A History of the Development of Newborn Mass-screening (NBS) for Inborn Errors of Metabolism in Japan

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Introduction

Newborn mass-screening and early dietary treatment for PKU were already available before 1963 in the US but not in Japan. Thus, there was a wide gap in the treatment of PKU between Japan and Western countries. Now, we would like to express our sincere appreciation for the cordial guidance given by Dr. R. Guthrie and Dr. H. Bickel, when we were working to establish NBS for IEM in Japan.

Table 1. Initiation of nationwide newborn screening (NBS) in Japan

In 1977, the Ministry of Health and Welfare (MHW) Japan directed to start publicly funded NBS for PKU, MSUD, HCU, histidinemia using BIA and for galactosemia using Beutler test and Paigen phage test.

Dseases	screening tests
PKU	Bacterial inhibition assay (BIA)
Maple syrup urine disease	
Histidinemia	
Homocystinuria	
Galactosemia	Beutler test Paigen Phage test

Table 2. A guideline for treatment of inborn errors of amino acid metabolism to be screened

In 1977, a study group of the Ministry of Health and Welfare formulated and recommended a guideline for the treatment of inborn errors of amino acid metabolism to be screened.

Amino acid (IEM)	Ages	Maintenance ranges of fasting blood levels
Phenylalanine (PKU)	Infancy	4-8mg/dL
	Early young children	4-12mg/dL
Branched chain amino acid (MSUD)		2-5mg/dL
Methionine (homocystinuria)		≦ 1.0mg/dL

- **Histidinemia**

In 1977, histidinemia was included as a target disease in our program. However, some patients with histidinemia in the families were found to lead a normal life without treatment.

Then, it was excluded as a target disease for screening.

- **Galactosemia and Galactokinase deficiency**

Breast milk, and infant formula etc., should be discontinued immediately after diagnosis, and dietary therapy with lactose-free milk should be initiated. Intake of lactose-containing food should be avoided all through the life.

Establishment of the Japan Cooperative Project on Special Formula (JCPSF) in 1980

- Dietary therapy with special formula was critical for preventing complications caused by IEM in children. The MHLW launched JCPSF in 1980 to ensure a stable supply of special formula for the treatment of IEM and its quality management.
- Additionally, the Special Formula Office took charge of follow-up of the patients and issued handbooks for dietary treatment of IEM.

Follow-up study to examine the effectiveness of NBS

According to the results of follow-up study, the IQ scores of PKU patients aged 6–10 years and treated according to the criteria of 1977, were ≥85 (about 75%), 71-84 (about 15%), and 51-70 (about 10%).

Table 3. Mean IQ scores by disease in 1992

Disease	IQ (Mean±SD)	Max.	Min.
PKU[1)]	103±13 (n=36)	136	72
HPA[2)]	111±10 (n=10)	125	89
BH_4 deficiency	81±27 (n=4)	124	50
MSUD	71±23 (n=10)	103	35
HCU	72±29 (n=8)	101	20

1) PKU : serum Phe levels ≧16.5 mg/dL, 2) HPA : serum Phe levels 5.0-16.5 mg/dL

Revision of PKU treatment guideline (1995)

- JCPSF referred to the results of the PKU survey above to organize the PKU Treatment Guideline Revision Committee in 1995
- The blood Phe maintenance ranges by age were revised as in Table 4.
- The Japanese guideline revised in 1995 was similar to those of the United Kingdom and Germany. Thus, the prognoses of affected infants in Japan seemed to be comparable with those of PKU infants in Western countries.

Table 4. Comparison of blood Phe level maintenance ranges in PKU treatment guideline among Japan, Britain, and Germany

(mg/dL)

Age \ Country		Japan		Britain 1993～	Germany 1997～1999
		1977-1994	1995～		
Infancy (age 0)		4-8	2-4	2-6	0.7- 4.0
Early childhood (age 1-5 years)	First half	4-12			
	Latter half		3-6		
Elementary school (age 6-12 years)	First half	—		2-8	
	Latter half	—	3-8		0.7- 15.0
Junior high school (age 13-15 years)		—	3-10		
≧ 15 years		—	3-15	2.0-11.7	0.7- 20.0

Diagnosis of BH_4 deficiency

BH_4 (10 mg per kg) is orally administered and blood samples are collected every hour for 4 hours and subsequently at 8, 12, and 24 hours to measure blood Phe levels and urine samples at 12 and 12-24 hours after BH_4 administration are collected for the measurement of pterin compounds. Changes in the measurements before and after BH_4 loading are shown in Fig. 1. and Table 5.

Fig. 1. Changes in serum Phe levels in BH_4 loading test among the patients with PKU and BH_4 deficiency

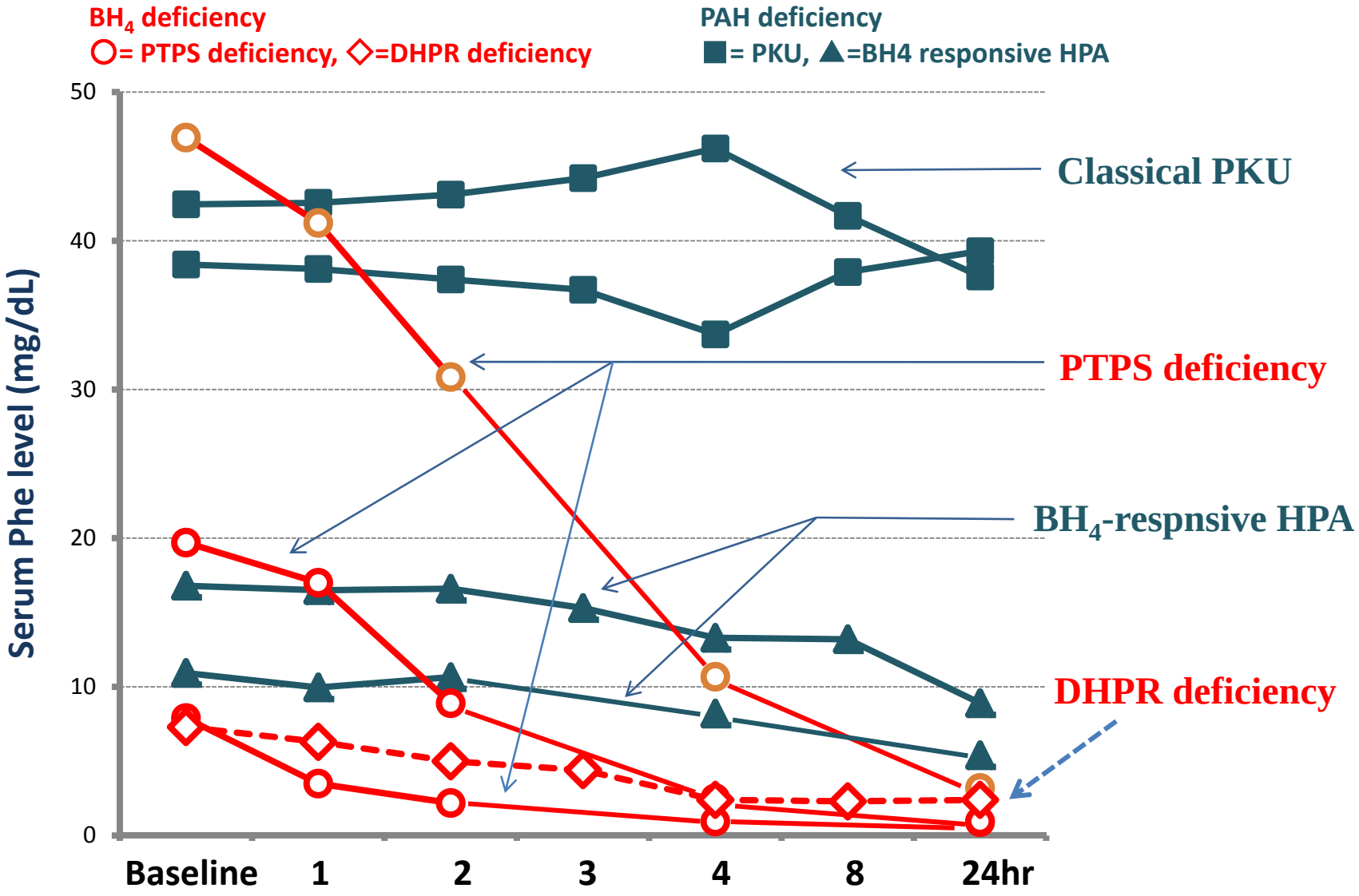

Table 5. Differential diagnosis of HPA caused by impaired BH_4 synthesis by using urinary pterin analysis

classification	Urinary pterin analysis			
	Neopterin	Biopterin	Ne/TB	% BH_4
<BH4 deficiency>				
1. GTPCH deficiency	Markedly low	Markedly low	Normal	Markedly low
2. PTPS deficiency	Markedly high	Markedly low	Markedly high	Markedly low
3. DHPR deficiency	High	High	Low-normal	Markedly low
1. Classiical PKU	High	High	Low-normal	High
2. Persistant HPA	High	High	Low-normal	High

* BH4 should be combined with Phe (100mg/kg) , if blood Phe levels are ≦6mg/dL.

** If it is difficult to make a diagnosis DHPR or PTPS deficiency, DHPR enzyme activity in blood should be measured.

Table 6. Recommended treatment guideline for patients with impaired BH_4 synthesis

mg/kg/day

	6R-BH_4	L-Dopa (Carbidopa)	5-HTP*
Daily dose	2-10**	5-15 (0.5-1.5)	3-13
Frequency of administration	Divided doses (3-4 times, at least 3 times)		

- Patients with BH_4 deficiency should receive oral administration of BH_4 and neurotransmitter precursors with reference to the doses listed in the above Table. In patients with DHPR deficiency, the BH_4 doses should be increased to reduce serum Phe levels. Low-Phe formula should be included if necessary.

Table 7. Incidence rate of patients with IEM detected by newborn mass-screening

Incidences in the almost of the disease in Japan were lower than that of Western countries.

IEM	No. of cases detected	Incidence rate
Classical PKU	174	1/114,379
Hyperphenylalanemia; HPA	88	1/226,159
(Total)	(262)	(1/75,962)
BH4 deficiency	13	1/1,530,926
MSUD	33	1/603,092
HCU	20	1/995101
Galactosemia type 1	19	1/1,047,475
Galactokinase deficiency	29	1/686,277

Classical PKU = Serum Phe level ≧ 1000μM at diagnosis, HPA = Serum Phe level < 1000μM at diagnosis

Newborn Mass-Screening for Inborn Errors of Metabolism by MS/MS

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- MS/MS screening, implemented in 1,277,670 newborns from 2004 until 2010, identified a total of 141 patients with following conditions: amino acid metabolism disorder (41 cases), organic acid metabolism disorder (61 cases), and fatty acid metabolism disorder (39cases).
- In response to the above report, the Ministry of Health, Labour, and Welfare decided to initiate publicly funded newborn mass-screening using MS/MS in April, 2012. The 16 diseases including inborn errors of amino acid metabolism (5 diseases), organic acid metabolism (7 diseases) and fatty acid metabolism (4 diseases) were the primary screening targets.

Cost/benefit of newborn mass-screening by using conventional method and Tandem mass-spectrometry (1,000 yen) –A comparative study -

- Referring to these incidences and outcomes of the diseases, Hisashige et al. in 1993, examined the cost/benefits of newborn mass-screening for IEM by using the conventional methods and reported loss of 146,150,000 yen a year.
- However, in 2007, Ohkusa et al found that newborn mass-screening by MS/MS yielded an incremental net benefit of 8.9 billion yen.
- Thus, the negative net benefit of screening for inborn errors of amino acid metabolism by using conventional method was negated by MS/MS screening as shown in Table 8..

Table 8. Cost/benefit of newborn mass-screening by using conventional method and Tandem mass-spectrometry (1,000 yen)

Target diseases and NBS methods		Cost	Benefit	Net benefit	Effect
PKU* + HPA**	Conventional methods (1977-2011)	333,240	838,390	505,150	Effective
MSUD		256,820	61,460	-195,360	Marginally effective
HCU		264,090	19,190	-244,900	Marginally effective
Galactosemia		220,330	9,290	-211,040	Marginally effective
Total		1,074,480	928,330	-146,150	Calculated in 1994
Inborn errors of amino acid metabolism 5 diseases organic acid metabolism 7 diseases fatty acid metabolism 4 diseases	Tandem mass-spectro-metry (2012~)	—	—	710,000 ~1,436,000	Very effective Calculated in 2011

Conclusion

- The Japanese nationwide NBS has been performed for 36 years since 1977.
- Screening methods to detected patients with IEM has been developed very much from BIA to HPLC, and more recently to Tandem mass spectrometry.
- Target diseases have been expanded from inborn errors of amino acid metabolism to inborn errors of organic acid and fatty acid metabolism.
- This paper reviewed the Japanese history of the development of NBS which has enabled more IEM patients to lead active and productive lives today.