Electroencephalograms in a Case of Maple Syrup Urine Disease: Their Relation to Serum Levels of Branched-Chain Amino Acids*

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IINUMA, K., SAITO, T., WADA, Y., ONUMA, A., TAKAMATSU, N., OTOMO, H. and KOIZUMI, Y. *Electroencephalograms in a Case of Maple Syrup Urine Disease: Their Relation to Serum Levels of Branched-Chain Amino Acids.* Tohoku J. exp. Med., 1976, 120 (2), 191-195 — During dietary treatment of a case of maple syrup urine disease, it was found that abnormal EEGs were observed when serum levels of leucine were abnormally high while those of valine and isoleucine were normal, and also when serum levels of valine and isoleucine were abnormally high while serum leucine levels were normal. — EEG; maple syrup urine disease

In a case of maple syrup urine disease, a serial electroencephalographic study was done before and during a dietary treatment and a relation between the EEG changes and serum levels of the branched-chain amino acids was investigated.

THE PATIENT AND METHODS

M.I., a 2-month-old boy was admitted to our University Hospital because of feeding difficulty and peculiar odor of the urine. He had four siblings, two of whom had died in the neonatal period from the same symptoms as those of the present patient.

The patient appeared well until the age of 7 days when he suddenly became difficult to feed. The patient's urine was noticed to have a peculiar odor at 5 weeks of life. On 73 days of life, the serum concentrations of leucine, isoleucine and valine were found to be 53.40, 12.04 and 16.44 mg/100 ml, respectively, while serum levels of other amino acids were all within normal ranges. Urinalysis revealed a positive reaction to the dinitrophenylhydrazin test. Maple syrup urine disease was diagnosed from these data.

As shown in Fig. 1, from 86 days of life, a dietary therapy with a special milk formula (Snow Brand Milk Products Co., Ltd., Tokyo, Japan), with the composition described in Table 1, was started. Fifteen per cent of this milk preparation was given in a daily amount ranging from 540 to 700 ml, giving 370 to 480 kcal per day.

Four days after the institution of the dietary treatment, serum levels of both valine and isoleucine were decreased below the normal range, while the serum leucine level remained abnormally high. Then, isoleucine, 30-50 mg/kg/day, and valine 40-50 mg/kg/day, were added to the diet as shown in Fig. 1.

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Electroencephalograms were recorded using a 13-channel electroencephalograph (Toshiba EEG 23A, Tokyo, Japan), in an awake state and in a natural sleep stage.

For the estimation of serum concentrations of amino acids, an autoanalyzer of amino acids (Hitachi KLA-3B, Tokyo, Japan) was used.

Fig. 1. Serum levels of the branched-chain amino acids before and during the dietary treatment with a branched-chain amino acids-free diet.

* BCAA free milk: a special diet with branched-chain amino acids-free milk (cf. Table 1).

TABLE 1. Composition of the branched-chain amino acids-free milk

Protein (mixture of amino acids except for leucine, isoleucine and valine*)	*Amino acids contents	(mg/100 g milk)
Fat	L-Alanine	700
Carbohydrate	L-Serine	1,100
Minerals	Glycine	600
Water	Sodium-L-aspartate	1,600
	Sodium-L-glutamate	4,500
	L-Cystine	1,000
	L-Histidine monohydrochloride	700
	L-Proline	1,600
Vitamins and minerals (per 100 g milk)	L-Phenylalanine	1,000
Vitamin A	L-Tyrosine	1,000
Thiamine	L-Threonine	1,100
Riboflavin	L-Arginine monohydrochloride	900
Pyridoxine	L-Lysine monohydrochloride	1,300
Ascorbic acid	L-Tryptophane	400
Vitamin D	L-Methionine	500
Calcium pantothenate	Leucine	0
Nicotinamide	Isoleucine	0
Choline chloride	Valine	0

* IU: International units.

RESULTS AND DISCUSSION

The EEG findings in our own case in relation to the child's age are shown in Table 2 and Fig. 2.

TABLE 2. *EEG findings in our case of maple syrup urine disease*

No. of EEG	Age of patient (days)	Date (1975)	Findings
1	74	Oct. 3	Periodic bursts of multiple-spike and waves with suppression bursts.
2	101	Oct. 30	Multiple-spike and waves and high voltage slow waves.
3	108	Nov. 6	Multiple-spike and waves and slow waves.
4	115	Nov. 13	Multiple-spike and waves in fronto-central region.
5	123	Nov. 21	Spike discharges were seen only in fronto-central region.
6	130	Nov. 28	Spike discharges without slow waves were scarcely seen in frontal portion.
7	144	Dec. 12	No spike discharges, slight asymmetry.

Fig. 2. Electroencephalograms of our case.

- 1: EEG taken at 74 days of age. 2: EEG taken at 101 days of age.
 4: EEG taken at 115 days of age. 6: EEG taken at 130 days of age.

Serial changes of EEGs were as follows: The first tracing (74 days of life) which was taken before the dietary treatment showed periodic bursts of multiple-spike and waves with suppression bursts. The second EEG (101 days of life) taken about 2 weeks after the institution of the dietary therapy showed multiple-spike and waves and high voltage slow waves.

Spike and waves were still observed in the fourth EEG (115 days of life) taken when serum levels of valine and isoleucine were above the normal range.

The sixth EEG (130 days of life) taken when all of the three branched-chain amino acids were within normal ranges showed scarce appearance of spike discharges without slow waves.

"Severely dysrhythmic" EEGs were reported in cases of maple syrup urine disease by several authors (Dancis et al. 1960; Morris et al. 1961; Silberman et al. 1961).

In 1969, Gaull reported a case of this disorder in which EEG with a high voltage triphasic pattern was observed when serum levels of the total branched-chain amino acids were abnormally high, while the EEG became normal when serum amino acid pattern was normalized after treatment with peritoneal dialysis.

TABLE 3. *Serum levels of branched-chain amino acids of our patient (mg/100 ml)*

Days of life	Leucine	Isoleucine	Valine
73	53.40	12.04	16.44
82	44.3	10.8	17.7
91	20.4	0.19	1.82
96	16.6	0.27	2.26
103	10.3	1.70	0.77
115	0.45	6.35	14.0
122	0.54	8.72	14.3
131	1.08	0.81	3.31
150	6.58	0.10	4.43

In 1971, Sonksen et al. investigated EEGs of 2 cases of maple syrup urine disease and described that abnormal EEGs of irregular 2 1/2–6 Hz activity were observed when the patients were critically ill, and that the EEGs were gradually improved when the clinical conditions of these patients were getting better after the exchange transfusion and peritoneal dialysis were performed.

In our case, it is worthy of notice that the abnormal EEGs were observed when serum leucine levels were abnormally high while serum levels of valine and isoleucine were normal (cf. EEG-2), and when serum levels of valine and isoleucine were abnormally high, while the serum leucine level was normal (cf. EEG-4); and that the almost normal EEG was found only when serum amino acid pattern became normal by a dietary treatment (cf. EEG-6). And the most severe changes in the EEG including periodic bursts of multiple-spike and waves with suppression bursts were observed when serum levels of leucine, isoleucine and valine were abnormally high (cf. EEG-1).

From view point of EEG changes and their relation to serum levels of the branched-chain amino acids, serum levels of all three branched-chain amino acids should be kept within the normal ranges by the dietary treatment, even though Snyderman et al. (1964) reported that acute symptoms such as ataxia, convulsions and coma were more directly related to excess of leucine than to that of valine and/or isoleucine in this disorder.

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