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CASE REPORT

Congenital adrenal hyperplasia with maple syrup urine disease: an example of consanguinity impact

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ABSTRACT

Background: Maple syrup urine disease (MSUD) is a rare autosomal recessive metabolically inherited disorder, caused by an abnormal function of the branched-chain α-keto acid dehydrogenase complex in the mitochondria.

Case Presentation: The proband was born after a full-term pregnancy and normal vaginal delivery, with a good Apgar score (8, 9 at 1 and 5 minutes) and the birth weight of 2.5 kg with ambiguous genitalia in the form of phallus-like structure (3 cm), the fusion of labio-scrotal folds and urogenital sinus. The third day after birth, the proband was lethargic and developed hyperkalemia and hyponatremia, which required intravenous fluid therapy and hormonal replacement with hydrocortisone and fludrocortisone. The treatment was based on the positive family history of congenital adrenal hyperplasia in an older male sibling. Laboratory tests, cytogenetic study, tandem mass spectroscopy, and surgery were performed for the affected individual (II-8) using standard procedures. The laboratory and the treatment revealed significant improvements. Follow-up tandem mass spectroscopy results were observed in the normal range. The affected individual was treated with prednisone (2.5 mg bid) and Florinef (Fludrocortisone) (0.1 mg OD). The subject had regular menses, while acne and hirsutism were not observed.

Conclusion: We are reporting the first case of MSUD associated with CAH, 21-hydroxylase deficiency salt-losing type and suggest that glucocorticoids might have an important role in treating MSUD cases.

Keywords: MSUD, 21-hydroxylase deficiency, congenital adrenal hyperplasia.

Introduction

Maple syrup urine disease (MSUD; MIM 248600) is an autosomal recessive metabolic disorder, mostly characterized by the impaired activity of the branched-chain α-keto acid dehydrogenase (BCKAD) complex. The clinical features of MSUD include encephalopathy, developmental and neurological delay, a maple syrup odor to the urine, feeding problems, vomiting, coma, and may cause death. Patients also exhibit elevated levels of urine branch chain keto acids along with increased plasma branched-chain amino acids (BCAAs) include leucine, isoleucine, and valine (1) (Figure 1). MSUD has been reported in almost all ethnic groups with a general incidence of about 1:185,000 live births (2,3). The neonatal onset of MSUD is considered as the classic form, which represents the most severe and most common form among other types of MSUD (4). Here, we report a rare case of classical MSUD associated with classical 21-hydroxylase deficiency. Upon treatment of both conditions, MSUD showed mild presentation.

Case Report

In the present study, the parents were the first cousins and had a consanguineous marriage. Written informed consent was obtained from the patients for publication of this article in compliance with the Helsinki Declaration. Among their offspring, two of the daughters died during

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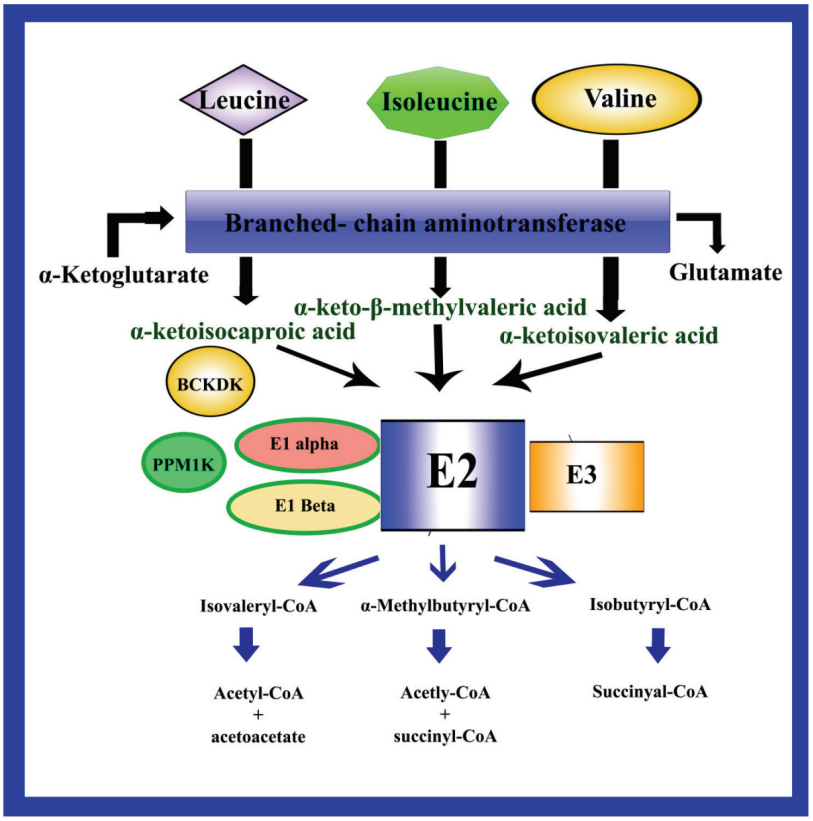

Figure 1. *Schematic representation of the branched-chain amino acid catabolic pathway: BCKAD (branched-chain α-keto acid dehydrogenase) is a multimeric enzyme complex that is composed of multiple subunits of the branched-chain α-keto acid decarboxylase (E1), dihydrolipoamide branched-chain transacylase (E2), and dihydrolipoyl dehydrogenase (E3). E1 subunit shows a heterotetrameric structure consisting of two α subunits (E1α) and two β subunits (E1β).*

the neonatal period (II-1: 11-days old and II-2: 17-days old) with lethargy, poor feeding, and convulsion (most likely classical MSUD). Furthermore, they had two daughters (II-5: 9 years, II-6: 6 years, II-7: 4-years old), two sons (II-3: 13 years, II-5: 9 years) with normal phenotype, and one son (II-4: 11 years) suffering from CAH, 21-OH deficiency (treatment going on, Figure 2). The proband was born after a full-term pregnancy and normal vaginal delivery, with a good Apgar score (8, 9 at 1 and 5 minutes) and a birth weight of 2.5 kg. The infant was found to have ambiguous genitalia in the form of a phallus-like structure (3 cm), the fusion of labio-scrotal folds and urogenital sinus. The third day after birth, the proband was lethargic and developed hyperkalemia (6.9 mmol/l), and hyponatremia (127 mmol/l), which required intravenous fluid therapy and hormonal replacement with hydrocortisone and fludrocortisone. The treatment was based on the positive family history of congenital adrenal hyperplasia in an older male sibling.

Results

Clinical tests for proband found high level of 17-α-OH-progesterone (604 nmol/l) (normal: < 6 nmol/l), testosterone 5.6 ng/ml (normal: 0.1–0.2 ng/ml), and ACTH 1138 ng/l (normal = 5–60 ng/l).The cytogenetic study was carried out using cultured peripheral blood lymphocyte and routine G-banding. The patient revealed 46, XX karyotype. Furthermore, an ultrasound scan confirmed the presence of a uterus and prominent adrenals, which confirmed the diagnosis of classic 21-OH-deficiency. At the age of seven days, her medical condition became worse and she rapidly required assisted ventilation. Ammonia level in her blood increased up to 205 µmol/l (normal: < 100) and had negative septic workup. Metabolic tests such as tandem mass/spectroscopy and urine for organic acids confirmed the classical MSUD with leucine (isoleucine) level of 2635 µm/l (normal: 117–295 µml/l) and blood valine level of 300 µm/L (normal: 56–154 µm/l) (Table 1). Later, she was resuscitated with fluid, treated with carnitine, thiamine, $NaHCO_3$, and MSUD formula, gradually, she was weaned from the ventilator and she became more active with good oral intake, she stayed in the hospital for 1 month. At six months of age, the proband had genital reconstructive surgery that involved vaginoplasty and clitoroplasty. Furthermore, she was restricted to hydrocortisone and fludrocortisone treatments and given a special diet for MSUD.

On regular follow-up, the proband recovered gradually. The family was compliant with MSUD formula at occasional times, they also admit non-compliance when the proband refuses the formula. Follow-up tandem mass spectroscopy scheduled after every 3 months always reported normal. Currently, the proband (II-8) is 18-years old on prednisone (2.5 mg bid) and Florinef (0.1 mg OD) medication. She had an infrequent metabolic crisis, which included mild episodes and no PICU admissions, and she had a normal neurological exam (normal tone, power and reflexes, normal gait, and intact cranial nerves), no MRI brain was done for her as her condition continued to be stable and on Bayley Scales of Infant Development, she was at near the ceiling of 30 months on form boards and pegboards. She had 2-word sentences but very dysarthric speech and very limited in her vocabulary. She can feed herself, dress herself, and toilet but needs some supervision, particularly around hygiene. At this point, she is functioning in the moderately impaired range globally with all skills at 3 years or less. Her growth parameters showed that she was growing well with her weight [17 kg (45 centile), 28.5 kg (64.41 percentile), 42 kg (50.81 centile)] at 4 years, 8 years, and 12 years, respectively, and with her height of (95 cm (0.81 percentile), 114 cm (9 0.11 percentile), 127.5 cm (–3.18 SD)) at 4 years, 8 years, and 12 years, respectively. And her final height is 135 cm (–4.8 SD), she ended short because of precocious puberty (she was growing at normal growth velocity 4–5 cm per year but she entered puberty very early at age 7 years), which could happen in patients with congenital adrenal insufficiency. As the proband has hyperandrogenism, she currently has regular menses, while acne and hirsutism were not observed.

Discussion

MSUD is a rare autosomal recessive metabolic disorder affecting BCAA metabolism. MSUD is classified into four sub-types (a) classic, (b) intermediate, (c) intermittent, and (d) thiamine-responsive types (5). Classic MSUD is the most common and the most severe form of MSUD. Newborns with classic MSUD are typically normal at birth, develop ketonuria within the first 48 hours of life, and show symptoms such as irritability, poor feeding, vomiting, lethargy, and dystonia. Within 4–7 days, neurological abnormalities are also observed including alternating lethargy, irritability, dystonia, apnea, seizures, and signs of cerebral edema such as obtundation or persistent emesis. The time of onset of the disease varies depending on the amount of protein in the feeding regimen. It has also been observed that exclusive breastfeeding may delay the onset to the second week of life. Maple syrup odor usually occurs late, during the crisis stage, and may be difficult to identify in the first few days of life (6). The majority of patient dies within the

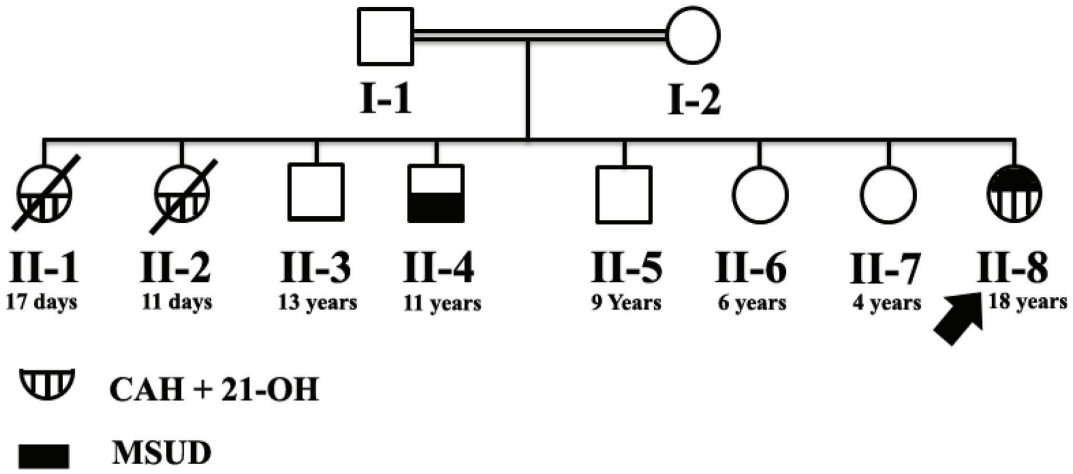

Figure 2. *Pedigree of the family showing autosomal recessive inheritance pattern: circles and squares represent females and males, respectively. Double lines between the symbols show the consanguineous union. White symbols represent the normal members. Slashes represent the deceased members, while the arrow represents the proband.*

Table 1. *Clinical tests performed for the patient.*

Individual	Blood leucine (isoleucine)	Blood valine	Urine organic acid
Patient	2635 µm/l	300 µm/l	• Positive (2 hydroxyisovaleric and isocaproic, leucine and isoleucine)
Normal	117–295 µm/l	56–154 µm/l	• Negative

early months of life from recurrent metabolic crises and neurologic deterioration. Sudden death has been reported previously in several studies with possible classic MSUD (7–9). Surviving patients suffer from severe neurological damage, including intellectual disability, spasticity, or hypotonia and occasionally cortical blindness. However, early diagnosis and timely treatment can greatly improve the outlook for the disorder. MSUD results from an inability to oxidatively decarboxylate the branched-chain α-keto acids (BCKA), which is a single complex enzyme that handles all three BCKA substrates produced from parent amino acids by reversible aminotransferase activity and enters the mitochondria via specific transport protein. BCKD complex is composed of four protein molecules that interact with oxidatively decarboxylate, their keto acids, and the gene for β subunit of E_1 located on chromosome 6P21-2 (10).

The 21-hydroxylase deficiency (21-OHD) is the most common cause of congenital adrenal hyperplasia (CAH), causing an autosomal recessive disorder involving an impaired synthesis of cortisol from cholesterol by the adrenal cortex. The 21-OHD CAH causes excessive adrenal androgen biosynthesis, which results in virilization and salt wasting. The classic 21-OHD is successfully treated with glucocorticoid replacement therapy, which needs to be increased during periods of stress and salt wasting usually requires fludrocortisone therapy. In the present study, first, we investigated the possible associations between CAH and MSUD. In one of the affected individuals (II-4), the 21-hydroxylase deficiency was observed without MSUD, while the other two affected individuals (II-1 and II-2) had MSUD without CAH and died few days after birth. Second, we determined whether hydrocortisone has a role in the treatment of MSUD, as our patient (II-8) showed excellent progress with no metabolic decompensation; the family was compliant with the treatment but still she did well during acute illnesses comparing her with similar cases, also she never required ICU admissions except at diagnosis and also she had no neurological damage. It was well known that the glucocorticoid increases gluconeogenesis by mobilizing amino acids and other substrates from plasma/muscle protein and adipose tissue and plasma lipids, so we suggest that glucocorticoids might help in clearing amino acids from the plasma. Consanguinity describes couples who share at least one common ancestor and their offspring has an increased chance of getting a genetic disorder due to autosomal recessive gene mutations, inherited from a common ancestor. This also results in patients having two or even three disease-causing mutations in different genes responsible for the clinical features of the patient. Similarly, the data from the center for Arab Genomic Studies (CAGS) indicate that 68% of the disorders follow an autosomal recessive inheritance pattern, corresponding to more than 1000 disorders (http://www.cags.org.ae/).

Conclusion

In conclusion, we are reporting the first case of MSUD associated with CAH, 21-hydroxylase deficiency salt-losing type. We regard this rare combination as a coincidental occurrence, and glucocorticoids might likely have an important role in treating MSUD cases. Also, the authors suggest advanced molecular and genetic tests including sequencing of previously reported genes for MSUD (BCKDHA, BCKDHB, DBT, and DLD) to further highlight and understand the pathogenesis involved.

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Declaration of conflicting interests
The authors declare that there are no conflicts of interest

Ethical approval
The study was approved by the research center at King Fahad medical city (IRB registration number H-01-R-012).

Consent for publication
Informed consent was obtained from the parents.

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