Maple syrup urine disease variant

Report of a case

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Maple syrup urine disease (branched-chain ketoaciduria), a genetic disorder with a well-defined biochemical defect, was first described as a clinical syndrome by Menkes et al in 1954.[1] It is characterized by an accumulation of three keto acids corresponding to a partial breakdown of leucine, isoleucine, and valine which occur in excess in urine, blood, and other body fluids. The symptoms of anorexia, vomiting, hypertonicity, mental retardation, and occasionally convulsions appear early in life. The clinically diagnostic feature is a maple syrup odor in the urine.[2, 3]

Patients and their families have been described with transient episodes of neurologic signs associated with elevations of branched-chain amino acids. The late onset of symptoms and the fact that the children appear to be normal between attacks are strikingly different from the classic picture of maple syrup urine disease. Enzyme activity of the peripheral leukocytes in the affected children showed a significant reduction, and decarboxylase activity of the branched-chain keto acids was not as severe as the classic form of maple syrup urine disease.[4]

Maple syrup urine disease after chronic infection has been reported by one of us.[5] In the case reported here the association with trauma appears to be significant. We review the central nervous system manifestations commonly associated with this disease.

Case report

A 9-year-old girl was admitted to the Cleveland Clinic Hospital on January 5, 1970, with a diagnosis of encephalopathy of undetermined etiology. One month before admission an inner ear infection developed, and the patient reported that three weeks before admission she had been struck on the head with a baseball bat. She had not lost consciousness, but complained of a headache which lasted one-half hour. The parents observed no lacerations or external evidence of trauma. The following morning she complained of headache, blurred and double vision, and dizziness which cleared in about 10 minutes. Similar episodes continued intermittently, especially in the morning. Her mother noted occasionally slurred speech, and on December 23 the child's teacher reported thick speech and an unsteady gait. An increasingly unsteady gait and urinary incontinence developed. On December 27 the child complained of headache with continuous teeth grinding during the night. On December 28 the mother noted episodes of staring and the child seemed unable to see. She groped for food at the table and missed her mouth when eating. She responded to questions but was restless and became obtunded for long periods. Grimacing increased, and the mother described extreme and involuntary movements of arms and legs. She was admitted to a local hospital on that day. Except for the neurological findings, results of the general physical examination were normal. There was unusual grimacing. Pronator's sign was absent. Her gait was narrow-based but staggering. The deep tendon reflexes were equal and normally active with bilateral Babinski signs. Her posturing suggested a catatonic state to the examiner. She became increasingly unresponsive and was transferred to the Cleveland Clinic Hospital on January 5, 1970.

Her birth, growth, and development had been normal. She had progressed satisfactorily in school. She was described as a "picky eater" with recent pica for plastic flowers. At age 2 years, she had struck her head and was unconscious for a "short time," but then recovered spontaneously. She frequently had high fevers associated with purulent ear infections. There was no family history of consanguinity or neurological illness.

On admission the patient weighed 60 pounds; pulse rate was 120; temperature, 98.6 F; the skin was dry. She was restless and had many disorganized semipurposeful movements. She responded to simple questions by nodding, and evaded simple commands. She responded to painful stimuli, retained oculocephalic reflex, and moved all extremities. The pupils were 4 mm and equal; reaction to light and funduscopic examination were normal and without papilledema. The chest, heart, and abdomen were normal. No muscle atrophy was noted.

In addition to the above findings, it was noted that her face was symmetrical. Her deep tendon reflexes were all hyperactive and equal with bilateral extensor plantar responses. She would not stand. The next day her pupils were 2 mm, equal, and divergent. She would not follow lights, and would not follow simple commands. The oculocephalic reflex was present. The plantar responses were extensor bilaterally.

Results of laboratory studies including blood count, serum electrolytes, lupus erythematosus preparation, sedimentation rate, serological test for syphilis, blood urea, and blood sugar were normal. The serum pH was 7.50 with a carbon dioxide content of 22.9 mEq/liter, and a CO_2

tension of 28 mm Hg. Serum lead and urinary porphyrins were within normal range.

An echoencephalogram was midline. Skull x-ray films were normal. An electroencephalogram was abnormal with depression of sleep spindles over the right side. There was a single burst of 3/sec activity approaching 70 μv through T3 and C3. On awakening, there was intermixed 8/sec alpha activity with 70 μv amplitude intermixed with theta activity and 6–7/sec more on the left side than on the right. The opening and closing reaction of the eyes was normal and there was a trace of photic driving. Lumbar puncture revealed an opening pressure of 150 mm with clear, colorless fluid that contained 20 mg/100 ml protein and no cells.

On January 8 one of us (RDM) noted the odor resembling maple syrup in the sweat of this child. Plasma was immediately subjected to two-dimensional chromatography which revealed the characteristic pattern of branched-chain amino acids. The leukocyte branched-chain decarboxylase activity was below normal (*Table 1*). On January 10 the patient underwent a 3-hour hemodialysis which did not change the semicomatose state. However, the next day she was able to drink small amounts of glucose solution, which she was given in an effort to spare endogenous protein digestion. Her condition improved. On January 14 she was able to eat a 25 g protein diet. This was changed on the following day to the specific diet for maple syrup urine disease. She continued to receive isoleucine 20 mg/kg body weight, leucine 50 mg/kg body weight, valine 30 mg/kg body weight, and a total protein of 2.81 g of gelatin mixture per kilogram of body weight.

An initial psychologic interview was given January 23. The patient, 9½ years of age and the youngest of five children, was a good student but a perfectionist and extremely competitive. The family background was chaotic and there was sufficient conflict to suggest an emotional component to the child's behavior. The parents had been divorced and remarried.

Table 1.—Branched chain decarboxylase activity[4]* in the blood of the patient and a control

Amino acid	Patient, nanomoles/min	Control, nanomoles/min
Leucine	0.13	0.26
Isoleucine	0.88	1.40
Valine	0.12	0.48

* Demonstrated in leukocytes sedimented with dextran from 3.75 ml of whole blood from each. Substrates used were DL-leucine-1-C14, DL-valine-1-C14, and L-isoleucine-1-C14.

On January 30 the neurological examination showed improvement. There was a mild intention tremor and slight imbalance when attempting to walk in a straight line, as well as difficulty in hopping on one foot. Plantar responses were flexor, and she was alert, oriented, and conversed fluently with the examiners.

On February 5 the Weschler Intelligence Scale for Children test yielded a verbal IQ of 101, a performance scale IQ of 99, and a full scale of 100. Although no previous test results were available, it was believed that these scores reflected less than her true capacity.

Discussion

The typical form of maple syrup urine disease is now well recognized,[1] and Dancis[6] has described the variant of the disease noting the intermittent nature of the encephalopathy. The intermittent nature of an inborn error of metabolism is not understood but is well documented. This is the third clinical experience here with head injury apparently an important stress factor.[5, 7] It is possible that this type of stress and others, such as vaccination and normally benign febrile dis-

orders, are more significant in the etiology than has been previously recognized. Neuropathy has been noted from time to time after antigenic stimulation such as vaccination. Convulsions have been noted in relation to fever in children; the first attack of epilepsy is often noted in a febrile episode.

The clinical challenge in this case is obvious. The child was referred because of a change in the level of consciousness of undetermined etiology and a history of head trauma. The differential diagnosis in such cases can be difficult. Failure to recognize the typical odor in this child's sweat and to establish the etiology of the encephalopathy could in some instances lead to more complicated studies such as pneumoencephalography and cerebral angiography. In our experience with maple syrup urine disease such investigation has been shown to be extremely dangerous. There is little doubt that intracranial contrast studies and general anesthesia would be an additional stress to the already strained physical condition.

It is our impression that other forms of metabolic encephalopathy are more common than is generally supposed, and it is essentially a challenge to the clinician and the laboratory. Harris[8] emphasized the normal distribution curve when the activity of an enzyme is graphed for a large population. The stress factor superimposed on a marginal enzyme situation might produce a potentially lethal metabolic error. If the patient recovers from the episode, it might be diagnosed as encephalitis of unknown origin, viral encephalitis, or another conventional disease. If the patient dies, nothing in the autopsy will identify a disease of this nature, unless it has been prolonged enough to produce degenerative changes in the central nervous system. Peters[9] has referred to this as the "biochemical lesion." Infection, a well-known complication in branched ketoaciduria, may result in secondary septicemia to which the patient finally succumbs, leading to a false assumption about the cause of death. Thus, recognition of this rare but potentially lethal condition is of utmost significance, and correct diagnosis and treatment can lead to complete recovery.

Summary

An odor resembling maple syrup was detected in the sweat of a 9-year-old girl with encephalopathy. The diagnosis of maple syrup urine disease variant was confirmed by chromatography and a quantitative evaluation of the branched chain decarboxylating enzyme in the white blood cells.

Treatment with special branched chain amino acid free diet led to complete recovery. The clinician's role is distinct from that of the laboratory and the dangers of advanced neurological studies are emphasized. Head injury is considered an important stress factor in conditions associated with marginal concentration of an enzyme.

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