LONG TERM FOLLOW-UP OF PATIENTS WITH INBORN ERRORS OF METABOLISM DETECTED BY THE NEWBORN SCREENING PROGRAM IN JAPAN

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Abstract. A newborn mass-screening program for the early detection of phenylketonuria, maple syrup urine disease, homocystinuria, galactosemia, congenital hypothyroidism, congenital adrenal hyperplasia, using filter paper blood specimens, was started throughout Japan in 1977. The total number of newborns screened by March 2000 reached 29,657,738; this represents 95% of the newborns during this period. A collaborative study group has performed a follow-up study of the cases detected by this program since the start of this screening program. The results we have obtained through this study to date include: hyperphenylalaninemia, 1:70,000; congenital hypothyroidism, 1:5,000; and, congenital adrenal hyperplasia, 1:20,000. The cases of maple syrup urine disease, homocystinuria, and galactosemia type 1 were too few for a reliable incidence. Accumulated data for PKU show that IQ is inversely related to blood phenylalanine level and stricter dietary control guidelines have resulted. We now have a number of adolescents with PKU and long-term follow-up data are being obtained.

INTRODUCTION

A newborn mass-screening program for the early detection of phenylketonuria (PKU), maple syrup urine disease (MSUD), homocystinuria (HCY), and galactosemia (GAL), using filter paper blood specimens, was started throughout Japan in 1977 (Aoki and Wada, 1988). The total number of newborns screened by March 2000 reached 29,657,738 (95% of the births). Table 1 presents the screening rate from 1977 to 1998. A follow-up study of the cases detected by this program was performed by a collaborative study group.

Blood from newborns was sampled onto filter paper on the 5th day of life and sent to local screening laboratories, where Guthrie's method was performed for PKU, MSUD, HCY, and GAL. Information about the results of diagnosis, blood amino acids and galactose levels, physical and mental development were accumulated through questionnaires (Table 2), which were sent to every physician once a year. The developmental quotient (DQ) for children below 3 years of age and the intelligence quotient (IQ) for the older age group were assessed by the Tsumori-Inage method and by the Wechsler Intelligence Scale for children respectively.

Figs 1 and 2 schematically show these processes and the data have been accumulated in the Aiiku Maternal and Child Health Center where the Office for Long-Term Follow-up system is located.

Table 1. The number of newborns screened in Japan.

Year	Number of births	Screened	Rate (%)
1977-1993	24,163,633	22,326,111	92.4
1994	1,235,553	1,253,198	101.4
1995	1,183,716	1,196,068	101.0
1996	1,203,313	1,222,850	101.6
1997	1,194,510	1,215,649	101.8
1998	1,199,183	1,229,518	102.5
Total	30,179,908	28,443,394	94.2

Table 2. Contents of questionnaires.

Contents of questionnaires
1. Physical Growth
2. Mental Development
3. Blood Level of Phenylalanine, Leucine or Galactose
4. EEG Finding
5. Nutritional Assessment
6. Intake of restricted amino acid

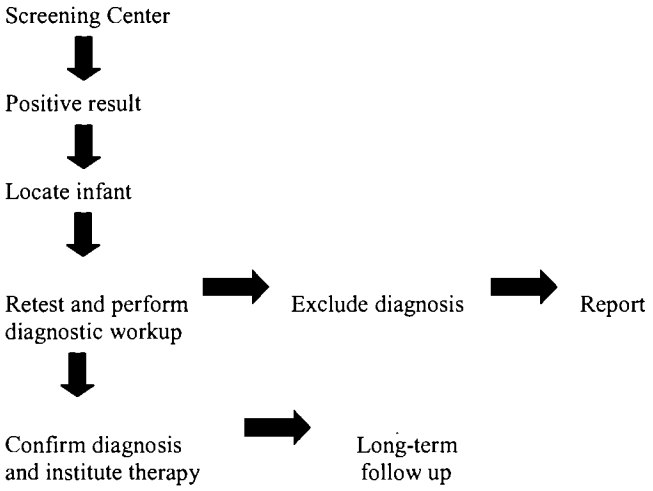

Fig 1. Flow diagram of follow-up.

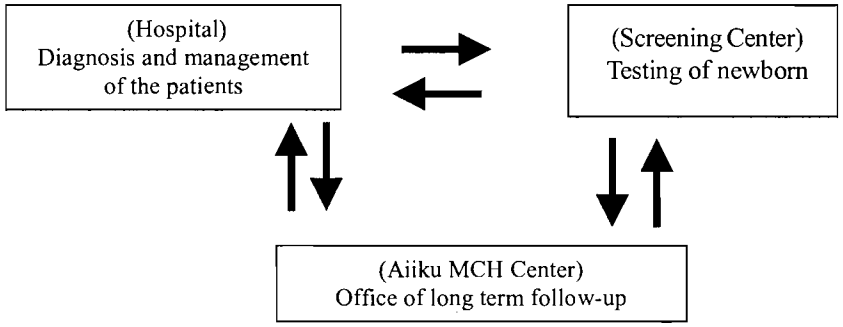

Fig 2. Long term follow-up system of the patients detected by newborn screening.

RESULTS

Incidence of the diseases detected by newborn screening system in Japan

Table 3 lists the incidences of the different disorders. Of the 312 patients with hyperphenylalaninemia (incidence of 1: 70,000), 194 cases were confirmed with classical PKU, 105 with hyperphenylalaninemia, and 13 cases with biopterin deficiency. The detected numbers of these diseases were quite low compared to other countries. The incidences of maple syrup urine disease, homocystinuria, and galactosemia type 1 were also found to be markedly low.

New treatment guideline for PKU

According to the accumulated data analysis of PKU, we found that intelligence quotient (IQ) was inversely correlated to blood phenylalanine level (Fig 3). Thus, a stricter guideline of dietary treatment was begun in 1995 (Table 4). By calculating the blood level of phenylalanine using follow-up data, it was clear that the blood level of phenylalanine decreased after the initiation of the new guideline (Table 5). It is thereby important to treat patients with PKU using a reasonable and stricter guideline (Aoki, 2001).

Table 3. Incidence of diseases detected by newborn screening in Japan (1977-1994).

Diseases	No. of patients	Incidence
Total hyperphenylalaninemia	312 (3)	1: 71,658
Phenylketonuria	194 (1)	1: 115,083
Hyperphenylalaninemia	105	1: 212,630
Biopterine deficiency	13 (2)	1:1,717,393
Maple syrup urine disease	36 (6)	1: 620,170
Homocystinuria	22 (4)	1:1,014,823
Galactosemia	203 (3)	1: 110,525
Galactosemia Type 1	20 (3)	1:1,116,306
Galactosemia Type 2	35	1: 637,889
Galactosemia Type 3	147	1: 151,878

( ) = Number of deceased patients

Table 4. Guideline for the dietary management of children with PKU (treatment range of serum phenylalanine level).

Age group	Old guideline (1977)	New guideline (1995)
0~3 yr.	4~8	2~4
4~8 yr.	4~12	3~6
9~12 yr.		3~8
13~15 yr.		3~10
>15 yr.		3~15

Table 5. Comparison of blood phenylalanine level before and after new guideline of the dietary treatment of children with PKU.

Age group	1977-1994	1995-1999
0-1 m	23.40±8.32	23.95± 7.92
1-2 m	13.60±8.70	13.32±10.62
2-6 m **	8.19±3.82	5.40± 5.13
6-12 m ***	7.09±3.62	4.96± 2.73
1-2 yr ***	7.97±3.82	4.28± 2.49
2-3 yr ***	8.92±4.42	5.41± 3.77
3-4 yr	9.63±5.12	6.30± 4.08

$p<0.05$* $p<0.01$** $p<0.001$***

Re-evaluation of the phenylalanine cut-off value for the detection of PKU

At the outset of the screening program, for positive assessment of PKU in newborn infants, the cutoff value for phenylalanine was set at 4 mg/dl by Guthrie's method at the fifth day of life (see Table 6). One case with classic PKU had a phenylalanine level of 3 mg/dl on the sixth day of life. This patient was re-examined on the 10th day of life and the phenylalanine level was over 20 mg/dl. On the 30th day of life, the result of the amino acid analysis using the automated amino acid analyzer was 47.9 mg/dl and treatment was started at that point (Aoki and Kinosita, 1998).

Preconception counseling of patients with phenylketonuria

More than twenty years have passed since 1977, and we are now faced with PKU adolescents. Counseling of females with PKU before pregnancy on fetal risks associated with high plasma phenylalanine concentrations is an important issue. Follow-up of the patients is important to solve these problems.

Prognosis of MSUD after detection by newborn screening

Thirty-six cases of MSUD were detected by newborn screening from 1977 to 1994. Six cases died due to irreversible ketoacidotic attacks following infection. Because of pseudo-negative screening results, three cases of intermittent type of MSUD were not detected. Table 7 shows the prognosis of MSUD according to the presence of symptoms during the neonatal stage. Classic MSUD has the most severe clinical manifestations and affected infants who are normal at birth develop clinical signs during the 1st week of life. When the screening result is positive for MSUD, prompt information to the hospital is necessary. Treatment of MSUD is usually started immediately following the positive screening result and the clinical diagnosis. Table 7 shows the prognosis of classic MSUD even with the early start of treatment. There are many problems encountered in treating MSUD. Table 8 compares IQ levels of patients with various diseases detected through screening and it is clear that the MSUD patients have fared the worst and have the lowest IQ levels (Aoki, 2002).

CONCLUSION

Long-term follow-up is essential in order to successfully evaluate the value of the newborn

Table 6. Re-evaluation of the phenylalanine cut-off value for the PKU detection.

Newborn screening data at the 5th day of life, for the positive assessment of PKU

1. The cut-off value of phenylalanine : 4 mg/dl
2. The average date of blood-sampling : 5.4 days
3. The average value of phenylalanine : 17.5 mg/dl

One case with classic PKU showed a phenylalanine level below 4 mg/dl (3 mg/dl) on the 6th day of life.
On the 10th day of life, the phenylalanine level was over 20 mg/dl by re-evaluation.
On the 30th day of life, the phenylalanine level was 47.9 mg/dl.

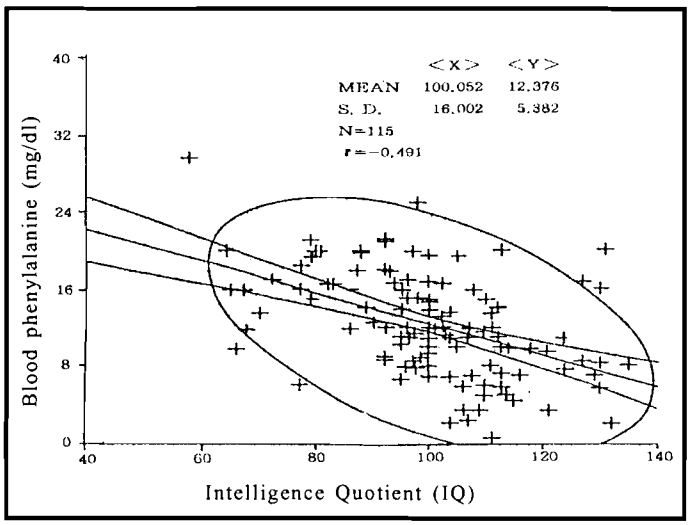

Fig 3. Correlation between serum phenylalanine level and intelligence quotient.

Table 7. Prognosis of MSUD according to the presence of neonatal symptoms (1977-1989).

Neonatal period		No. of cases	Intelligence Quotient			No. of deaths
			<50	50-80	80-120	
Signs	+	16	3	5	5	3
	-	5			5	
Blood	<20	6			6	1
leucine level	20-40	8	1	3	3	1
(mg/dl)	>40	7	2	2	1	2

Table 8. IQ of the patients detected by screening (1977-1990).

Disease	IQ(mean ± SD)	Max IQ	Min IQ
PKU	103 ± 13(n=36)	135	72
Hyperphenyl-alaninemia	111 ± 10(n=10)	125	89
Biopterin deficiency	81 ± 27(n=4)	124	50
MSUD	71 ± 23(n=10)	103	35
HCY	72 ± 29(n=8)	101	20

screening program. It is imperative that evaluation include not only validation of testing procedures but also assessment of efficiency of the follow up system and the assessment of the benefits to the patient, family and society. Such studies allow for program changes based on whether or not the mission of the program is being accomplished. Outcome data allow the program to advance scientifically.

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