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Congenital Metabolic Disorders in Japan

- Present status and Perspectives -

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1. Introduction

A considerable progress in the diagnosis and treatment of inborn errors of metabolism(IEM) has been achieved in recent year.

A nation-wide neonatal screening for treatable IEM was started in 1977 in Japan and about 33.3 million newborn babies, which correspond to 95.6% of babies born in Japan from 1977 to 2004, have been tested. According to our nation-wide survey, 526 patients with inborn errors of amino acid and carbohydrate metabolismwere diagnosed by the newborn screening from 1977 to 1996, and most of the patients have developed normally thanks to an early initiation of dietary treatment. Subsequently, a nation-wide newborn screening for congenital hypothyroidism(CHT), and congenital adrenal hyperplasia(CAH) was started in 1979 and in 1989, respectively, and as the results of the screening and of the early treatment for these congenital disorders the prognosis were very much improved.

These results clearly indicated that the newborn screening for congenital disordersplays an essential role in prevention of handicapped children.

More recently, with the advances of

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recombinant enzymeproduction, enzyme replacement therapy (ERT) for certain IEM such as Guacher disease and Fabry disease, is available to improve theirprognosis. Clinical trials of ERT for Hurler, Hunter, Morquio syndrome, Pompe and Niemann-Pick disease are currently underway or scheduled in Japan. If these disorders are diagnosed before irreversible damage in tissue has occurred, affected individuals would have more benefit from ERT.

This paper presents present status and perspectives of the early diagnosis and early treatment of IEM in Japan.

2. Results of newborn screening for IEM

A nation-wide screening program for PKU, maple syrup urine disease (MSUD), homocystinuria, and galactosemia conducted by the governmentwas started in 1977. Subsequently in 1979 and in 1989, the newborn screening for CHT and CAH, respectively, was undertaken on a nation-wide scale covered by public expenses.

The results of newborn screening for congenital disorders including CHT and CAH are shown in Table 1. Incidence rate of PKU and hyperphenyla- laninemia (HPA) in Asian and European countries is shown in Table 2, indicating that there are considerable difference in incidence between the countries in Asia and in Europe. According to our nation-wide surveys on the prognosis of patients detected by the screening for IEM, death rates in patients detected by the screening were unexpectedly high. From 1977 to 1995, approximately 18.7% of the patients with BH4 deficiency, MSUD and homocystinuria died during the

Table 1. Results of Neonatal Screening for Inborn Errors of Metabolism in Japan rep orted in 1997

Inborn errors of metabolism	No of cases detected	Incidence rate
Classical PKU	227	1/ 113,266
Hyperphenylalaninemia	141	1/ 182,350
BH4 deficiency	15	1/ 1,714,091
Hyperphenylalaninemia (total)	383	1/ 67,132
Maple syrup urine disease	39	1/ 659,266
Homocystinuria	27	1/ 952,273
Galactosemia type 1	26	1/ 988,898
Galactosemia type 2	51	1/ 504,144
Congenital hypothyroidism	4,685	1/ 4,800
Congenital adrenal hyperplasia	671	1/ 14,900

Table 2. Incidence Rate of PKU and Hyperphenylalaninemia in Asian and Eropean Countries

Country		Incidence	Authors
Asia	Japan	1/67,132	Aoki K(1998)
	Korea	1/44,928	Lee DH(1997)
	China	1/17,000~/11,000	Chen R.G(1997)
Europe	Garmany	1/ 6,706	Guthrie R(1974) Beckers RG(1973)
	England	1/14,755	
	France	1/13,411	
	Sweden	1/24,334	

follow up, while that in classical PKU and HPA was only 0.55%. It seemed that management of BH4 deficiency, MSUD and homocystinuria were more difficult than that of PKU and HPA.

A considerable number of PKU, BH4 deficiency, MSUD, homocystinuria and galactosemia type 1 patients detected by newborn screening showed lower school record than those in general population, though the most of these patients did show higher school record than those detected by symptoms.

A diet regimen for PKU was recommended by the Study Group of Diet Therapy for IEM which is organized by the Ministry of Health and Welfare. In 1977, this study group also recommended the optimum blood phenylalanine (Phe) level during the dietary therapy for infants as 4-8mg/dl, and for toddlers as 8-12mg/dl respectively (Table 3).

The latest IQ scores of 114 patients with PKU detected by the screening and treated on the low phenylalanine diet under the guideline established in 1977 are as follows. The IQs in 24 patients (21.1%) and 14 patients (12.3%) were less than 89 and 79, respectively.

Table 3. Recommendation on the Dietary Management of Phenylketonuria in Japan

Recommendation in 1977		Revised in 1995	
Ages	Phelevels	Ages	Phelevels
0~1 years	4~8 mg/dl	0~3 years	2~4 mg/dl
1~6 years	4~12 mg/dl	4~8 years	3~6 mg/dl
		9~11 years	3~8 mg/dl
		12~14 years	3~10 mg/dl
		15 years ≦	3~15 mg/dl

Negative correlation was observed mean yearly blood Phe levels and the latest IQ scores.

From the above results, the Committee for the Dietary Treatment for PKU in Japan made a much stricter recommendation of blood Phe levels in PKU in 1995 as shown in Table 3. To maintain blood Phe levels at non-toxic levels, they should receive enough amount of semi-synthetic diet low in Phe and adequate in other nutrients, such as low-Phe formula. A better mental development and educational career are expected in patients who have been treated on the newly recommended dietary regimens.

Not only in PKU but also in CHT and CAH a tentative guideline for the diagnosis and treatment was established in 1980 and in 1988, respectively. The mean IQ among affectedpatients with CHT detected by newborn screening was reported as 99.1 and 77% of them revealed an IQ above 90.

Data on more than 10 million of newborns screened for the years from 1988 to 1996 indicate that the incidence of 21- hydroxylase deficiency is 1/14,900 newborns which was nearly twice as much as before the newborn screening. This result indicates that before the newborn screening, an unexpectedly large number of affected patients with salt-wasting form died and those with simple -virilizing form were neglected without adequate corticosteroid therapy.

3. Activities of the Committee on Treatment of Inborn Errors of Metabolism(IEM) and PKU Parent Association in Japan.

An organization for the treatment of IEM, named the Committee on Safety and Development of Special Dietary Products for IEM, supported by the Ministry of Health, Welfare, and Labor was organized in 1980 in Japan. This committee organizes follow up studies and evaluates dietary treatment. This committee plays an important role not only in the revising the guideline on PKU treatment in Japan, but also in the supply of special formula low in phenylalanine and Low Phe Peptide(LPP) products.

LPP is a more palatable and has a less offensive taste andsmell than the Phe free amino acid mixture, and contains much nitrogen than conventional low Phe formulas. At present LPP is widely used in the treatment of elder PKU patients as well as maternal PKU.

In fact, we have treated 3 patients with maternal PKU using LPP from the preconceptional period, and 4 healthy babies were born.

From our experience we have drawn up a recommendation for dietary treatment for Japanese maternal PKU as shown in Table 4.

To maintain a stable control of blood Phe levels for long periods in PKU requires not only the support of medical staffs, but also the social environments such as

Table 4. Recommendation on the Dietary Management of Phenylketonuria in Japan

	Body weight (Kg)	Phe intake mg/day(mg/kg)	Prote in g/day	Energy kcal/day
Before pregnancy -First trimester	50	500(10)	70	2,150
second Trimester	55	750(14)	75	2,250
Third Trimester	58	1,100(17)	80	2,350

family, school teachers and friends. The various activities of the PKU Parent Association has played the most important role in the long term manage- ment of PKU for the past 25 years in Western countries, and for 15 years in Japan. Some of the results revealed decrease in blood Phe levels in patients and increase in social activities, as well as improvement in school performance. The activities of PKU Parent Association in Japan seem to be quite satisfactory.

4. Effectiveness and cost-benefit balance of the newborn screening for IEM in Japan

Effectiveness and cost-benefit balance of the newborn screening for IEM has been carefully evaluated in 1993 by Dr. Hisashige. According to his report, a positive cost-benefit balance by the newborn screening for IEM was obtained in PKU, CHT and CAH. The highest benefit accounting approximately 3056.6 million yen per year was estimated in the screening for CHT while the benefit of the screening for PKU was only 505 million yen, because incidence rate in CHT is about five times higher than that in PKU. A negative cost-benefit balance was observed in the screening for MSUD, homocystinuria and galactosemia type 1. However it has been reported that the annual costs of the benefit in the newborn screening in Japan is accounted as much as 3,113 million yen(Table5).

5. Early diagnosis and early treatment of IEM under dissemination or evaluation

a) Lysosomal storage disease

At present, approximately 36 inherited metabolic disorders with deficiencies in the lysosomal enzymes, sphingolipid-activator proteins and lysosomal enzyme phospho-rylation systems are known as a lysosomal storage disease (LSD).

With the advances of recombinantprotein production, enzyme replacement therapy (ERT) for selected LSDs, is already available. In Japan, all medical expenses for Fabry and Gaucher patients, including cost of

Table 5. Cost benefit balance in newbom screening in Japan

	Cost*	Benefit	Benefit-Cost	Effectiveness**
Classical PKU	333.24	838.39	505.15	○
Maple syrup Urine disease	256.82	61.46	−195.36	△
Homocystinuria	264.09	19.19	−244.90	△
Galactosemia type 1	220.33	9.29	−211.04	△
Congenital Hypothiroidism	771.27	3827.90	3056.63	○
Conjenita Adrenal hyperlasia	1018.85	1241.90	223.05	△
Total	2864.60	5998.13	3133.53	

Cost/benefit Ratio = 1:2.1 (The above data on 1.2million newborn screening)
*:1million yen **:benefit is apparent, △:benefit is not apparent

diagnosis and ERT, are covered by the public health insurance system and government funding. So, our experiences in an early diagnosis and early treatment of Gaucher and Fabry disease will be presented.

b) Inborn errors of organic acid metabolism and fatty acid oxidation systems

At present, only few screening laboratories in Japan have used tandem mass spectrometry (MS/MS) to detect certain amino acidemias, organic acidemias and fatty acid oxidation disorders.

Tentative guideline for the treatment of the patients with organic acidemias and fatty acid oxidation disorders detected by MS/MS in Japan will be reported.

6. Conclusion

For an improved prognosis, early onset type IEMs such as PKU, MSUD, MCAD, Pompe disease should be diagnosed and treated in neonatal period and late onset type IEMs such as Wilson and Fabry disease, are better to be diagnosed and managed in school age population using an appropriate methods.