **Message**: Breast milk is a valuable and necessary adjunct to specialized formula in maple syrup urine disease to prevent specific amino acid deficiency in the neonatal period.

Keywords: *Branched-chain amino acid, Restrictive diets, Treatment.*

Maple Syrup Urine Disease (MSUD) is an autosomal recessive inherited inborn error of metabolism, which can be managed by specific dietary modifications to reduce branched chain amino acid intake [1]. If not treated early, irritability and poor feeding can manifest within 2-3 days of life and encephalopathy with opisthotonus and intermittent apnea can start by day 4-5 [2]. Coma and respiratory failure occur by 7-10 days [2].

We report a baby with antenatally diagnosed MSUD who developed isoleucine deficiency while on specialised formula in the neonatal period and presented with cutaneous lesions mimicking acrodermatitis enteropathica. The skin lesions resolved after addition of breast milk to the diet with normalization of isoleucine levels.

CASE REPORT

A 29-year-old gravida 2, para 1 lady in a second degree consanguineous marriage presented to the clinic for prenatal testing. Her first baby had seizures in the neonatal period and was later diagnosed to have MSUD. He had global developmental delay with seizures and died at 2 years of age.

During this pregnancy, both parents were counseled about the chances of recurrence of MSUD in the baby. Sanger sequencing of branched chain keto acid dehydrogenase E1 alpha polypeptide (*BCKDHA)* and branched chain ketoacid dehydrogenase E1 beta polypeptide (*BCKDHB)* genes were done on the couple and chorionic villous sample from the fetus. All the variants were analyzed and annotated using Human (GRCh38.p3) public databases using Ensembl and HGMD (Human Gene Mutation Database). *In silico* analysis was performed for all the variants using SIFT (Sorting Intolerant From Tolerant) and POLYPHEN2 (Polymorphism Phenotyping version 2).

Both parents were detected to be heterozygous for the *BCKDHA* gene mutation (c.757 G>A; p.Ala253Ser.). Mother was heterozygous for *BCKDHB* variation (c.1039-5T>C.). Father did not have any variation of the *BCKDHB* gene. The *BCKDHB* variation is a novel variant of unknown significance and is not known to cause MSUD. Chorionic villous sample was homozygous for the c.757 G>A; p.Ala253Ser. mutation in the *BCKDHA* gene, a known mutation causing MSUD. Based on these results, a diagnosis of MSUD was made in the fetus.

Both parents were extensively counseled about the nature of the disease before and after the results. However, they opted to continue the pregnancy. The neonate was delivered uneventfully by caesarian section at 39 weeks gestation. Due to a delay in shipment of specialised formula for MSUD from the USA, the neonate was started on intravenous fluids. MSUD-specific formula was started on day 5. Initial biochemical analysis before starting the formula showed a valine level of 423µmol/L (Normal 80-246 µmol/L), leucine level of 217 µmol/L (Normal: 46-109 µmol/L) and isoleucine level of 153 µmol/l (Normal: 27-53 µmol/L). In order to

avoid encephalopathy and neurological sequelae the neonate was not started on breast milk.

On day 8, the neonate developed watery stools. On day 10, the neonate developed excoriative skin lesions in the perianal and perioral regions, and both feet which rapidly progressed (***Fig.* 1**); scalp was spared and hair was normal. On day 12, the neonate developed fever and lethargy. The neonate was started on intravenous antibiotics (cloxacillin, cefaperazone and amikacin). Blood culture revealed *Klebsiella sp*. sensitive to cefaperazone. The neonate became afebrile, active and well within 48 hours of starting antibiotics. However, the skin lesions continued to worsen. An amino acid profile revealed Isoleucine level 8 µmol/L, Leucine level 232 µmol/L and Valine level 226 µmol/L. Zinc deficiency causing acrodermatitis enteropathica was ruled out as serum zinc levels were normal (74 µg/dL). Staphylococcal sepsis was ruled out as blood culture and skin swab culture did not show growth of *S. aureus*. A final diagnosis of acrodermatitis enteropathica like skin lesions due to low isoleucine levels was made based on the clinical profile and isoleucine level profiles through this time period. Expressed breast milk was added to the feeds to amount to 30% of total feed volume to compensate for isoleucine deficiency. This amount was arbitrarily chosen with a plan to modify it based on further clinical and biochemical progress. The neonate showed a rapid improvement in the skin lesions which started healing. Repeat amino acid profile showed a normal isoleucine levels (66 µmol/L).

DISCUSSION

Management of MSUD involves use of specialized diet with restricted branched chain amino acids [1]. However, amino acid profile needs to be checked frequently to ensure that branched chain amino acid levels are within normal levels. Elevated levels of branched chain amino acids can result in encephalopathy, seizures and developmental delay [1].

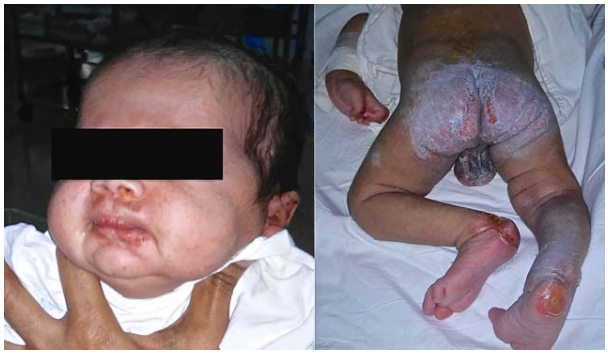

FIG. 1 *Skin lesions in the perioral, perianal regions and feet mimicking acrodermatitis enteropathica seen in an infant with isoleucine deficiency.*

The neonate, described herein, developed isoleucine deficiency and presented with skin lesions similar to acrodermatitis enteropathica. These skin lesions have also been described during treatment of organic acidemias (methyl malonic acidemia, glutaric aciduria and propionic acidemia) [3,4] and amino-acidopathies (maple syrup urine disease) [5,8] due to iatrogenic deficiency of isoleucine. It has been called acrodermatitis acidemica [3-9] or acrodermatitis dysmetabolica [9]. Similar lesions have also been described in biotin deficiency and free fatty acid deficiency [10]. The neonate described here had the clinical profile and response to treatment similar to the cases with isoleucine deficiency described previously.

Special formulae with restricted branched chain amino acids is essential for managing neonates with MSUD. However, when used alone even for a short time, neonates can quickly develop branched chain amino acid deficiency as highlighted in this case report. Expressed breast milk (EBM) supplementation is an effective way to avoid and treat deficiency of branched chain amino acid in the neonatal period and early infancy in these babies as was seen in the neonate described herein. The amount of EBM to be added needs to be adjusted depending on the clinical response and repeated amino acid profile testing. The other options to prevent deficiency of branched chain amino acids include supplementation with specific amino acids, use of infant formula and low dose protein supplementation. It is also necessary to frequently monitor amino acid profiles in the growing infants to optimize their dietary intake, growth and ensure normal levels of branched chain amino acids.

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