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Clinical Onset and Prognosis of Japanese Children with Mitochondrial β -oxidation Disorders: Significance of Newborn Mass Screening

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Background

Since the 1980s when medium-chain acyl-CoA dehydrogenase (MCAD) deficiency was first discovered in children presenting with SIDS-like illness, mitochondrial fatty acid β -oxidation disorders (FAODs) have attracted attention. FAODs may be claimed to be a potential cause of severe illness in childhood, including acute encephalopathy, Reye syndrome, SIDS or myopathy of "unknown origin". In recent years, newborn mass screening for FAODs as well as organic and amino acidemias using tandem mass spectrometry (MS/MS) is becoming popular worldwide. Determining the natural course of children with FAODs will be of help in evaluating the benefit of MS/MS screening in the future. We surveyed the clinical onset and prognosis of Japanese patients with FAODs. I would like to present the data, and discuss the significance of newborn screening for FAODs.

Procedures

The clinical course, age at onset, symptoms, laboratory findings, and outcome of 71 Japanese patients with FAODs detected between 1985 and 2001 (modified from ref. Tamaoki, 2002) were surveyed, and we studied the clinical types of very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency.

Results and Discussion

The number of Japanese patients with FAODs are listed in Table 1, compared with that of the foreign countries (Europe and America) reported (Bennet et al. 2000). Of 71 cases of FAODs, carnitine palmitoyltransferase II (CPT2) deficiency was most common (N=17), followed by glutaric acidemia type II (GA2, N=14) and VLCAD deficiency (N=12). There were only 3 Japanese patients with MCAD deficiency, although MCAD deficiency is common among Caucasian people (about 1: 10,000).

Table 1. Patients with fatty acid β-oxidation defects

Deficiency	Japan	Foreign*
CRNT	5	>30
LCFAT	-	2
CPT1	5	>20
CPT2	17	>120
TRANS	1	>20
VLCAD	12	>60
TFP (plus LCHAD)	2	>120
MCAD	3	>300
SCAD	-	>20
SCHAD	-	10
S/MCHAD	-	1
MCKAT	-	4
SCKAT	6	>30
ERED	-	1
ETF or ETFDH (GA2)	14	>60
HMGS	-	2
HMGL (HMG-emia)	6	>20
Total	71	(2000, Bennett)

Abbreviations: CRNT = carnitine transporter; LCFA = long-chain fatty acid transporter; CPT1 and CPT2 = carnitine palmitoyl trnsferasel and 2, respectively; TRANS = carnitine acylcarnitine translocase; VLCAD, MCAD and SCAD = very-long-chain-, medium-chain-, and short-chain-acyl-CoA dehydrogenases, respectively; TFP = trifunctional protein; LCHAD and SCHAD, and S/MCHAD = long-chain-, short-chain-, and short/medium-chain-3-hydroxyacyl-CoA dehydrogenases, respectively; MCKAT and SCKAT = medium-chain-, and short-chain-3ketoacyl-CoA thiolases; ETF and ETFDH = electron transfer flavoprotein and ETF dehydrogenase; GA2 = glutaric acidemia type 2; ERED = 2,4-dienoyl-CoA reductase; HMGS = 3-hydroxy-3-methylglutaryl-CoA synthetase; HMGL = 3-hydroxy-3-methylglutaryl-CoA lyase.

Regarding age at onset of the 71 cases, 13% was in neonates; 47% in infants (1 mo to 2 yrs); and 40% in children of 2 yrs or more as shown in Figure 1. Although clinical symptoms differed with diseases and ages, totally, encephalopathy was seen in 36% of FAODs patients; muscle involvement in 64%; cardiomyopathy in 19%; liver dysfunction in 89%; hyperammonemia in 59%; hypoglycemia in 42%; and abnormality of family history in 44%. We might have to pay attention to the family history, especially of sudden death or Reye-syndrome-like illness, when we come across patients suspected of having FAODs. Clinically, non-specific symptoms such as feeding difficulty, tachpnea or hypotonia were often seen in neonates; acute illness such as encephalopathy or sudden death were often noted in infants (1 mo to 2 yrs of age); and muscular symptoms such as hypotonia, fatigue after exercise, or myalgia were in later childhood or adolescence.

Regarding the outcome, only 22% in the neonatal onset groups of FAODs achieved

normal development, whereas 70% and 100% did in infant and later childhood groups, respectively. Namely, FAOD patients whose age at onset was after the neonatal period could be at least mentally normal.

The number of patients with VLCAD deficiency seems to be rapidly increasing in Japan, as of 2003 we detected 21 cases. VLCAD deficiency is divided into 3 types: early onset severe form; intermediate form and later onset myopathic(mild) form. Of the 21 Japanese cases of VLCAD deficiency, only 3 (14%) were the intermediate form, and 18 (86%) were the mild form, whereas in Caucasian, 46% were the severe form; 39% the intermediate form; and 15% the mild form. There may be an ethnic difference in clinical severity of VLCAD deficiency. The prognosis of all VLCAD deficiency patients was normal.

In case of organic acidemias (OAs), the outcome of "symptomatic" patients was reported to be often severe (Hori et al, 2004). To achieve a favorable prognosis in patients with OAs or FAODs, it is essential to detect patients in the "presymptomatic" or "asymptomatic" stages. Therefore, newborn mass screening using MS/MS may be expected to prevent impairments or sudden death by detection of "presymptomatic" patients and early intervention.

Conclusions

There are difference in incidence of FAODs between Japanese and European people. Age at onset of FAODs are often after the neonatal period, and the prognosis of such patients may often be favorable. There seems to be difference in clinical severity of VLCAD deficiency patients between Japanese and European cases. Early detection of presymptomatic patients with FAODs as well as OAs in the neonatal period by newborn screening can be expected to prevent severe illness, impairments or death in childhood

References

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