Title
Nutritional deficiency dermatitis related to branched-chain amino acid restriction in a child with maple syrup urine disease

Journal
Dermatology Online Journal, 25(9)

Authors
Campuzano-García, Andrés Eduardo
Castanedo-Cázares, Juan Pablo

Publication Date
2019

DOI
10.5070/D3259045509

Nutritional deficiency dermatitis related to branched-chain amino acid restriction in a child with maple syrup urine disease

Andrés Eduardo Campuzano-García[1] MD, Juan Pablo Castanedo-Cázares[2] MD

Affiliations: [1]Dermatology service, Hospital General de Zacatecas, Zacatecas, México, [2]Department of Dermatology, Hospital Central Dr. Ignacio Morones Prieto, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México

Corresponding Author: Dr. Juan Pablo Castanedo Cázares, Departamento de Dermatología, Hospital Central Dr. Ignacio Morones Prieto, Venustiano Carranza No. 2395, Zona Universitaria, 78210, San Luis Potosí, S.L.P. México, Tel: 52 444 8342795, Email: castanju@yahoo.com

Abstract

We present a one-year-old girl with maple syrup urine disease with dermatitis secondary to the restriction of amino acids as part of the treatment. We present the clinical evolution and histopathological correlation.

Keywords: deficiency dermatitis, branched chain amino acid restriction, maple syrup urine disease, isoleucine

Introduction

Maple syrup urine disease (MSUD) is a rare, inherited metabolic disease caused by a deficiency in branched-chain α-ketoacid dehydrogenase complex, an enzyme of the metabolic pathway of the three branched-chain amino acids, leucine, isoleucine, and valine [1]. It is characterized by psychomotor delay, hypotonia, seizures, and urine with a distinctive maple syrup odor. The aim of treatment aim is to reduce toxic metabolites that lead to cytotoxic brain edema. This is achieved by ensuring adherence to a restricted diet of branched-chain amino acids that are commercially available as an infant formula [2]. The cutaneous manifestations of MSUD are infrequent and mainly comprise an acrodermatitis enteropathica-like dermatitis resulting from the restriction of selected amino acids [3]. Skin manifestations associated with therapy for this enzymatic deficiency have been reported in approximately 12 MSUD cases in the literature [4]. A case of dermatitis caused by branched-chain amino acid restriction that improved following dietary supplementation with leucine in the context of MSUD is described.

Case Synopsis

A one-year-old girl was diagnosed with MSUD at eight months following extensive epilepsy studies. She had no family history of consanguinity. She did have a family history of maternal epilepsy and a sister who died in the first two weeks of life. Her pharmacologic treatment was levetiracetam, a commercially available BCAA-restricted infant formula and a multivitamin supplement.

She presented with a dermatitis that had evolved over two weeks and was characterized by erythematous macules and papules with a predominance in the diaper area, flexural sites, and proximal thighs. She also manifested with marked irritability and worsening hypotonia. The only periorificial site slightly involved was the perianal zone, but there were no changes in hair, nails, or mucous membranes. The possible presence of scabies was eliminated on direct observation of the skin scrapings. Topical zinc oxide with 1% hydrocortisone was initiated following an initial diagnosis of diaper dermatitis with *"id"* phenomenon. However, the dermatitis worsened over two weeks, affecting the occipital area, trunk, palms, soles, and buttocks. It was characterized by perifollicular papules and erythematous urticarial plaques, with erosions and brownish scales in the diaper area (**Figure 1**). An elevation in blood eosinophil count

(480 eosinophils per mm^3) was noted. The levetiracetam was withdrawn. An intravenous administration of methylprednisolone (1mg/kg/day) was initiated on suspicion of drug eruption. There was no improvement after two days and an acrodermatitis enteropathica-like eruption was suspected because it was not responsive to corticosteroids and it exhibited eroded skin with some predominance in the diaper area. A skin biopsy was performed. The histopathologic examination is shown in **Figure 2**:

Plasma zinc and ammonia levels were normal. Blood samples were sent to a specialized center to determine the leucine levels. In the interim, leucine was administered orally on suspicion of an amino acid deficit. The cutaneous lesions started to resolve over the next two days and were characterized by a faint erythema, generalized desquamation, and postinflammatory hyperpigmentation. The patient's neurologic condition also improved, with decreased irritability and hypotonia. A few days later, a serum leucine level of 20µmol/L was confirmed (normal values are 80–200µmol/L).

Case Discussion

Maple syrup urine disease affects one in 86,800–185,000 live births. It is more prevalent in populations with increased frequency of consanguinity [1]. The condition is characterized by elevation in branched-chain amino acids plasma levels and α-keto acid concentrations [1], thus triggering ketonuria, seizures, hypotonia, irritability, cognitive impairment, and death related to cerebral edema and herniation [5].

Isoleucine, an essential amino acid, is involved in keratinocyte growth and differentiation. Its depletion is correlated with arrested keratinocyte culture growth [6]. However, the skin manifestations are not primarily related to toxicity, but as a consequence of dietary restrictions [4].

Numerous metabolic deficits produce clinical entities typified by skin manifestations. Of these, an acrodermatitis enteropathica-like eruption is most frequently observed [4]. Other inherited metabolic diseases, such as methylmalonic and propionic,

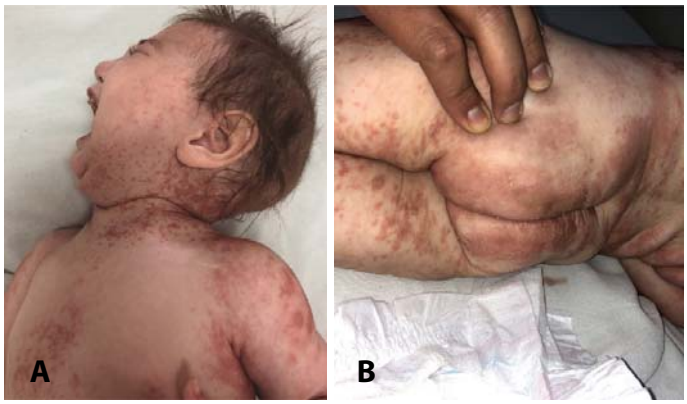

Figure 1. *Cutaneous presentation.* ***A)*** *Perifollicular papules, erythematous plaques of the trunk and brownish crusts of the neck and shoulders. The child exhibited marked irritability.* ***B)*** *Erythematous plaques and brownish crusts with predominance in waist and buttocks, with scale in the margin of plaques.*

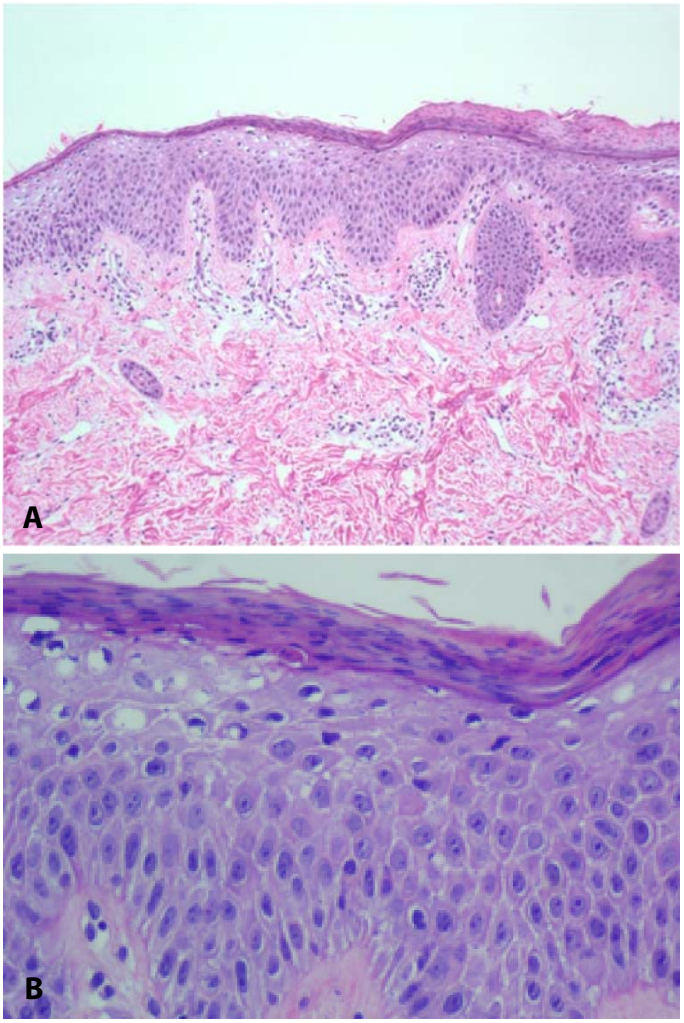

Figure 2. ***A)*** *Psoriasiform and superficial perivascular dermatitis with foci of parakeratosis.* ***B)*** *Epidermis showing spongiosis, keratinocytes with irregular contour nucleus, and broad eosinophilic cytoplasm. H&E,* ***A)*** *100×;* ***B)*** *400×.*

glutaric type I acidemia, ornithine transcarbamylase deficiency, and citrullinemia, exhibit cutaneous features that resemble acrodermatitis enteropathica [3, 7]. There are approximately 40 cases of acrodermatitis entropathica-like dermatitis in the literature, 13 of which involved a diagnosis of MSDU [4].

As in other cases related to amino acid restriction, the infant in this case presented with systemic disease manifestations, such as fever, irritability, and muscular weakness. This clinical scenario is typical of nutritional deficiency diseases and was not initially considered. However, the polymorphous eruption that began in the diaper area and consisted of erythematous papules and eroded plaques with crusts were suggestive of amino acid deficit in the clinical setting of innate metabolic diseases (MSUD or other enzymatic disorders). The intertriginous zones may be most affected because of repetitive cutaneous friction, causing increased epidermal turnover. The absence of mucosal involvement, particularly stomatitis and glosssitis, that is relatively common in acrodermatitis entropathica-like conditions, was an interesting finding in the current case [7]. This difference may relate to the minor role of leucine in mucosal morphology and epithelial replacement.

Additionally, histopathology can be used to differentiate between other entities, such as necrolytic acral erythema and drug reactions. We are unaware of specific cutaneous MSUD lesions. These findings reported resemble the histological features present in other dermatoses related to micronutrient deficiencies [8]. The determination of ammonia blood levels is useful for evaluating the extent to which leucine is restricted if serum quantification levels of leucine, isoleucine, and valine are unavailable [9]. Ammonia is the final product of amino acid metabolism and indirectly reflects their deficit. If ammonia levels are normal or less than normal, leucine should be increased empirically in the diet [8, 9].

Conclusion

It is important for dermatologists to be aware of signs of leucine deficit and monitor patients with clinical features of MSUD undergoing the treatment of amino acid restriction. Observation of the diaper area may be a key to early diagnosis. If dermatitis related to branched-chain amino acid restriction is suspected, a skin biopsy should be performed and the plasma levels of valine, leucine, isoleucine, and zinc should be assessed. Subsequently, ammonia levels may be monitored to assess leucine deficiency.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Burrage LC, Nagamani SC, Campeau PM, et al. Branched-chain amino acid metabolism: from rare Mendelian diseases to more common disorders. *Hum Mol Genet.* 2014;15:23-8. [PMID: 24651065].
2. Frazier DM, Allgeier C, Homer C, et al. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. *Mol Genet Metab.* 2014;112:210-7. [PMID: 24881969].
3. Flores K, Chikowski R, Morell DS. Acrodermatitis dysmetabolica in an infant with maple syrup urine disease. *Clin Exp Dermatol.* 2016;4:651-4. [PMID: 27334242].
4. Vitoria Miñana I, Dalmau Serra J. Enteropathic acrodermatitis-like lesions in valine deficiency methylmalonic acidaemia, *An Pediatr* (Barc). 2010;96-7. [PMID: 19955028].
5. Morton DH, Strauss KA, Robinson DL, et al. Diagnosis and treatment of maple syrup disease: a study of 36 patients, *Pediatrics.* 2002;109:999-1008. [PMID: 12042535].
6. Templier I, Reymond JL, Nguyen MA, et al. Acrodermatitis enteropathica-like syndrome secondary to branched-chain amino acid deficiency during treatment of maple syrup urine disease.*Ann Dermatol Venereol.* 2006;133:375-9. [PMID: 16733455].
7. Tabanlioğlu D, Ersoy-Evans S, Karaduman A. Acrodermatitis enteropathica like eruption in metabolic disorders; acodermatitis dysmetabolica is proposed as a better term. *Pediatr Dermatol.* 2009;150-4. [PMID: 19419460].
8. Wu D, Fung MA, Kiuru M et al. Acquired bullous acrodermatitis enteropathica as a histologic mimic of pemphigus foliaceus in a patient on parenteral nutrition. *Dermatol Online J.* 2017:15-23. [PMID: 30142747].
9. Holecek M. Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma and as supplements, *Nutr Metab (Lond).* 2018;3:15-33. [PMID: 2975574].