CASE PRESENTATION

Maple Syrup Urine Disease in Bahrain

By Akbar Mohsin Mohammad* and
A. Hadi K. Ebrahim**

ABSTRACT :

Two siblings with maple syrup urine disease (MSUD) are described here. The first patients was diagnosed rather late and second patient in the neoborn period. Both had signs of severe mental subnormality and cortical damage. They manifested with peculiar odour in the urine. The diagnosis of the disease was confirmed by plasma and urine chromatography. The two patients succumbed to the disease despite introduction of a special formula used in the treatment of this illness.

Maple syrup urine disease (MSUD) is an inborn error of protein metabolism. It was first described by Menkes et al. in 1954[1]. It is due to a defect in the metabolism of the branched-chain aminoacids leucine, isoleucine and valine. Although it is generally accepted that the disease is inherited as an autosomal-recessive trait, the inheritance by a mutant gene has been described in many races and ethnic groups, including the Negro and the Japanese[2,3]. MSUD is characterised by manifesting early in infancy with neurological signs and an almost pathognomonic urine smell, described as sweet, burned sugar and maple-syrup like. The disease can be diagnosed antenatally by enzymatic assay of amniotic fluid[4,5]. Plasma and urinary aminoacid chromatography are used to confirm the diagnosis of the disease postnatally where leucine, isoleucine and valine are abnormally elevated[6].

The basic defect of the disease is due to inability to oxidatively decarboxylase the branched-chain aminoacids arising from leucine, isoleucine and valine[7]. This results in an accumulation of these aminoacids and their ketoacids in the blood which are excreted excessively in the urine, hence MSUD is also known as "branched-chain Ketonuria"[6]. The high level of these aminoacids and their ketoacids in the blood causes the neurological insult. Post-mortem studies have revealed changes in the white matter of the brain and included a deficiency of myelinization, spongy changes and decrease in the number of oligodendroglia. The ultrastructural changes however, remained speculative[8]. In addition to the classical form of MSUD, there are three variants [9,10], each has a deficiency of a ketoacid and different clinical feature. There is also a fifth type, a thiamine (Vit. B_1) responsive[11].

*Chairman, Paediatric Dept.,
Salmaniya Medical Centre,
Asst. Professor,
College of Med. & Medical Sciences,
Arab Gulf University,
State of Bahrain.

**Chief Resident,
Paediatric Dept,
Salmaniya Medical Centre,
State of Bahrain.

To date, MSUD is not reported in Bahrain or in the Arabian Gulf region. In this paper, we present our experience with two siblings with this disease in a Bahraini family.

CASE No. 1

M.A.A.H. a 13 week old male infant was admitted to Salmaniya Medical Centre for excessive crying, refusal of feeds and vomiting since the second week of life. There also was history of excessive crying on micturition that started in the second month of life. A few days prior to admission the parents noticed that there was a peculiar smell to his urine.

The baby was the product of an uneventful term pregnancy and normal delivery on 19th Dec. 1979. He was the first baby born to a healthy Bahraini couple who are first cousins. There was no family history of a similar condition, mental retardation, cerebral palsy or convulsive disorders. There were no immediate neonatal problems. He was on breast feeding initially and later changed to a proprietory milk (Similac). Social smile was not noticed by the parents. Immunization was not given.

On examination, the baby looked fairly nourished but was non-communicative, pale, crying persistently with a moaning tone. His weight was 4.3 kgm. (25th centile), length was 57 cm. (25th centile) and head circumference was 36.5 cm (below 10th centile). Anterior fontanelle was open. Vision and hearing could not be asessed. Muscle tone was increased all over the body and his deep tendon jerks were normal. He kept his arms extended and there was a flexion of the hands and fingers. The rest of the examination including external genitalia was normal. His urine smelled sweet, had a malt like odour, later simulated to maple syrup. Provisional diagnosis of maple syrup urine disease was made on clinical grounds and because of the unavailability of facilities for aminoacid chemotography, the baby was sent Al-Sabah Hospital in Kuwait for further evaluation.

LAB. TEST AND INVESTIGATIONS

Serum aminoacid chromatography (see table) Urine aminoacid chromatography*: generalised aminoaciduria with marked elevation of leucine, isoleucine and valine.

Serum aminoacid chromatography*

Serum aminoacid chromatography (mmol/L)		Maximum normal limit (mmol/L)
Aminoacid	Result	
Leucine	3719	307
Isoleucine	459	105
Valine	711	230

* Test performed at the Children's Hospital, Temple Street, Dublin, Ireland.

Other laboratory studies including blood sugar, serum electrolyte were normal. E.E.G. showed findings consistent with irritable brain cortex.

COURSE OF ILLNESS

The baby was put on maple syrup urine disease special formula (MSUD Aid, a product of Mead Johnson & Co.) and thiamine (Vit. B_1) 25 mgm once a day orally. The formula was tolerated well and urine smell reverted to normal. However, the neurological status persisted and the baby expired at the age of 18 weeks at home.

CASE 2

H.A.A.H. a male infant born normally at term after uneventful pregnancy. He is the third child in his family, the first is M.A.A.H. (Case 1). The second is a male, 5½ years old well and alive. At birth he had perinatal asphyxia with Apgar of 2 and 6 at 1 min. and 5 min. respectively. This needed resuscitation by intubation, positive pressure ventilation and intravenous 25% dextrose and alkali. At birth, weight was 3850 gm (75th centile). Head circumference was 33 cm (10th centile) and his length was 49 cm (25th centile). The infant was put on proprietory formula, (Similac) and was doing well until the 6th postnatal day when he was noticed to have frequent abnormal movements in the form of extension and abduction of the upper limbs along with opisthotonos posturing and he became hypoactive with a staring look in his eyes. Moro's reflex was hyperactive; sucking reflex however, was normal. Anterior fontanelle was open. His eyes were not

fixing to the light. Hearing could not be assessed. The rest of the systemic examination was normal.

The urine smelled sweet. Based on the history of his sibling and clinical features, the baby was managed as a case of maple syrup urine disease with hypertonic glucose and parentrovite. He also received thiamine (Vit. B_1) 25mgm I.M. daily and phenobarbitone. At this time Similac formula was stopped pending the MSUD Aid formula which was administered on 19th postnatal day. The baby developed skin lesions as maculopapular initially and later the skin became denuded and excoriated. These lesions were first noticed at the perianal and periorbital regions then spread to the neck, trunk and upper part of extremities and were complicated by pustule formation which grew Pseudomonas aeruginosa on culture.

LAB. STUDIES

Urinary aminoacid chromatography was normal, serum aminoacid chromatography was abnormal (fractionation was not performed). Urine ferric chloride test was strongly positive. Other tests including blood sugar and electrolyte were normal.

COURSE OF ILLNESS :

The condition worsened at three weeks of age; he lost 670 gms and developed focal convulsions and primitive reflexes disappeared. The head circumference increased to 35 cms. Urine smell remained as before. The condition deteriorated and the baby expired at the age of 37 days.

The parents were counselled about the disease after the diagnosis of both first and second cases. They were also given the option for termination of pregnancy if in the future it showed abnormal findings on amniocentesis consistent with MSUD in the unborn foetus. However, they disagreed and elected to take the chance.

DISCUSSION

Neurological signs and symptoms associated with elevation of branched-chain aminoacids in the blood and urine confirm the diagnosis of maple syrup urine disease in the proband (Case−1); however, the diagnosis was made late and introduction of maple syrup urine disease aid (MSUD Aid: a product of Mead Johnson & Co.) a special formula that contains no leucine, isoleucine or valine, did not change the clinical status. MSUD formula is considered to be the ideal formula in the management of maple syrup urine disease.[12] Unfortunately plasma aminoacid chromatography is not available at Salmaniya Medical Centre to assist in monitoring the elevated branched-chain aminoacids after introducing this formula[13,14].

In Case 2, the diagnosis was easy on clinical grounds, peculiar urine smell and family history. Serum aminoacid chromatography was abnormal, but inadvertantly fractionation was not carried out to show precisely the elevated aminoacids. Urinary aminoacids chromatography (at 3 days of life) was reported normal; the reason for this normal result is due to early testing[9]. The level might not be sufficiently high prior to the end of the first week.

Three factors contributed to refractoriness to MSUD Aid formula. Firstly, the late introduction of this formula (19th postnatal day), a fact strongly stressed upon in the dietotherapy[9]. Secondly, lack of facilities for monitoring serum level of leucine, isoleucine and valine, also an important principle for manipulating the dietary requirement [13,14]. Thirdly, the presence of skin infection would easily disturb the patients biochemical equilibrium and increase these three aminoacids in the blood[12,15]. Administration of thiamine (Vit. B_1) daily to both patients, in the hope of activating the carboxylation failed to alter the clinical picture of the disease, this excludes one variant, a thiamine-responsive MSUD.[11] The normal blood sugar (checked once) in each patient does not rule out hypoglycaemic episodes reported by others[16,17,18,19].

In the second patient peculiar skin lesions were seen, these resemble that of acrodermatitis enteropathica and are due to the alteration in leucine to isoleucine ratio. The latter was also observed by Marshall JR et al. who reported the disappearance of these rashes by administration of isoleucine diet[14].

In conclusion, we must stress the existence of this rare disease in this part of the world which should be suspected in neonates with sweetish, malt like odour to their urine. Dietary principles are simple, but dietary management of these infants especially in the neonatal period is extremely difficult. In case of

positive family history our main aim should be directed towards prevention of the disease by genetic counselling and antenatal diagnosis by amniocentesis and termination of the pregnancy, if the unborn foetus is affected. For optimal results to be achieved it is mandatory to manage such cases in a centre where the expertise and facilities for quick and frequent monitoring of plasma aminoacids are available.

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