

Original Article

Central Congenital Hypothyroidism Detected by Neonatal Screening in Sapporo, Japan (2000–2004): It's Prevalence and Clinical Characteristics

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Abstract. In Sapporo, Japan, a neonatal screening program for congenital hypothyroidism (CH) has employed measurement of free thyroxine (T4) and TSH in the same filter-paper blood spot. This system has enabled us to identify primary CH and central CH during the neonatal period. The aim of this study was to clarify the prevalence and clinical characteristics of central CH. For this purpose, the screening program requested serum from infants with free T4 concentrations below the cut off value regardless of the TSH levels. Between January 2000 and December 2004, 83,232 newborns were screened and six central CH patients were detected as a result of follow-up of low free T4 and non-elevated TSH screening (1:13,872). This frequency is higher than in other studies. Four patients showed multiple pituitary hormone deficiency with pituitary malformations on magnetic resonance imaging. One patient was diagnosed as having Prader-Willie syndrome. The remaining patient was considered to have isolated central CH. Our study demonstrated that the frequency of central CH is 1:13,872. Free T4 measurement would also be advantageous in early recognition of multiple pituitary hormone deficiency.

Key words: neonatal mass screening, free T4, filter paper, congenital hypothyroidism (CH), central CH

Introduction

Introduction of neonatal mass screening for congenital hypothyroidism (CH) during the past three decades has enabled early diagnosis and treatment of affected infants, and the benefits

of these programs are well recognized (1–3). Since most screening programs for CH in Europe and Asia, including Japan, use primary TSH screening, these programs are useful for detection primary CH, but not central CH. In contrast to TSH based screening program, thyroxine (T4)-based neonatal screening could detect central CH. North American Regional Screening Programs for CH employ measurement of blood spot T4 concentrations with supplemental TSH determinations (4–7). In the Netherlands, a screening program for primary T4 determination with supplemental TSH and T4-binding globulin

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is effective for detection of central CH (8). Zamboni *et al.* have reported the diagnostic effectiveness of simultaneous T4 and TSH screening in the Northeast Italian Screening Program (9).

In Sapporo, Japan, neonatal screening for CH has been based on simultaneous TSH and free T4 measurements (5). Herein, we report the prevalence and clinical characteristics of central CH detected by neonatal screening between 2000 and 2004.

Patients and Methods

Neonatal CH screening

The neonatal CH screening program in Sapporo was based on simultaneous TSH and free T4 measurement in dried blood on filter paper specimens (5). Dried blood samples on filter paper are collected from neonatal infants born in Sapporo at 4–6 days of age from maternity and parturition clinics by the Sapporo City Institute of Public Health. TSH and free T4 were measured simultaneously on blood spots on the filter paper. TSH and free T4 were measured by ELISA kits (Bayer Medical Enzaplant Neo-TSH and Enzaplant N-FT4 kits, Japan).

To detect severe CH, children with TSH concentrations of at least $50 \mu\text{U/ml}$ and/or free T4 $< 0.5 \text{ ng/dl}$ were directly referred to a specialized hospital. Second heel puncture was requested if one of the following criteria for recall testing was met: (1) free T4 $< 1.0 \text{ ng/dl}$ or a (2) high TSH concentration ($>10 \mu\text{U/ml}$). Infants whose TSH or free T4 in the second testing were successively out of the normal range were sent to a specialized hospital.

Study patients

Between January 2000 and December 2004, 83,232 infants born in Sapporo were screened. In patients diagnosed with central CH, perinatal characteristics, clinical features and pituitary function were studied as much as possible. Magnetic resonance imaging (MRI) was

performed to assess the anatomical integrity of the hypothalamic-pituitary region.

Pituitary hormone assessment

Free T4, free triiodothyronine (T3) and TSH levels were determined by a commercially available chemiluminescent immunoassay (Ciba Corning Diagnostic Corp., Medfield, MA, USA). Serum cortisol was measured by radioimmunoassay (Amerlex RIA, Ortho Clinical Diagnostics Co., Tokyo, Japan). Serum GH level was measured by immunoradiometric assay (IRMA) (TFB, Ltd., Tokyo, Japan). GH provocative tests were performed using arginine (0.5 g/kg. iv ; Morinaga Co., Tokyo, Japan).

Results

From January 2000 to December 2004, a total of 83,232 infants were screened. The results of screening are shown in Table 1. We found 41 patients affected by primary CH identified high TSH. These patients were treated with T4 supplementation. Therefore, the incidence of primary CH was 1 in 2,030. It has not been determined whether or not the conditions of most of these patients are permanent.

During this period, 22 infants showed low free T4 levels by the 1st and 2nd screening and were referred to a specialized hospital. Of these 22 infants, 6 showed normal thyroid results at the time of evaluation and were judged to be normal. Among these infants, two were preterm with birth weights of $< 2,000 \text{ g}$. The other 3 infants were found to have a deficiency of thyroxine-binding globulin. The other 4 infants showed low free T4 at the time of evaluation without any signs of hypothyroidism. The thyroid function of these infants normalized during the next six months of life, and thus, these infants were judged to have transient central CH. No information was available for three infants. None of the mothers of the infants had hyperthyroidism. Overall, 6 infants with central CH were detected (Table 1). Therefore, the

Table 1 Results of neonatal screening for congenital hypothyroidism in Sapporo (2000–2004)

Total number of screened newborns	83232
TSH	
Recall	542
Further evaluation	70
Free T4	
Recall	629
Further evaluation	22
Central hypothyroidism	6 (1/13,872)
Primary hypothyroidism [#]	41 (1/2030)

[#]It has not been determined whether or not these patients have permanent primary hypothyroidism.

frequency of central CH during this period was 1:13,872. In Table 2, the results of the 1st and 2nd neonatal screenings and initial serum determinations are shown. All infants had low free T4 concentrations (0.62–0.96 ng/dl) despite normal or low TSH concentrations (<0.5–3.3 μ U/ml) at the 1st screening. The clinical characteristics, hormone deficiencies and findings of brain MRIs for six infants are shown in Table 3. Four of the six patients (patients 1, 2, 3 and 4);(67%) had multiple pituitary hormone deficiency. The clinical course of patient 1 was previously reported (10). Patients 1, 3 and 4 had symptoms of hypopituitarism. Patient 3 had a cleft palate

Table 2 Patients with central CH detected by neonatal screening in Sapporo city

Patient	Sex	Results of the 1 st neonatal screening		Results of the 2 nd neonatal screening		Age (day)	Initial serum determination	
		TSH (μ U/ml)	Free T4 (ng/dl)	TSH (μ U/ml)	Free T4 (ng/dl)		TSH (μ U/ml)	Free T4 (ng/dl)
1	M	1.3	0.75	2.2	0.54	21	2.53	0.77
2	M	3.2	0.96	5.2	0.78	27	7.14	0.80
3	F	3.1	0.62	2.3	0.82	39	2.96	0.75
4	F	3.3	0.75	4.4	0.73	26	6.89	1.12
5	F	<0.5	0.78	1.5	0.47	45	1.15	0.92
6	M	1.2	0.68	0.31	0.62	22	2.70	0.57

Table 3 Clinical characteristics, MRI findings, and defective hormone of patients

Patient	Clinical features	Brain MRI	Pituitary hormone deficiency
1	Hypoglycemia, Hyperbilirubinemia, Micropenis	Small anterior pituitary lobe, ectopic posterior pituitary lobe, invisible stalk, left optic nerve dysplasia	TSH, GH, LH, FSH, ACTH
2	Schizencephaly	Small anterior pituitary lobe, ectopic posterior pituitary lobe, invisible stalk	TSH, GH
3	Hypoglycemia Cleft palate and lip	Ectopic posterior pituitary lobe, very thin stalk	TSH, GH
4	Hyperbilirubinemia, Nystagmus	Very thin stalk	TSH, GH
5	Prader Willi syndrome	Not done	Not done
6	Normal	Normal	TSH

and patient 4 had nystagmus. Brain MRI showed anomaly of the hypothalamic-pituitary region, such as a small anterior pituitary lobe, ectopic posterior pituitary lobe, invisible stalk and very thin stalk in these patients. In addition, patient 2 had schizencephaly, a rare type of cerebral malformation.

Patient 5 was diagnosed as having Prader-Willi syndrome. Brain MRI showed that patient 6 had a normal hypothalamic-pituitary region. At the age of 5 years, a thyrotropin releasing hormone (TRH) test was performed after temporary discontinuation of T4 supplementation. At this time, his serum free T4 was 0.67 ng/dl and free T3 2.76 pg/ml. His serum TSH levels after TRH stimulation showed a high peak (56.4 μ U/ml) and delayed decline (27 μ U/ml at 120 min). Thyroid imaging demonstrated a normal thyroid gland. Secretion of other anterior pituitary hormones was normal, and thus he was diagnosed as having isolated central CH.

Discussion

Our newborn screening program based on simultaneous TSH and free T4 measurements identified 41 infants with primary CH (1:2030) and 6 infants with central CH (1:13,872). The frequency of primary CH was higher than the previously reported frequency in Japan (11). However, it is noteworthy that the permanence of hypothyroidism in these patients has not been fully assessed. Moreover, as this study was short term and the number of patients included in it was small, we can not draw any conclusion concerning the high frequency of primary CH.

Regarding central CH, initial estimates of the prevalence of central CH in the United States and Canada range from 1:110,000 to 1:29,000 (1). However, Hanna *et al.* (4) reported detection of five infants with central CH by neonatal screening and 10 infants after clinical presentation among 430,000 infants screened. Thus, the rate detected by neonatal screening was 1 in 86,000, and the actual incidence was likely 1 in 28,667.

One of the reasons for the high incidence could be a more comprehensive screening system in Oregon than that in other states in the USA. Recently, Lanting *et al.* (8) reported the results of a neonatal screening program based on initial T4 and consecutive TSH determination with T4 binding globulin (TBG) measurement in the Netherlands. According to their study, among 385,000 infants screened during the 1995–2000 period, the prevalence of central CH was 1 in 16,404 live born infants. They compared this data with the results of their previous research from 1981–1989. In past 9 years, the incidence of central CH was estimated as 1:26,000 (12). They mentioned that the higher incidence in recent data is presumably due to the representative and unbiased cohort. It is also speculated that both the mildest and most severe cases were missed in the previous survey. In the Northeast Italian Screening Program, four patients with central CH were identified by low T4 levels (9).

In our study, the frequency of central CH (1:13,872) was higher than other studies. One reason for this is that it is easier to identify all children diagnosed with central CH in one particular city as opposed to larger area. Further long-term study is necessary to clarify the actual prevalence of central CH in the Japanese population.

Hanna *et al.* (4) described that 16 of 19 patients with central CH detected by neonatal screening had clinical features of hypopituitarism. In the report of van Tijn *et al.* (7), 78% of patients with central CH had multiple pituitary hormone deficiency and 53% had pituitary malformations on MRI. In our study, 4 patients had abnormal findings in pituitary and hypothalamic regions on MRI, and these patients had multiple pituitary hormone deficiency. If we had measured TSH alone in our screening program, we would have missed patients 1, 2, 3 and 4. Thus, free T4 measurement would be advantageous in early recognition of multiple pituitary hormone deficiency.

In conclusion, the frequency of central CH is 1 out of 13,872 in Sapporo. As suggested, simultaneous TSH and free T4 measurement is useful for early recognition of multiple pituitary hormone deficiency.

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