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Skin Lesions Associated with Dietary Management of Maple Syrup Urine Disease: a Case Report

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Abstract

Leucinosis (maple syrup urine disease - MSUD) is an inherited aminoacidopathy and organic aciduria caused by severe enzyme defect in the metabolic pathway of amino acids: leucine, isoleucine, and valine. The classical variant of the disease is characterized by accumulation of both amino and α-keto acids, particulary the most toxic rapid elevation of circulating leucine and its ketoacid, α-ketoisocaproate, which cause encephalopathy and life-threatening brain swelling. However, patients with the most severe form, classical maple syrup urine disease, may appear normal at birth, but develop acute metabolic decompensation within the first weeks of life with typical symptoms: poor feeding, vomiting, poor weight gain, somnolence and burnt sugar-smelling urine, reminiscent of maple syrup. Early diagnosis and dietary intervention improve the patient's condition, prevent severe complications, and may allow normal intellectual development.

We present a 4-month old infant with leucinosis dignosed 3 months earlier, due to elevated levels of amino acids: leucine, isoleucine and valine. The patient was full-term neonate with an uncomplecated delivery, without any family history of metabolic disorder or consanguinity. The infant was referred to a dermatologist, because of maculopapular exanthema on the scalp, trunk, upper and lower extremities, and exfoliative dermatitis of the perioral, particularly anogenital regions, associated with diarrhea. Skin involvement was associated with poor general condition of the infant exhibiting severe hypotension, anemic syndrome, dyspepsia and neurological symptoms. Exanthema developed a few days after the initiation of nutritional therapy for MSUD: isoleucine-, leucine-, and valine-free powdered medical food (MSUD-2) supplemented with iron. Zink levels were within normal ranges. Rapid skin improvement occurred after adequate branched-chain amino acids supplementation was commenced under regular laboratory control (normal zinc serum level with deficiencies of leucine and valine), skin hygiene with antiseptics, emollients and low potent topical corticosteroids.

Treatment of acute metabolic decompensation and dietary restriction of branched-chain amino acids are the main aspects in the management of maple syrup urine disease. Common findings in patients with MSUD include: plasma amino acid imbalance, particularly of essential amino acids, failure to thrive attributed to restriction of particular precursor amino acids and natural proteins, micronutrient deficiencies or higher energy requirement due to chronic illness or inflammation. Due to low intake of branched-chain amino acids, some patients develop skin lesions known as acrodermatitis enteropathica-like syndrome.

Here we report a case of an infant who developed acrodermatitis enteropathica-like skin eruptions due to branched-chain amino acid deficiency during treatment of maple syrup urine disease. According to available world literature, this is the first report of acrodermatitis enteropathica-like syndrome in an infant with maple syrup urine disease (leucinosis) in the Republic of Bulgaria.

Key words

Maple Syrup Urine Disease; Diet Therapy; Infant; Acrodermatitis; Isoleucine + deficiency; Signs and Symptoms; Treatment Outcome; Case Reports; Bulgaria

Leucinosis (maple syrup urine disease - MSUD) is an inherited aminoacidopathy caused by severe enzyme defect in the metabolic pathway of amino acids (AA): leucine, isoleucine, valine and their α-ketoacid derivatives. The classical variant of the disease is characterized by accumulation of both amino and α-keto acids, particulary the most toxic rapid elevation of circulating leucine and its ketoacid

derivate, α-ketoisocaproate (α-KIC), which causes encephalopathy and life-threatening brain swelling. However, patients with the most severe form, classical MSUD, may appear normal at birth, but develop acute metabolic decompensation within the first weeks of life (1). The disease is characterized by poor general condition, ketoacidosis, poor feeding, poor weight gain, somnolence, ataxia and burnt sugar-smelling urine, which is reminiscent of maple syrup. Severe complications such as encephalopathy, progressive neurodegeneration and coma are observed in untreated patients (1, 2). Treatment of acute metabolic decompensation and dietary restriction of branched-chain amino acids are the main therapeutic aspects, but they are commonly associated with muscular hypotonia, nausea, metabolic decompensation, infections, retardation and swallowing difficulties. Common findings in treated patients include: imbalances in the plasma essential AA and failure to thrive due to restriction of micronutrients or because of a higher energy need due to chronic illness or inflammation (3). Due to low intake of branched-chain amino acids (BCAA), some patients develop skin lesions known as acrodermatitis enteropathica (AE)-like syndrome.

Case report

A 4-month-old female infant was referred to the Department of Pediatrics due to poor general condition, poor weight gain and maple syrup urine odor. The patient was full-term neonate with an uncomplecated delivery, without any family history of metabolic disorder or consanguinity. The disease started 3 months earlier, when an adapted milk formula was introduced. The infant was previously treated in another hospital and received blood and plasma transfusion twice, because of severe anemic syndrome, but without any improvement.

On phisical examination, the measured infant 3000 g and 50 cm length; it was somnolent and hypotonic exhibiting: dysmorphic facies with retrognathia; tense fontanelle, increased chest diameter and tachycardia. Neurological examination revealed that the baby was unable to hold head up without support, lethargy, inability of sitting without support, as well as overactive knees and exaggerated Achilles tendon reflexes.

Biochemical examination showed high levels of lactatae dehydrogenase (LDH), creatine phosphokinase (CPK), uric acid, and ammonia (>145 μmol/l, reference values 11 - 31 μmol/l) along with metabolic acidosis, serum leucine level (> 8000 μmol/l, reference values 2.07 - 4.57 μmol/l), serum valine level (>100 μmol/l, reference values 2.0 - 4.8 μmol/l), and severe anemic syndrome.

Cervical edema was established by transfontanelle ultrasound; electroencephalography (EEG) showed uniform low-amplitude complex of electrical potential and almost no differentiation of cortical areas.

The diagnosis of MSUD was made based on clinical, biochemical and imaging data.

The treatment included fluid and electrolyte imbalance management, dietary restriction of BCAA by using an isoleucine-, leucine-, and valine-free powdered medical food MSUD 2, and adjunct treatment of neurological complications. A few days after starting the dietary restriction of (AA): leucin, isoleucine and valine, a disseminated maculopapular exanthema appeared on the skin of the scalp, face, trunk and extremities, as well as exfoliative dermatitis of the perioral and particularly anogenital region, together with diarrhea. Erosions, yellowish crusts and lamellar exfoliation were observed in the periorificial region and extremities (Figures 1 - 4). Skin involvement was associated with poor general condition of the infant exhibiting lethargy, severe hypotension, anemic syndrome, dyspeptic syndrome and neurological symptoms. Zink levels were within normal ranges. (AE)-like syndrome, secondary to leucine and valine deficiency, was suspected.

Rapid skin improvement, observed after BCAA supplementation under laboratory control (normal zinc serum level with deficiencies of leucine and valine) confirmed our suspicions. In addition, skin hygiene control with antiseptics, emollients and low potent topical corticosteroids was administrated. Mycological and mycrobiologicyl examination was performed and gave negative results.

Discussion

Leucinosis or MSUD is an aminoacidopathy secondary to defective activity of the human mitochondrial branched-chain alpha-keto acid dehydrogenase (BCKD) multienzyme complex,

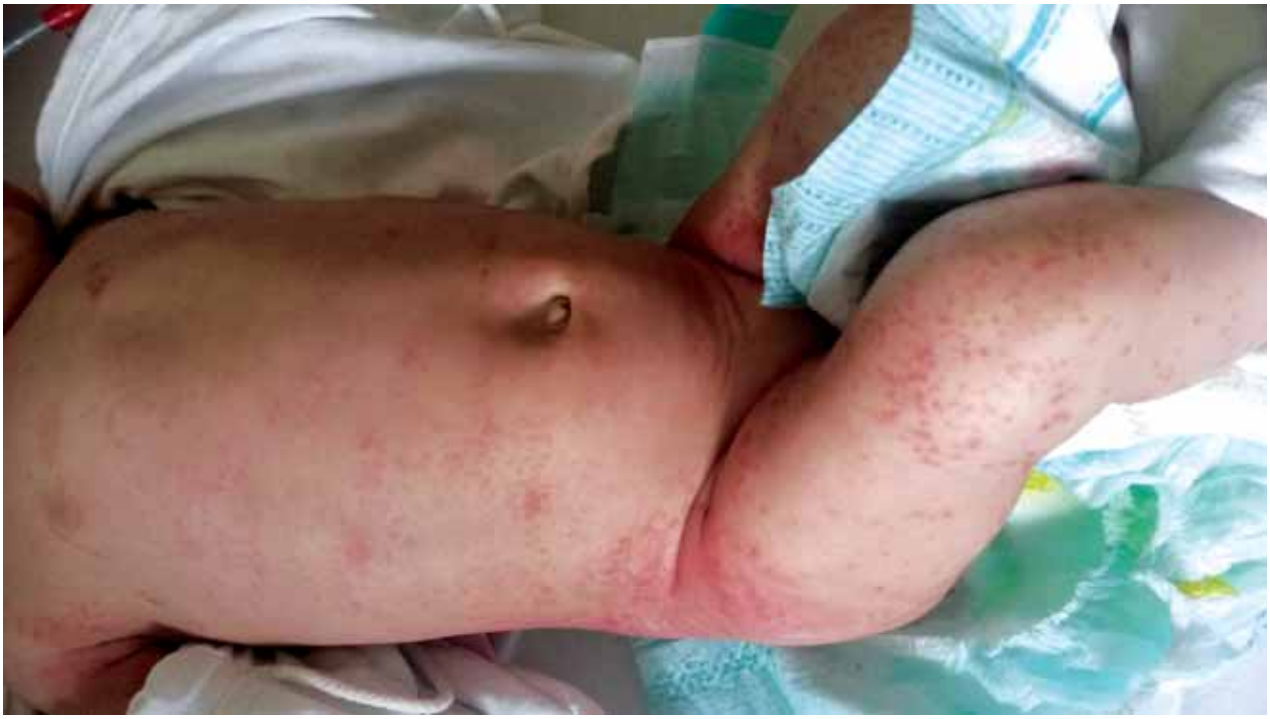

Figure 1. Disseminated maculopapular exanthema

which catalyzes decarboxylation of BCAA (leucine, isoleucine, and valine) to their corresponding metabolites-α-keto acids (1). Catabolic pathways of BCAA consist of multiple steps including reversible transamination, irreversible oxidative decarboxylation and dehydrogenation. Congenital errors of these pathways are inherited in an autosomal recessive fashion. As a consequence, degradation of 3 BCAA: leucine, isoleucine, and valine, is blocked in MSUD after the first catabolic step (transamination), resulting in accumulation of BCAA and their corresponding branched-chain α-keto acids (BCKA) in biological fluids. Because of the combined toxic effects of AA, particularly leucine, and organic acid intermediates, such as the keto- and hydroxyacid metabolites of BCAA, MSUD can be considered both an amino acidopathy and organic aciduria (3). Accumulation of leucine causes neurological symptoms, whereas high level of isoleucine in plasma is associated with a sweet-smelling odor of the urine. Leucine is rapidly transported across the blood-brain membrane and is neurotoxic at high concentrations (4). By inhibiting the transport of essential AA across the blood-brain barrier e.g, tyrosine, tryptophan, hyperleucinemia limits cerebral catecholamine, serotonin, and protein synthesis. Transaminases in brain tissue normally convert leucine to α-ketoglutarate. Accumulation of α-KIC - ketoacid derivative of leucine, depletes the brain of glutamate since it favors synthesis of leucine by consuming glutamate in the bidirectional transaminase reaction. Glutamate is an important metabolic currency that is used as a neurotransmitter as well as a source of energy. Proposed mechanisms of neurotoxicity in MSUD include unbalanced cerebral essential AA uptake, neurotransmitter deficiencies, energy deprivation, osmotic dysregulation, inhibition of mitochondrial enzymes and respiratory chain (2, 5). Moreover, MSUD patients present with deficiency of l-carnitine (l-car), a compound with antioxidant properties whose supplementation has recently been shown to decrease DNA damage in treated MSUD patients (6).

The BCKD complex, which catalyzes an irreversible second step within the inner mitochondrial membrane, represents a multi-enzyme macromolecule consisting of three different catalytic components E_1 ($E_{1\alpha}$, $E_{1\beta}$), E_2, E_3 which require cofactors thiamin flavin and two regulatory enzymes, a-kinase and

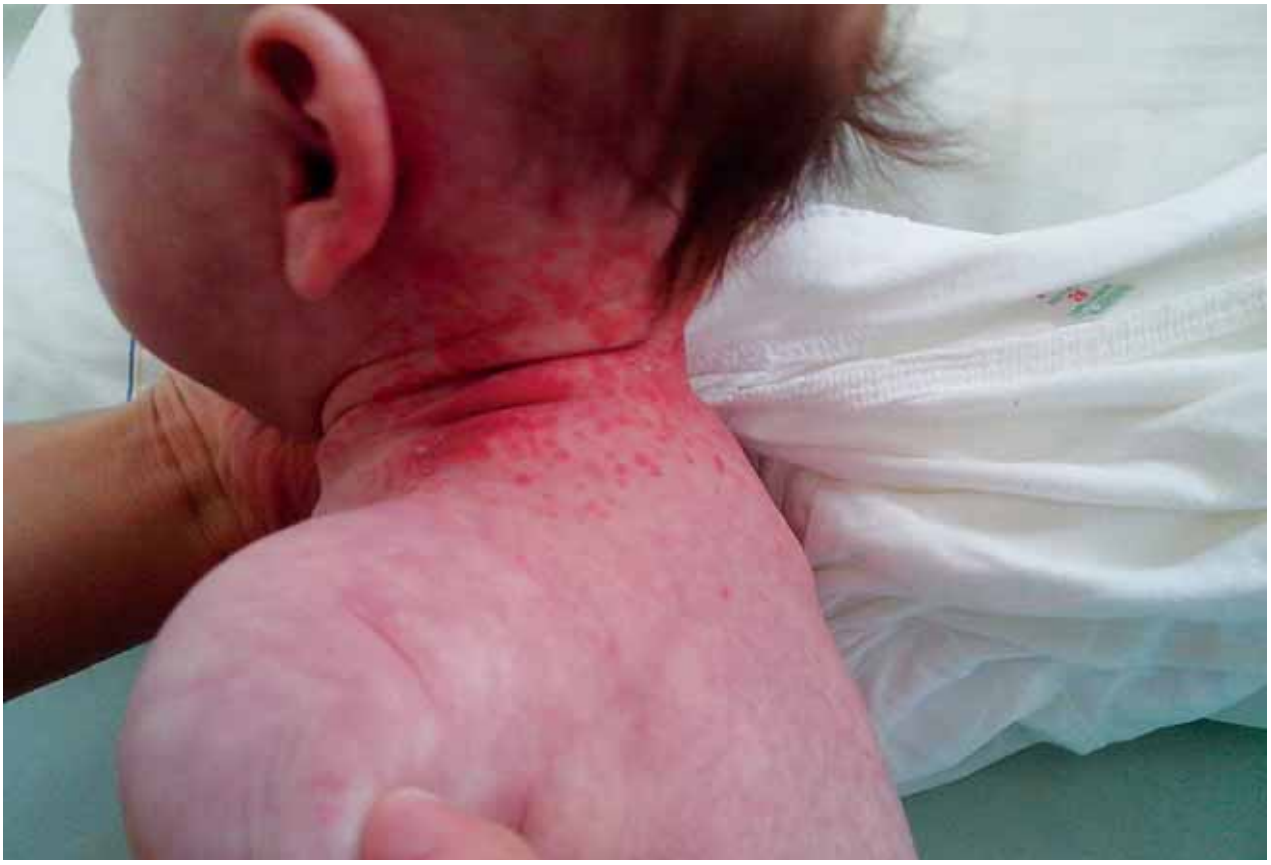

Figure 2. Sharply demarcated erosions and macular exanthema on the scalp, face, trunk and extremities

a-phosphatase. The genes encoding the various BCKD complex catalytic subunits/components E1α, E1β, E2, E3, kinase and phosphatase have been mapped to chromosome loci: 19q13.1–13.2; 6q14; 1p31; 7q31–32, 16p11.2 and 4q22.1, respectively. MSUD is predominantly caused by mutations in the BCKDHA, BCKDHB, and DBT genes, which encode for the E1a, E1b, and E2 subunits of the human mitochondrial BCKD complex (1).

In 1954, Menkes et al. reported that four siblings from a single family from Massachusetts died within the first 3 months of their lives because of neurodegenerative complications. The urine of these infants had an odor resembling maple syrup (burnt sugar) (7). Later, Dancis et al. identified the pathogenic compounds in the pathway of branched-chain amino acids (BCAA) BCAA (8). Maple syrup urine disease (MSUD) is a rare inherited central nervous system (CNS) disorder described in all ethnic groups and occurs in about 1/185.000 and 1/101.624 newborns in the USA and Taiwan, respectively (1, 9). Five different clinical phenotypes are distinguished based on the age of onset, severity of clinical symptoms and response to the therapy – classical, intermediate, intermittent, thiamine-responsive and E_3-deficient. All forms are characterized by poor feeding, vomiting, poor weigh gain, somnolence, maple syrup odor of the urine. Encephalopathy and progressive neurodegeneration resulting in accumulation of BCAA and their corresponding BCKA may occur in untreated infants. Asymptomatic newborns with MSUD have better outcome compared to infants diagnosed after they have become symptomatic (2). Because early detection and dietary restriction can prevent complications and may allow normal intellectual development, MSUD has been added to metabolic screening program of newborns (9). However, the screening becomes uncertain in non-classical forms of the disease, e.g. the intermittent form where symptoms usually appear between the ages of 5 months and 2 years (10).

As the basis of treatment includes a specific dietary therapy, it must comprise careful adjustment of caloric and protein intake along with micronutrient and vitamin supplementation in selected instances (e.g., rare cases of thiamine-responsive MSUD), carnitine administration and adjunct treatment (e.g., neurotropic and psychotropic drugs when neurological symptoms form a component of the phenotype) as was required in our patient. The mainstay in the treatment of MSUD encompasses acute-phase treatment of acute episodes, which gradually shifts to long-term management, depending on the patient's condition (11). Prospective studies are needed to optimize current therapeutic strategies including life-time risk in affected individuals by testing the effectiveness of adjunct therapies such as antioxidants or-alpha-ketoglutarate in addition to specialized precursor/protein restriction diets and substitution (3). Liver transplantation may be performed in very severe cases as an effective way to eliminate acute decompensation risks, but currently available evidence suggests it may not improve the intelligence quotient (IQ) or reverse psychiatric disease (12).

Along with infant's aminoacidopathy, particularly in children with BCAA disorders, cutaneous lesions, with special predilection to diaper periorificial regions and neck folds, resembling acrodermatitis enteropathica (AE) may develop, (13 - 19). Acrodermatitis AE is a rare autosomal recessive disease characterized by zinc deficiency attributed to the inability to absorb zinc from the gastrointestinal system. Clinical presentation is based on the triad: dermatitis, diarrhea and alopecia. Skin eruptions resembling acrodermatitis enteropathica can be caused by deficiencies of other nutrients such as biotin, essential fatty acids and AA. Apart from "AE-like skin lesions", the term "acrodermatitis acidemica" and recently "acrodermatitis dysmetabolica" have been proposed. Since acrodermatitis acidemica is rarer than AE, children are first treated with zinc supplements, instead of higher amounts of natural proteins rich in essential AA. The exact pathogenesis of skin lesions has not been established yet, but it is believed that BCAA are essential for normal growth and differentiation of keratinocytes. In our patient the diagnosis of AE-like iatrogenic acrodermatitis enteropathica-like syndrome in MSUD was made based on the following: clinical picture of exfoliative dermatitis, failure to trive, diarrhea, lethargy and encephalopathy; diet free of

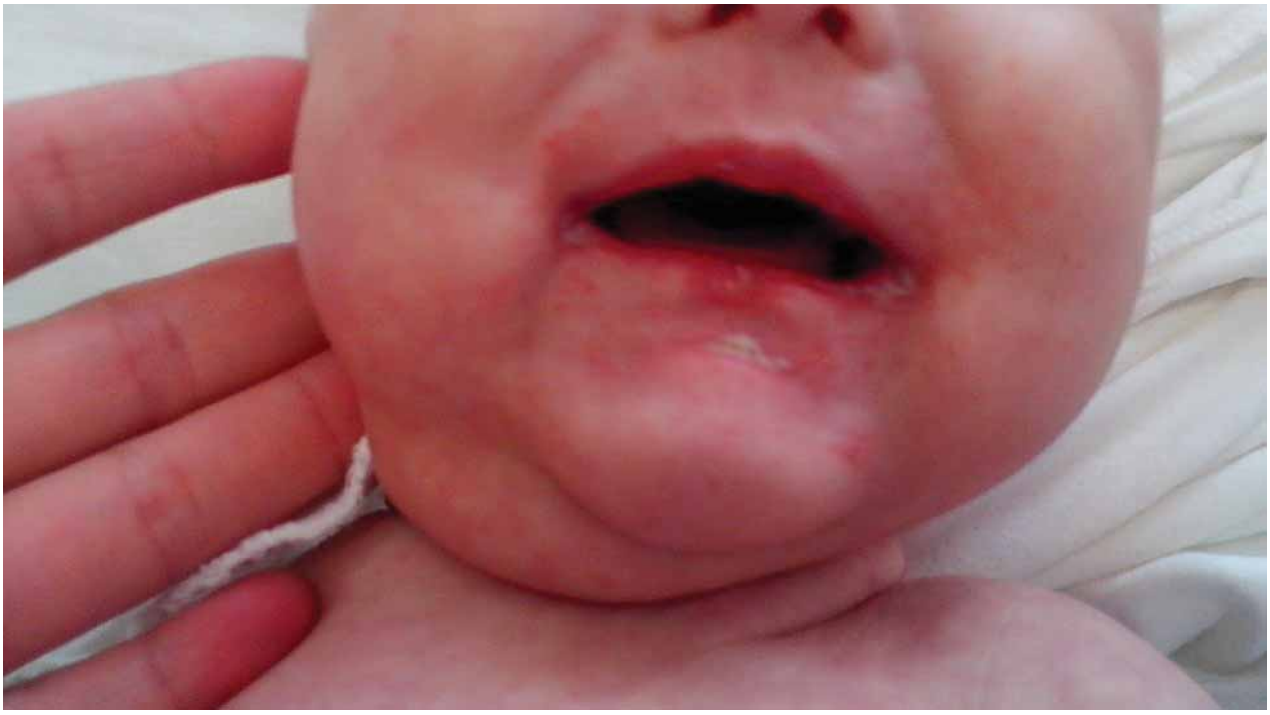

Figure 3. Perioral exfoliation, erythematous patches and erosions

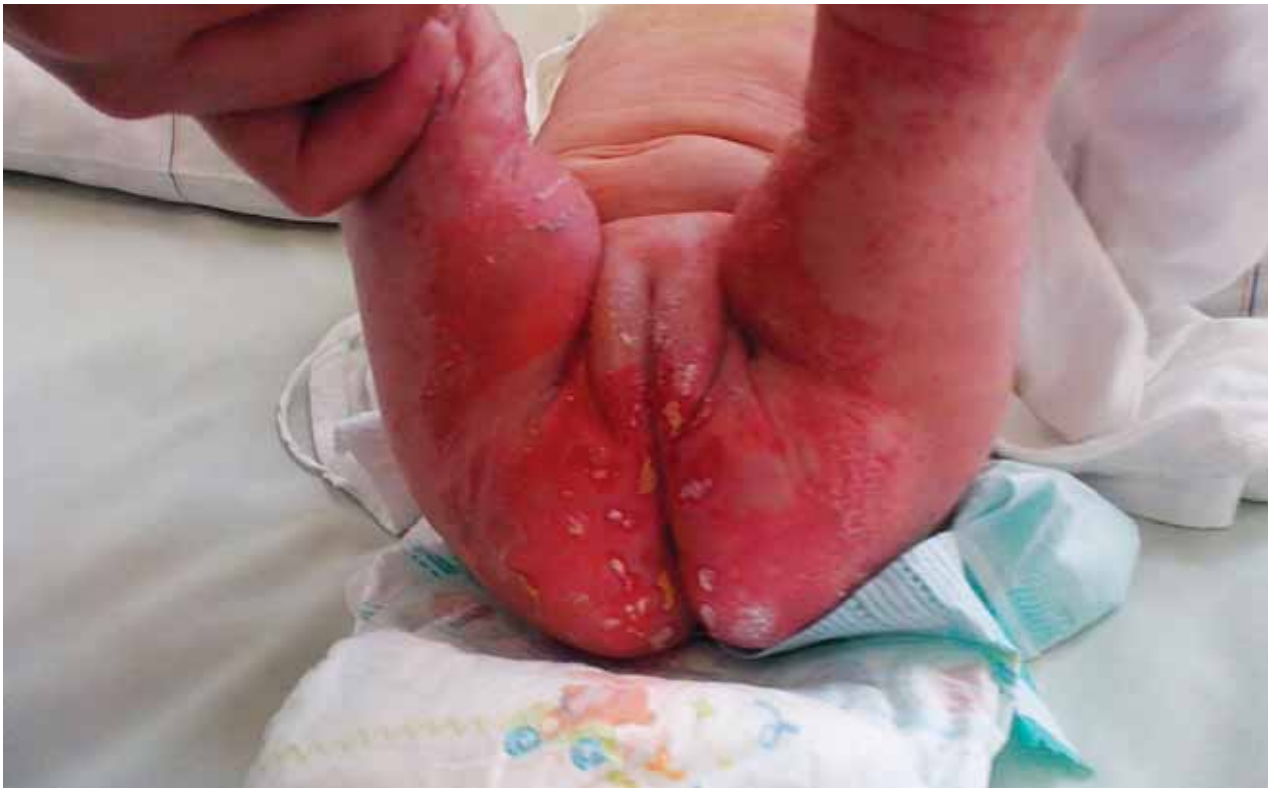

Figure 4. Diaper exfoliative dermatitis

isoleucine, leucine and valine, as well as valine and isoleucine supplementation resulted in prompt resolution. In differential diagnosis we ruled out other conditions such as acrodermatitis entheropathica, candidosis, atopic dermatitis, staphylococcal scalded skin syndrome and toxic epidermal necrolysis.

Recently, formulas enriched with AA that compete with BCAA for transport (e.g., tryptophan, tyrosine, phenylalanine, methionine, threonine etc.) and also help maintaining physiological AA plasma levels and transport into the brain, have been designed for patients with MSUD. They improve growth and adequate nutritional status by providing energy and protein required by patients with growth disorders (5). Moreover, in order to develop nutrition management guidelines for inherited metabolic disorders, Genetic Metabolic Dietitians International (GMDI) and Southeast Regional Newborn Screening and Genetics Collaborative (SERC) used a model that gathers both evidence- and consensus-based guidelines for MSUD, which turned to be the first one to be completed (20).

Still, there is an uknown risk for skin eruptions when the so-called "branched-chain amino acid-free formula" is used. We believe that the list with causes of acrodermatitis enteropathica-like syndrome should include diet restriction of branched-chain amino acids for maple syrup urine disease. Although being more prevalent in populations with high incidence of consanguinity, (incidence rate: 1:200 births), most clinics see very few individuals with MSUD. With such a small patient populations, only multicenter collaboration may provide new data and allow creation of new strategy achievements (20).

Conclusion

The acrodermatitis enteropathica–like syndrome in our patient was due to a iatrogenic amino acid nutritional imbalance. According to available world literature, this is the first report of acrodermatitis enteropathica-like syndrome in a child with maple syrup urine disease (leucinosis) in the Republic of Bulgaria.

Abbreviations

MSUD – maple syrup urine disease
MSUD-2 - nutritional formula for MSUD with iron
AA - amino acid
α KIC - α-ketoisocaproate
BCAA – branched-chain amino acids
AE - acrodermatitis enteropathica
LDH - lactatae dehydrogenase
CPK - creatine phosphokinase
EEG – electroencephalography
BCKD – branched-chain alpha-keto acid dehydrogenase
BCKA - branched-chain α-keto acid
l-car - l-carnitine
GMDI - Genetic Metabolic Dietitians International
SERC - Southeast Regional Newborn Screening and Genetics Collaborative

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Promene na koži u toku nutricione terapije leucinoze – prikaz slučaja

Sažetak

Uvod. Leucinoza ili bolest sa mirisom urina koji podseća na sirup javora (sinonim engl. *maple syrup urine disease* – MSUD) nasledna je aminoacidopatija koju izaziva defekt u metabolizmu amino-kiselina (AA): leucina, izoleucina i valina, kao i njihovih α-ketoacidnih derivata. Kod obolelog sa klasičnom formom MSDU, nastaje encefalopatija i otok moždanog tkiva, kao posledica akumulacije navedenih AA i njima odgovarajućih derivata, α-keto kiselina, naročito leucina i njegovog ketoacidnog derivata, α-ketoizokaproata (α KIC) u serumu. S obzirom da se u najtežoj, klasičnoj formi MSUD bolest ispoljava tokom prvih nedelja života, na rođenju novorođenče odaje utisak zdravog deteta. Bolest karakteriše pojava ketoacidoze, otežana ishrana i napredovanje, somnolencija, ataksija i karakteristični miris mokraće koji zbog sličnosti sa šećerom koji gori, podseća na sirup od javora (engl. *maple syrup*). U nelečenim slučajevima, dete umire sa znacima encefalopatije, progresivne neurodegeneracije i kome. Lečenje akutne metabolijske dekompenzacije kroz restriktivni unos navedenih AA koje pripadaju grupi amino- kiselina sa razgranatim lancem (engl. *branched-chain amino acids* – BCAA), predstavlja stub terapije, ali ishranu otežava mišićna hipotonija, mučnina, infekcija, metabolijske komplikacije, retardacija i otežano gutanje. Kod lečene dece, glavne komplikacije nastaju zbog disbalanasa u esencijalnim AA, otežanog razvoja usled restriktivnog unosa mikroelemenata u uslovima njihove povećane potrebe ili usled povećanih energetskih potreba koje izaziva hronično oboljenje, odnosno inflamacija. Usled smanjenog i nedovoljnog unosa BCAA, kod obolelog novorođenčeta/dojenčeta nastaju promene na koži koje po svojim osobinama odgovaraju promenama enteropatskog akrodermatitisa.

Prikaz slučaja. Četvoromesečna devojčica je hospitalizovana na dečjem odeljenju zbog opšteg lošeg stanja, slabe uhranjenosti i karakterističnog mirisa mokraće. Prvi znaci bolesti su se kod deteta javili tri meseca ranije, u vreme kada je počela ishrana deteta adaptiranim mlekom. Prethodno je devojčica bila lečena u drugoj bolnici gde je zbog teškog stepena anemije primala transfuzije krvi i plazme, ali bez željenog efekta. Na pregledu, telesna težina je iznosila 3 kg a dužina 50 cm, dete je bilo somnolentno, hipotono, lice dizmorfno sa retrognacijom, fontanele su bile napete, dijametar grudnog koša bio je povećan a sračani rad ubrzan. Neurološkim statusom su dominirali: nesposobnost da samostalno drži glavu, nemogućnost viđenja detalja (otežana konvergencija očnih jabučica), nemogućnost samostalnog sedenja, hiperpokretljivost kolenih zglobova i povišeni Ahilovi refleksi.

Rezultati biohemijskih analiza ukazali su na povišene vrednosti serumske laktatne dehidrogenaze (LDH), kreatin fosfokinaze (CPK) i amonijaka (> 145 μmol/l, referalne vrednosti 1–31 μmol/l), metabolijsku acidozu, visok serumski nivo leucina (> 8 000 μmol/l, referalni raspon 2,07–4,57 μmol/l) i valina (> 100 μmol/l, referalni raspon 2–4,8 μmol/l) i tešku anemiju. Ultrazvučni pregled je ukazao na postojanje otoka mozga; elektroencefalografski (EEG) utvrđen je uniformno nizak električni potencijal čija se amplituda nije skoro uopšte razlikovala od kortikalne.

Dijagnoza MSUD je postavljena na osnovu kliničkog, biohemijskog i radijacijskog nalaza.

Lečenje je podrazumevalo korekciju hidro-elektrolitskog disbalansa, restrikciju unosa BCCA upotrebom medicinske hrane sa MSUD-2 formulacijom i simptomatsko lečenje neuroloških komplikacija.

Nekoliko dana posle započinjanja ovog dijeteskog režima MSUD-2 formulacijom koja se zasniva na restrikciji unosa leucina, izoleucina i valina, na koži nastaje makulopapulozni egzantem sa zahvatanjem kože kapilicijuma, lica, trupa i ekstremiteta i eksfolijativni dermatitis perioralne i angenitalne regije, praćeni dijarerom. Dermatološkim pregledom su dominirale erozije, žućkasto prebojene krustozne naslage i lamelozna periorificijelna eksfolijacija koja se širila i na susedne delova ekstremiteta (slike 1–4). Opšte stanje je bilo ozbiljno narušeno, sa znacima letargije, hipotenzije, anemije, dispepsije i neorološkim simptomima. Na osnovu svega navedenog, kod

devojčice je postavljena dijagnoza sekundarnog sindroma nalik na enteropatski akrodermatitis nastao kao posledica nedostatka amino-kiselina leucina i valina. Posle supstitucije BCAA pod laboratorijskom kontrolom (nivo cinka unutar referalnih vrednosti, snižen nivo leucina i valina ispod referalnih vrednosti), nastupilo je promptno povlačenje svih simptoma uključujući i promene na koži, što je potvrdilo našu radnu dijagnozu; za negu kože korišćeni su lokalni antiseptici, emolijensi i lokalni niskopotentni kortikosteroidi. Diskusija. Leucinoza (sinonim *maple syrup urine disease* – MSUD) predstavlja sekundarnu amino-acidopatiju nastalu usled defektne aktivnosti multienzimskog kompleksa mitohondrijske BCAA α-keto kisele dehidrogenaze (BCKD), koja katalizuje dekarboksilaciju BCAA (leucin, izoleucin i valin) do njima odgovarajućih metabolita, α-keto kiselina. Katabolijski put BCAA odvija se u nekoliko etapa: reverzibilna transaminacija, ireverzibilna oksidativna dekarboksilacija i dehidrogenacija. Do kongenitalnih poremećaja može doći, a oni se nasleđuju autozomno recesivnim putem. U MSUD degradacija tri BCCA, leucina, izoleucina i valina biva zaustavljena posle prve etape, transaminacije), te dolazi do nakupljanja BCAA i njihovih α-keto kiselina (BCKA) u biološkim tečnostima. MSUD spada u grupu aminoacidopatija i u grupu organskih acidurija istovremeno, s obzirom na toksične efekte nakupljanja amino-kiselina (AA), naročito leucina i organskih kiselih intermedijernih – keto i hidroksikiselih BCCA metabolita. Akumulacija leucina izaziva neurološke simptome, a izoleucina karakterističan miris urina, po kome je bolest dobila naziv. Pri visokim koncentracijama leucin brzo prolazi hemato-encefalijsku barijeru i u moždanom tkivu izaziva neurotoksične efekte: inhibicija transporta esencijalnih AA preko hemato-encefalijske barijere, npr. tirozina i triptofana zbog čega u mozgu dolazi do smanjenjene sinteze kateholamina, serotonina i proteina. U fiziološkim uslovima, transaminaze vrše konverziju leucina u α-ketoglutarat; ukoliko nastupi nakupljanje ketoacidnog derivata leucina, α-ketoizokaproata (α KIC), nastupa smanjenje glutamata u moždanom tkivu, s obzirom da α KIC povratnim mehanizmom (tzv. dvosmerna transaminazna reakcija) stimuliše sintezu leucina i tom prilikom koristi glutamat. Glutamat ima dve značajne uloge: u stvaranju energije i procesima neurotransmisije. Pretpostavlja se da mehanizmi odgovorni za nastanak neurotoksičnosti u MSUD uključuju sledeće: poremećaj preuzimanja esencijalnih AA u mozgu, nedostatak neurotrasmitera, smanjenje energetskog nivoa, osmotska disregulacija, inhibicija mitohondrijskih enzima i respiratornog lanca. Oboleli od MSUD imaju deficit l-karnitina, supstancije sa antioksidativnim osobinama, čijom se suplementacijom smanjuje oštećenje DNA kod obolelih sa MSUD.

Multienzimski BCKD kompleks katalizuje ireverzibilnu sekundarnu metabolijsku etapu kao multienzimski makromolekul unutar unutrašnje mitohondrijske membrane, sastavljen od tri različite katalizatorske komponente E_1 ($E_{1\alpha}$, $E_{1\beta}$), E_2, E_3, za čije funkcionisanje su potrebni kofaktori tiamin, flavin i dva regulatorna enzima, kinaza i fosfataza. Geni koji kodiraju sintezu subjedinica/komponenti BSKD kompleksa, E1α, E1β, E2, E3, kinaze i fosfataze smešteni su na odgovarajućim hromozomskim lokusima: 19q13.1–13.2; 6q14; 1p31; 7q31–32, 16p11.2 i 4q22.1. MSUD u najvećem broju slučajeva izazvan je mutacijama gena BCKDHA, BCKDHB, i DBT koji kodiraju sintezu E1a, E1b, i E2 subjedinice humanog mitohondrijskog BCKD kompleksa.

MSUD predstavlja redak nasledni poremećaj CNS, koji se javlja u svim etničkim grupama sa incidencijom koja iznosi npr. 1/1/185 000 novoređene dece u Sjedinjenim Američkim Državama ili 1/101 624 novorođenčadi na Tajvanu. Opisano je pet različitih fenotipova koji se međusobno razlikuju po vremenu nastanka, kliničkoj slici i terapijskom odgovoru: klasični, intermedijerni, intermitentni, zavisan od tiamina i sa deficitom E3 subjedinice. Sve navedene fenotipske forme oboljenja karakteriše: poremećena ishrana, povraćanje, slabo, usporeno dobijanje na težini, somnolencija i karakteristični miris urina. Kod nelečene dojenčadi, encefalopatija i pregresivna neurodegeneracija nastaju kao posledice nakupljanja BCAA i njihovih odgovarajućih metabolita BCKA; slučajevi MSUD kod kojih je bolest otkrivena u asimptomatskom stadijumu imaju bolju prognozu od slučajeva koji su imali simptome u trenutku postavljanja dijagnoze. S obzirom da rana detekcija i sprovođenje dijetetskog režima sprečavaju nastajanje komplikacija i omogućuju nesmetan intelektualni razvoj, MSUD je uključena u metabolijski skrining

program za novorođenčad; ipak, ovaj program nije efikasan ukoliko je u pitanju neklasična, npr. intermitentna forma oboljenja, s obzirom da se simptomi tada javljaju između pet meseci i dve godine starosti.
Lečenje se temelji na primeni specifičnog dijetetsko restriktivnog reežima u akutnoj fazi, da bi se kako vreme odmiče, postepeno terapija usmeravala u određenom pravcu u zavisnosti od individualnog stanja pacijenta. Potrebne su prospektivne studije kako bi se optimizirala terapijska strategija zasnovana na životnom riziku svakog pojedinca, putem testiranja efikasnosti adjuvantne terapije antioksidansima ili alfa-ketoglutaratom uz specijalizovani prekurzor/protein restriktivni unos ili supstituciju. Transplantacija jetre se može primeniti u veoma teškim slučajeviam MSUD sa ciljem kupiranja i smanjivanja razika od akutne dekompenzacije, ali rezultati novijih istraživanja ukazuju da transplantacija ne poboljšava koeficijent inteligencije niti smanjuje psihijatrijsku simptomatologiiju.
Paralelno sa simptomima i znacima aminoacidopatije, naročito kod dece sa poremećenim metabolizma BCAA, mogu se razviti promene na koži koje predilekciono zahvataju periorificijsku pelensku regiju i vratne nabore, a po svom izgledu odgovaraju onima koje nastaju u enteropatskom akrodermatitisu. Kliničku trijadu čine dermatitis, dijareja i alopecija; promene na koži smatraju se direktnom posledicom deficita biotina, esencijalnih masnih kiselina i AA. Pored sindroma sličnog enteropatskom akrodermatitisu, u novije vreme predlažu se nazivi *acrodermatitis acidemica* ili *acrodermatitis dysmetabolica.* Tačan mehanizam nastanka lezija na koži nije dovoljno rasvetljen ali se smatra da su BCAA od esencijalnog značaja za normalan rast i diferencijaciju keratinocita. Dijagnoza sindroma sličnog enteropatskom akrodermatitisu sekundarno nastalog u okviru MSUD je u slučaju opisanom u ovom radu postavljena na osnovu sledećeg: klinička slika eksfolijativnog dermatitisa, otežan rast, dijareja, letargija, encefalopatija, dijagnostikovan MSUD, lečena dijetom bez leucina, izoleucina i valina, da bi supsticija izoleucinom rezultirala promptnom rezolucijom svih promena.
U novije vreme, proizvedene su dijetetske formulacije za pacijente sa MSUD obogaćene AA (npr. triptofan, tirozin, fenilalanin, metionin, treonin) koje stupaju u kompeticiju sa BCAA za transport i pospešuju održavanje fiziološkog nivoa AA u plazmi i transport u mozak, čime se obezbeđuje dovoljan unos proteina i dovoljna količina nergije.
I dalje je nepoznat rizik za nastajanje promena na koži kada se u ishrani koriste formule bez BCAA. Predlažemo da se na listu mogućih uzroka sindroma sličnog enteropatskom dermatitisu, upiše i restrikciona dijeta sa BCAA radi lečenja MSUD.
Zaključak. Sindrom sa promenama na koži sličnim enteropatskom akrodermatitisu se kod prikazanog deteta razvio kao posledica jatrogenog nutricionog disbalansa u unosu aminokiselina. Prema nama dostupnoj svetskoj literaturi, ovo bi bio prvi objavljen slučaj koji se javio kod deteta sa leucinozom u Republici Bugarskoj.

Ključne reči

Bolest urina s mirisom javorovog sirupa; Dijetetska terapija; Odojče; Akrodermatitis; Isoleucin + deficijencija; Znaci i simptomi; Ishod terapije; Prikazi slučajeva; Bugarska