Further Studies on Episodic Occurrence of Congenital Dysgenetic Hypothyroidism in Osaka, Japan

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Abstract. A total of 1,228,551 newborn babies, who were almost all of babies born in Osaka for 14 years (168 months), were screened for congenital primary hypothyroidism by an identical mass-screening program using the thyrotropin method, and 429 patients with hypothyroidism due to thyroid dysgenesis (dysgenetic hypothyroidism) were found. The occurrence of the patients in every month was not random but episodic and the incidence was higher in the late autumn (from October to December). These observations support a hypothesis that some environmental factors may cause this disorder overtime and the possibility of relation with intrauterine viral infection was discussed.

Key words: Neonatal screening, Congenital hypothyroidism, Episodic occurrence, Environmental factors, Intrauterine viral infection

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CONGENITAL hypothyroidism (CH) is a well known disease causing mental and growth retardation and various types of the disease have been recognized [1]. The etiology of the developmental defect of the thyroid termed thyroid dysgenesis including thyroid aplasia, hypoplasia and ectopic thyroid has not yet been clarified, even if the congenital hypothyroidism due to thyroid dysgenesis (dysgenetic CH) is the most common cause of CH [1]. In 1954 Childs and Gardner [2] reported that occurrence of CH had no significant seasonal variation. On the contrary, Miyai *et al.* [3] demonstrated the seasonal occurrence of CH in the Osaka area in Japan and proposed a hypothesis that an unknown environmental factor may cause the disease. Subsequent studies revealed that the seasonal occur-

rence of the disease was observed in some areas (Japan, Australia, Quebec and Toronto) but the seasons were not identical and such seasonality could not be found in other areas (Pennsylvania, Norway, France and Switzerland) [4]. Even if an environmental factor may relate to the occurrence of CH, they would be masked when a small number of patients from heterogeneous sources (from hospitals or general population by different mass-screening programs) were analyzed in wide areas for short periods.

Therefore this study was designed to analyze the occurrence of dysgenetic CH with a large number of patients found in the general population by an identical mass-screening program in a restricted area for long period.

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Subjects and Methods

The study was performed in Osaka prefecture and Osaka city (total area: 1,893 km², averaged general population: 8,800,000) for 14 years (168 months) from January 1989 to December 2002.

Subjects

The original data of CH were obtained from the Report of the CONISO with its permission. The patients with primary CH were found in the general population by an identical neonatal mass-screening program. Thyrotropin in dried blood samples on filter paper taken from the neonatal babies was measured by the enzyme immunoassay using a commercial kit (Eiken Co., Tokyo) [5–7]. The final diagnosis of CH was made from their laboratory findings, signs and symptoms by clinical pediatric endocrinologists. Among these, cases of suspected dysgenetic CH were selected by excluding familial, iatrogenic (including excess or deficient iodine intake), transplacental autoimmune, goitrous and transient cases.

A total of 1,228,551 newborn babies (almost 100% of live births in the general population) (the ratio of male to female babies = 1.058 : 1) were screened and 429 patients with suspected dysgenetic CH (the ratio of male to female patients = 1 : 1.201) were found. The incidence of the patients was calculated as 3.5 cases/ 10^4 tests (1/2,850). The averaged incidence of the disorder in each month was calculated as follows. [averaged incidence of each month] = [number of patients born in 3 months (in each month and one month pre- and post-the particular month)] / [number of newborn babies screened in the same 3 months].

Data of the prevalence of influenza were obtained from the Report on Survey of Infectious Diseases in Osaka.

Statistical analysis

The test for the proportion of the averaged incidence of the patients in each month throughout the tested period was performed by the Poisson distribution and by the χ^2 test using the contingency table. The incidence of the patients in various seasons, its relation with the prevalence of influenza and that in sex differences were analyzed by the χ^2 test.

Results

Fig. 1 shows the averaged incidence of dysgenetic CH in each month during the tested period. The occurrence was episodic, and the incidence was significantly higher in 14 months. The seasonal variation of the

incidence of the patients is shown in Fig. 2. The incidence was significantly higher in the late autumn (from October to December).

Discussion

In the present study the incidence of occurrence of primary CH may be reliable since the study involved almost all newborn infants born in the Osaka area during the tested period by means of an identical mass-screening program. Most of the patients were assessed to be dysgenetic type since thyroid dysgenesis is known to be the most common cause of primary CH, and diagnosis of suspected dysgenetic CH was made by experts of clinical pediatric endocrinologists who ruled out familial, iatrogenic, transplacental autoimmune, transient, and goitrous types of CH.

The etiology of dysgenetic CH has been studied extensively and some candidate genes were reported [8–10] but it has not yet been clarified completely. The present study supports the hypothesis postulated by Miyai *et al.* that some environmental factors cause this disease [3, 4]. It is well known that intrauterine infection of the fetus during early pregnancy induces some congenital anomalies of newborn babies [11–14]. The findings that congenital anomalies occurred epidemically after the prevalence of rubella in a restricted area supported a clinical entity of congenital rubella syndrome [15, 16]. We made an analogical approach to examine the relationship between viral infection and occurrence of CH. As an example, Table 1 shows that the incidence of dysgenetic CH in the period of 9 to 10 months after the prevalence of influenza is statistically higher than that in any other period. Although the correlation may be spurious this is suggestive data. Contradictory results have been reported concerning the relationship between maternal influenza and fetal anomalies [17–20]. A preliminary survey by Miyai *et al.* [21, 22] failed to obtain significant positive data of various antiviral antibodies including influenza in CH. It is well known that some diseases are due to both the genetic background and environmental factors. For example, persons who had HLA-B27 often developed Reiter's syndrome after an episode of shigellosis [23]. Miyai *et al.* also reported that the incidence of the HLA-Aw24 antigen was significantly higher in mothers of Japanese patients of dysgenetic CH [24, 25].

Fig. 1. Averaged incidence of dysgenetic CH in each month (see subjects and methods). J: January, F: February, M: March, A: April, M': May, J': June, J'': July, A': August, S: September, O: October, N: November, D: December. *Statistically significant by the Poisson distribution(a), and by the χ^2 test using the contingency table (b), *1: $p < 0.05$ (a, b), *2: $p < 0.03$ (a, b), *3: $p < 0.005$ (a, b), *4: $p < 0.0005$ (a), $p < 0.001$ (b).

Fig. 2. Seasonal variation of incidence of dysgenetic CH. Statistically significant by χ^2 test, *1: $p < 0.01$, *2: $p < 0.002$.

Table 1. Relationship between the prevalence of influenza and incidence of dysgenetic CH

	CH	no CH	total
prevalence of influenza	181	413903	414084
no prevalence of influenza	248	814219	814467
total	429	1228122	1228551

Statistically significant by χ^2 test ($p < 0.0001$)

prevalence of influenza: period for 57 months which were 9 to 10 months after the prevalence of influenza (when more than 1,000 patients of influenza per month were found in the Osaka area), no prevalence of influenza: period for 111 months other than the above period, CH: number of patients with dysgenetic CH, no CH: number of newborn babies without dysgenetic CH found by the mass-screening in the period

Furthermore, the present study revealed that the incidence of dysgenetic CH was significantly higher in female than in male babies ($p < 0.02$). These findings

suggest some genetic factors for occurrence of CH. Further studies are necessary to verify the hypothesis that an environmental factor such as viral infection in

association with genetic background causes dysgenetic CH.

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