"MAPLE SYRUP URINE DISEASE"

AN INBORN ERROR OF THE METABOLISM OF VALINE, LEUCINE, AND ISOLEUCINE ASSOCIATED WITH GROSS MENTAL DEFICIENCY

BY

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The following case of maple syrup urine disease is the first one to be recorded in this country in this century. Only two definite cases have been reported in the United States.

Case Report

A girl aged 4 months with severe mental deficiency was admitted to the Hospital for Sick Children. She is the first child of healthy non-consanguineous parents, with no family history of mental deficiency. Her condition at birth appeared normal, and breast-feeding was started without difficulty. When 1 week old she stopped sucking and had to be tube-fed. She made slow progress from this time, remaining in hospital for the first three months of life because of feeding difficulty and failure to thrive. At 4 months she was noticed to be jerking her limbs and occasionally to become breathless and cyanosed.

On examination she was a fair-haired, blue-eyed infant weighing 9 lb. 10 oz. (4,365 g.). She was anaemic (haemoglobin 9.47 g. per 100 ml.) and had a mild bilateral seborrhoeic blepharitis. The head configuration was within normal limits and the head circumference 16 in. (40 cm.). There was no control of head movements, although she occasionally attempted to follow a bright light with her eyes. The limbs were thin, with a slight increase of tone, and brisk tendon reflexes equal on both sides. The optic disks were pale. A firm liver edge was palpable one to two fingerbreadths below the costal margin.

Lumbar puncture produced a normal cerebrospinal fluid under normal pressure. The E.E.G. showed an abnormal record with a severe generalized abnormality with multifocal discharges of a kind often seen in those metabolic disorders which are accompanied by seizures. The I.Q. on the Griffiths scale was 55.

The urine was examined to exclude phenylketonuria. The urine was free from protein, and gave a heavy precipitate with 2:4-dinitrophenylhydrazine, but an equivocal reaction with ferric chloride. On smelling a fresh specimen the similarity to maple syrup was detected. On two-dimensional paper chromatography of the urine, valine, leucine, and isoleucine were found in very large amounts. These amino-acids were also present in the blood, C.S.F., and saliva in great excess.

Keto-acids were present in the urine in very large amounts, as were non-keto-acids with the properties of α-hydroxy-acids. The "maple syrup" smell is due mostly to the α-hydroxy-acids, though modified by the keto-acids.

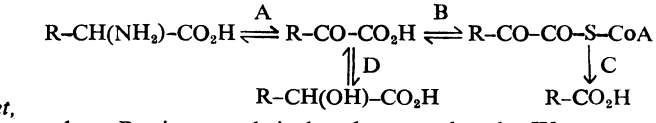
Two-dimensional paper chromatography of the urine for indole derivatives (Jepson, 1955) revealed an excessive excretion of indolylacetic and indolyllactic acid, the other indole derivatives being normal. Abnormal phenolic substances were not detected.

The blood true sugar concentration after a feed was only 60 mg. per 100 ml., non-sugar reducing substances being equivalent to 7 mg. of glucose per 100 ml. Fasting blood apparent sugar concentration (Folin–Wu) was 52 mg. per 100 ml.

Discussion

We suggest that this child is suffering from an inborn error of the metabolism of valine, leucine, and isoleucine, similar in some ways to phenylketonuria.

Coon, Robinson, and Bachhawat (1955) have shown that these three aliphatic amino-acids are metabolized as follows: (A, B, C)



where R = isopropyl, isobutyl, or sec-butyl. We suggest that stage B or stage C is blocked in this child (very possibly through the absence of an enzyme), that there is a build-up of keto-acid and hence amino-acid, and that some keto-acid is reduced by the (abnormal) path D. The three amino-acids with their keto-acids and hydroxy-acids are therefore excreted in large amount.

Unlike what occurs in phenylketonuria, the keto-acid is the normal major metabolite and builds up through the failure of the second link in the metabolic chain. We suggest that, as in phenylketonuria, the abnormal metabolites and/or amino-acid concentrations cause the cerebral dysfunction; they also interfere with tryptophan metabolism, thus causing the observed excretion of indolylacetic and indolyllactic acids exactly as in phenylketonuria.

Menkes, Hurst, and Craig (1954) reported four cases, in one family, of severe progressive cerebral dysfunction, associated with the presence in the urine of an organic acid smelling like maple syrup. Westall, Dancis, and Miller (1957) reported one case of "maple syrup urine disease" with raised blood and urine concentrations of valine, leucine, and isoleucine. Our case seems very similar to this one, and it is probable that the explanation advanced here will cover both cases. The similarity to the four cases of Menkes *et al.* (1954) is perhaps less close, since they found in their cases a decreased excretion of α-amino-nitrogen. Their cases had proteinuria, and the outcome was death within a few days or weeks of birth. Smith and Strang (1958) described the case of a child with a disease which, if not the same as in our case, was very similar.

The hypoglycaemia is not severe enough to account for the mental state. At the moment no explanation can be given for the occurrence of hypoglycaemia in this case, though it is tempting to try to link it to the leucine-precipitated hypoglycaemia described by Cochrane, Payne, Simpkiss, and Woolf (1956).

A diet low in valine, leucine, and isoleucine might help this child, just as a low phenylalanine diet causes improvement in some cases of phenylketonuria (Woolf, Griffiths, Moncrieff, Coates, and Dillistone, 1958). However, there is no economically practicable way of preparing such a diet in the amount needed for a lifetime. In any case, the degree of mental damage is such as to make it unlikely that the child's mental condition would be greatly improved. Nevertheless, a short trial of such a diet is proceeding in order to see whether the abnormal amino-acids and metabolites vanish from the urine. The prognosis in this condition may be worse than in phenylketonuria, the patient of Westall *et al.* dying at 20 months and other children with what is probably the same or a similar condition also dying young (Menkes *et al.*, 1954; Smith and Strang, 1958).

The resemblance to phenylketonuria is so marked that a similar genetic mechanism suggests itself, especially as the four cases of Menkes *et al.* were in one family. This aspect is being pursued.

After this paper was written we heard that Cusworth, Dancis, Menkes, Miller, and Westall had independently found keto-acids in the urine of their cases and identified them as the α-keto-acids corresponding to valine, leucine, and isoleucine (Westall, private communication). A possible explanation of the presence of keto- and hydroxy-acids in the urine in their cases, while the urinary concentrations of the parent amino-acids were not always raised, would be that the blood and tissue keto-acid concentration has to build up to a critical level before enough amino-acid is formed by transamination to exceed the renal threshold. The reverse situation holds in phenylketonuria, where the blood phenylalanine concentration has to build up to a critical level before phenylpyruvic acid appears in the urine. The alternative explanation, that the metabolic error is becoming more severe and more extensive with time, seems unlikely; it would suggest an acquired rather than an inborn error of metabolism.

This condition could easily be mistaken for phenylketonuria. Clinically they are very similar, they give exactly similar reactions with 2:4-dinitrophenylhydrazine reagent and identical urinary indole patterns. However, the ferric chloride reaction, while somewhat similar, is not identical in the two conditions. The smell of the urine is easily missed, and can be masked by preservatives; in this case the smell was not noticed until we deliberately examined the urine for it, having been led by the chemical reactions to consider "maple syrup urine disease" as a possible diagnosis. Acidification with dilute sulphuric acid in the cold enhances the smell considerably; it may be worth investigating, in this way, every case diagnosed as having phenylketonuria. Of course, amino-acid chromatography can differentiate the conditions conclusively.

"Maple syrup urine disease" is not a satisfactory name for the condition. Although one could use for example "leucic aciduria," there is no logical reason for picking one rather than another substance in the urine to provide a name for the disease. If it is confirmed that the metabolic defect suggested above is the cause of the condition, "carboxylase deficiency disease" might best meet the need.

Further work on the identification of the abnormal substances present in the body fluids and on determining the site and extent of the metabolic defect is continuing.

Summary

A grossly mentally retarded infant was found to excrete large amounts of keto-acids; these were identified as the α-keto-acids corresponding to valine, leucine, and isoleucine. The free amino-acids were also found in great excess in the urine, blood, and C.S.F. The urine had a characteristic smell resembling maple syrup; this seems to be largely due to the α-hydroxy-acids corresponding to valine, leucine, and isoleucine. It seems probable that this is an inborn error of the metabolism of the three amino-acids with a block at the oxidative decarboxylation stage. Tryptophan metabolism is also interfered with, as in phenylketonuria. Differentiation of this condition from phenylketonuria needs special care.

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Menkes, Hurst, and Craig (1954) described a familial syndrome characterized by early onset of central nervous system symptoms, a maple syrup odour to the urine, and a fatal outcome. We have more recently studied a similar case, that of a child, in which the characteristic odour of maple syrup was first noted in the urine when he was 4 months old.

The patient was obviously mentally retarded and died at the age of 20 months, the longest survival on record. Samples of urine and plasma collected shortly before death and analysed by the Moore and Stein (1954) method revealed elevations of the branched chain amino-acids—leucine, isoleucine, and valine—strongly indicating a block in the further metabolism of these amino-acids. Other abnormalities were a high methionine and low cystine level, and reduced levels of several other amino-acids, notably alanine, serine, and threonine (see Fig.). Transaminase activity (Awapara and Seale, 1952) for the branched chain amino-acids was demonstrated in the tissues of the patient obtained at necropsy, indicating that the block lay somewhere below the level of the formation of the respective keto-acids. These observations have been previously presented (Westall, Dancis, and Miller, 1957; Westall, Dancis, Miller, and Levitz, 1958). Menkes (personal communication) later succeeded in demonstrating the keto-acids of leucine, isoleucine, and valine in the urine of this patient, adding significantly to the evidence that the metabolic block lay below the level of transamination.