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Mild variant of maple syrup urine disease

By

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The case of a three-year-old boy with mental retardation, moderate muscular hypotony and speech delay is presented. The mild form of maple syrup urine disease was suspected at the first blood screening test by means of ion-exchange thin-layer chromatography. The diagnosis was confirmed by quantitative serum amino acid analysis and protein loading. On a low protein (2 g/kg body weight) diet completed with leucine–isoleucine–valine free formula prompt and lasting normalization of the serum amino acid level ensued with steady improvement of the clinical and neurological status.

Since the first report of maple syrup urine disease (MSUD) in 1954 [10] several papers were concerned with the recognition, biochemical and genetic background, treatment and prognosis of this inborn error of amino acid metabolism.

According to the latest surveys its incidence is about 1 : 2—500 000 [12, 16]. Since the world-wide organization of routine screening procedures for detecting the various inborn errors of amino acid metabolism, much knowledge has accumulated concerning the nature and biochemical differences of the different aminoacidopathies, and it was discovered that MSUD has four different forms. These are,

1. classical form
   complete lack of branched chain keto acid decarboxylase activity;
2. intermittent form
   the enzyme activity is 5—15% of normal and manifests in episodes during intercurrent diseases;
3. mild form
   the enzyme activity is below 50% of the normal;
4. thiamine responsive form
   high doses of thiamine are sufficient to control the serum amino acid levels.

In the present paper we shall report a case of the mild variant of MSUD in which the changing pattern of the serum amino acid level has led to the correct diagnosis.

REPORT OF A CASE

A 3-year-old boy was referred to genetic counselling in order to ascertain the cause of somato-mental retardation. The child had been born from the second pregnancy of healthy non-consanguineous 29 and 23

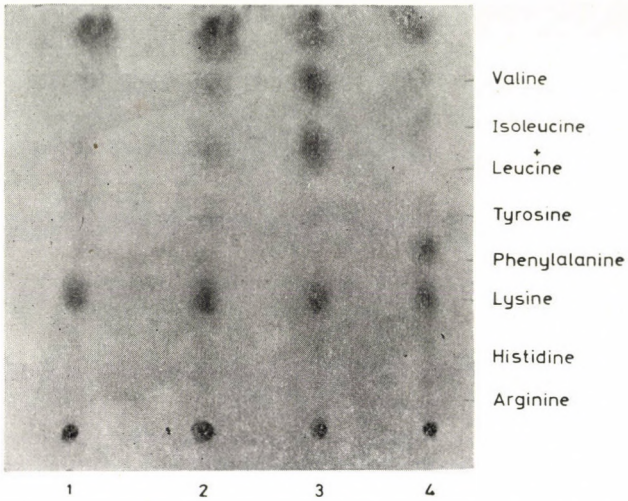

FIG. 1. Thin-layer ion-exchange chromatographic screening test for aminoacidaemias, on 10 × 10 cm IONEX 25 SA chromatoplate: No. 1. normal serum; 2. normal serum; 3. serum of patient with MSUD: pathologically increased level of valine and isoleucine + leucine; 4. serum of a patient with PKU: pathologically increased level of phenylalanine

years old parents. His only brother is apparently healthy.

After uneventful pregnancy a mature baby had been delivered with a birthweight of 3000 g. In the first week of life the baby was admitted to a neonatal ward on account of failure to thrive, apnoeic and cyanotic spells. X-rays had revealed aspiration pneumonia and RDS. A Robin anomalad has been supposed to be responsible for the feeding difficulties. After a couple of weeks of tube feeding and treatment with alkali-glucose infusions the infant had slowly recovered but at discharge his bodyweight was only slightly over the birthweight. Except a bilateral inguinal hernia and strange posture of the forearms, no other pathological signs had been observed. A Guthrie test had not been performed.

The child's somatic and mental development was delayed. He had begun to walk at 2 years of age. He does not speak, but hears well and is house-trained. At 2 years of age bilateral herniotomy and adenotomy were performed without complications. Convulsions or other neurological disorders or acidotic attacks had never occurred. His appetite was always poor and the parents never observed any strange smell of the urine.

Clinical findings and laboratory data. A routine blood sample was drawn for aminoacidopathy screening. Thin-layer ion-exchange chromatography [4, 8] showed a well-distinguishable spot in the region of valine and leucine (Fig. 1), and the child was admitted for clinical and biochemical evaluation. He was then three years and two months old, with fair complexion, blonde hair and eyelashes and a gracile constitution. His body weight was 11.7 kg, height 89 cm (both values below the third percentile), head circumference 48 cm (Fig. 2).

He had moderate general muscular hypotony which was particularly remarkable in the facial region, manifesting itself with blepharophimosis and poor mimicking. The child did not speak, although his hearing was adequate, he obeyed simple calls. Audiological examination revealed no organic hearing loss. Ophthalmological

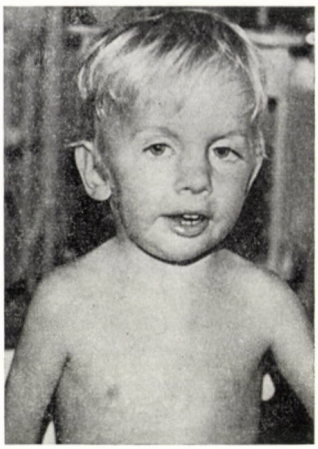

FIG. 2. Three years old mentally retarded boy with mild variant of MSUD

examination showed marked hypermetropy and astigmatism, which was corrected later with 6—7 Ds eye-glasses. No other internal or neurological disorder could be detected, except the strange posture of the hands which was supposed to be the consequence of the muscular hypotony.

Routine laboratory tests showed normal values.

Quantitative serum amino acid analyses were carried out by Beckman Unichrome Amino-Acid Analyser and the values were expressed in μmoles/litre.

Table I shows the complete serum amino acid pattern on admission and 3 days later after the ingestion of 200 ml cow's milk, in comparison with normal values [9]. The elevated levels of valine, leucine and isoleucine were remarkable.

In order to establish the type of branched chain amino acid disorder, after 3 weeks of low-protein diet and 12 hours fasting a protein load was performed with 3 g/kg protein. Results are shown in Table II. The initial values for all three branched chain amino acids were in the normal range and the increase following the protein load was moderately above the upper limit of normal. Subsequently, the level of the branched chain amino acids persisted in this range, failing to return to the initial level, whereas no marked change occurred in the pattern of the other amino acids.

A low-protein diet (2 g/kg protein) completed with valine–leucine–isoleucine free formula (Maizena) was introduced immediately after the first result of serum amino-acid analysis had become known. It had a striking effect on the neurological status. The child's behaviour, the muscular hypotony and his speech showed a slow but steady improvement. He became more alert and the most obvious sign was the improvement of his appetite. After six weeks of diet he gained 1.5 kg. The former unsuccessful logopaedic attempts were promising and the child soon learned to speak a few simple words.

DISCUSSION

The biochemical disturbances leading to the full clinical picture of MSUD are well-known. The main enzymatic defect is a deficient branched-chain keto acid decarboxylase activity, which can be demonstrated in the leukocytes and fibroblasts of patients [2, 3].

The consequence is a highly elevated plasma level of the branched chain amino acids valine, leucine and isoleucine, and the elevated urinary excretion of these substances and their metabolites. The latter are responsible for the characteristic sweet maple syrup odour.

In the classical form the clinical symptoms are present in the early newborn period. The outcome of undetected and therefore untreated cases is fatal [10, 13].

The improvement of diagnostic methods and the spread of knowledge in the field of amino acid disorders led to the discovery of several forms of MSUD. In a variant the accumulation of keto acids occurs intermittently under the effect of febrile diseases. These attacks are usually accompanied with severe acidosis and coma [1, 6, 17].

In a third variant the elevation of branched chain amino acids in the serum is moderate but constant. In spite of this it involves no serious neurological damage [7, 11, 14].

A fourth variant [15] is the thiamine responsive form. This variant resembles in many of its aspects the third one, with the exception that thiamine in high doses is effective in maintaining the control of the serum amino,acid level.

The present case resembles the third MSUD variant. In this form of the condition a moderate but consequently elevated valine, leucine and isoleucine level could be demonstrated [7, 13]. In our patient the initial values for the serum valine, leucine and isoleucine level were threefold of the normal (Table I). On three weeks protein restriction the level returned to almost normal. A challenge with 3 g/kg protein caused a moderate but constant increase in the level of these three amino acids and the elevated level persisted well beyond 24 hours (Table II). As it is seen in Fig. 3, compared to the healthy control, the protein load did not cause any significant change in the level of the other amino acids. It was remarkable that the 2,4-dinitrophenylhydrazine test in the urine was always negative.

The said changes were quite distinct if the quantities of the branched chain amino acids (valine, leucine, isoleucine) as well as of the basic ones (lysine, histidine, arginine) were added and the values expressed in percentage of the initial values. In MSUD (Fig. 3, curve No. 1) the rise of branched chain amino acids after 24 hours was more than 200%, compared to that of the basic amino acids (curve No. 3). In a healthy child (curves Nos 2 and 4) the flat curves point to a normal enzymatic and metabolic activity. This fact is interpreted as an indirect sign of diminished branched chain keto acid decarboxylase activity, supporting the diagnosis of the mild form of MSUD in our patient.

In the literature available, only three cases of the mild variant of MSUD have been reported [5, 7, 13]. Comparing to these the serum amino acid pattern of our patient (Table III), it is noteworthy that in this case the level of branched chain amino acids

TABLE I

Serum amino acid pattern on admission and after ingestion of 200 ml cow's milk
All values expressed in μmoles/litre

	On admission	After ingestion of 200 ml milk	Normal values [9]
Lysine	227	161	162 ± 23.2
Histidine	98	101	73.9 ± 17.1
Arginine	126	66	85.3 ± 18.5
Serine	202	158	147 ± 34.9
Proline	399	245	215 ± 69.7
Glycine	310	152	253 ± 70.8
Alanine	325	289	365 ± 103.1
Valine	486	571	211 ± 34.8
Isoleucine	149	178	47.1 ± 18
Leucine	229	267	106 ± 19.1
Tyrosine	105	83	60.9 ± 13.3
Phenylalanine	83	80	51.1 ± 9.5
Methionine	40	40	16.7 ± 4.2

TABLE II

Serum amino acid pattern after 5 weeks protein restriction, 12 hours fasting, and after 3 g/kg protein loading

	Serum amino acid levels at hours			
	0	2	4	24
Lysine	120	228	177	124
Histidine	67	115	108	88
Arginine	59	93	104	83
Serine	133	143	166	142
Glutamic acid	89	55	89	86
Glycine	261	240	226	170
Alanine	250	288	236	164
Valine	89	101	160	200
Isoleucine	41	60	96	91
Leucine	56	93	128	124
Methionine	20	33	34	17
Tyrosine	29	68	77	56
Phenylalanine	30	65	72	62

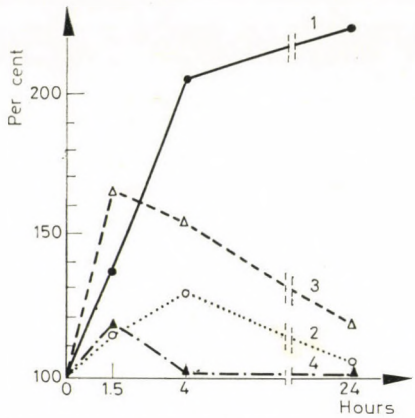

FIG. 3. Serum amino acid pattern after 3 g/kg protein load in MSUD and healthy control. The changing pattern of all branched chain as well as basic amino acids is expressed in per cents of the fasting levels. Curve 1. branched chain amino acids in MSUD; 2. branched chain amino acids in control; 3. basic amino acids in MSUD; 4. basic amino acids in control

TABLE III

Branched chain amino acids in serum (μmoles/l) in four cases of mild variant of MSUD

	Schulman et al. [13]	Fischer, Gerritsen [5]	Kodama et al. [7]	Present case	Normal values [9]
Leucine	1930	723	1988	229	106.0 ± 19.1
Isoleucine	630	287	867	149	47.1 ± 18
Valine	1040	776	914	486	211.5 ± 34.8

was considerably lower, although still distinctly higher than the normal values. This finding may explain the moderate mental retardation as well as the lack of the characteristic sweet odour of the urine. This is one of the reasons why the mild form of MSUD is easily overlooked. Only a reliable serum amino acid analysis combined with appropriate loading tests ensures the correct diagnosis and consequently the adequate therapy.

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REFERENCES

1. DANCIS, J., HUTZLER, J., ROKKONES, T.: Intermittent branched-chain ketonuria. Variant of maple syrup urine disease. New Engl. J. Med. **276**, 84 (1967).
2. DANCIS, J., HUTZLER, J., SYNDERMAN, S. E., COX, R. P.: Enzyme activity in classical and variant forms of maple syrup urine disease. J. Pediat. **81**, 312 (1972).
3. DANCIS, J., HUTZLER, J., COX, R. P.: Maple syrup urine disease: branched chain keto acid decarboxylation in fibroblasts as measured with amino acids and keto acids. Amer. J. hum. Genet. **29**, 272 (1977).
4. DÉVÉNYI, T., BÁTI, J., KOVÁCS, J., KISS, P.: Thin-layer ion-exchange chromatographic screening test for

aminoacidaemias in blood samples dried on filter paper. Acta biochim. biophys. Acad. Sci. hung. **7**, 237 (1972).
5. Fischer, M. H., Gerritsen, T.: Biochemical studies on a variant of branched chain ketoaciduria in a 19-year-old female. Pediatrics **48**, 798 (1971).
6. Goedde, H. W., Langenbeck, V., Brackertz, D., Keller, W., Rokkones, T., Halvorsen, S., Kiil, R., Merton, B.: Clinical and biochemical aspects of intermittent branched-chain ketoaciduria. Report of two Scandinavian families. Acta paediat. scand. **59**, 83 (1970).
7. Kodama, S., Seki, A., Hanabusa, M., Morisita, Y., Sakurai, T., Matsuo, T.: Mild variant of maple syrup urine disease. Europ. J. Pediat. **124**, 31 (1976).
8. Kovács, J.: Ion-exchange thin layer chromatographic screening test for phenylketonuria and other aminoacidaemias. Acta paediat. Acad. Sci. hung. **14**, 165 (1973).
9. Liappis, N., Jäkel, A.: Über die freien Aminosäuren im Serum gesunder Kinder. Mschr. Kinderheilk. **122**, 6 (1974).
10. Menkes, J. H., Hurst, P. L., Craig, J. M.: A new syndrome: progressive familial infantile cerebral dysfunction associated with an unusual urinary substance. Pediatrics **14**, 462 (1954).
11. Miller, H., Bickel, H., Feist, D., Lutz, P.: Ahornsyrupkrankheit mit intermittierendem relativ gutartigem Verlauf. Dtsch. med. Wschr. **96**, 1552 (1971).
12. Rüter-Schmied, E.: Ergebnisse des europäischen Screening-Programmes auf hereditäre Stoffwechselstörungen. Mschr. Kinderheilk. **121**, 205 (1973).
13. Scheibenreiter, S., Thalhammer, O.: Ahornsyrupkrankheit (MSUD). Zwei Jahre erfolgreiche Behandlung eines früherkannten Falles. Mschr. Kinderheilk. **121**, 163 (1973).
14. Schulman, J. D., Lustberg, T. J., Kennedy, J. L., Museles, M., Seegmiller, J. E.: A new variant of maple syrup urine disease (branched chain ketoaciduria). Amer. J. Med. **49**, 118 (1970).
15. Scriver, C. R., Mackenzie, S., Clow, C. L., Delvin, E.: Thiamine responsive maple-syrup-urine disease. Lancet **1**, 310 (1971).
16. Thalhammer, O.: Frequency of inborn errors of metabolism, especially PKU, in some representative newborn screening centers around the world. A collaborative study. Humangenetik **30**, 273, (1975).
17. Valnan, H. B., Patrick, A. D., Seakins, J. W. T., Platt, J. W., Gompertz, D.: Family with intermittent maple syrup urine disease. Arch. Dis. Childh. **48**, 225 (1973).

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