NOTE

DiGeorge Syndrome with Graves' Disease: A Case Report

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Abstract. DiGeorge syndrome (DGS) is characterized by aplasia or hypoplasia of the thymus and parathyroid glands, cardiac defects and anomaly face. This syndrome is usually associated with hypocalcemia resulting from hypoparathyroidism. In most cases the initial symptom is tetany caused by hypocalcemia within 24–48 hours after birth, with symptoms by immune abnormality appearing later. We report a woman who passed with no symptoms before age 18 and was diagnosed DiGeorge syndrome by tetany with developing auto-immune thyroid disease (Graves' disease). She had surgery for intraventricular septal defect at age 3, hypoparathyroidism, decrease of T cells in peripheral blood and the deletion of the 22nd chromosome long arm (22q11.2). It is supposed that abnormalities of immune function of this case are not complete as indicated by complicating of Graves' disease, and contributing to her long-term survival.

Key words: DiGeorge syndrome, Hypoparathyroidism, Graves' disease

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DIGEORGE syndrome is third and fourth pharyngeal pouch/arch syndrome, and characterized by aplasia or hypoplasia of the thymus and parathyroid glands, cardiac defects and anomalies of the face [1, 2]. It also affects other portions of the pharyngeal pouch besides the third and fourth pharyngeal pouch, and abnormal migration of neural crest cells is thought to be the cause of this anomalies [1, 2]. More than 95% of the subjects reveal the deletion by translocation of the 22nd chromosome long arm q11 [3–15]. The initial symptom is tetany due to hypocalcemia within 24–48 hours after birth, with symptoms associated with immune defects appearing later. Most of patients die of infections or cardiovascular problem before 2 years of age [16]. We reported a case of partial DiGeorge syndrome passing without symptom until 18 years of age. She

was also diagnosed as Graves' disease, an auto-immune thyroid gland disease although she has immune deficiency. To our knowledge, there are only 2 reported cases of DiGeorge syndrome complicated with Graves' disease, hence it is extremely rare [17, 18].

Case Report

An 18-year-old Japanese woman was admitted to our hospital because of numbness in both hands. She had a history of surgery for intraventricular septal defect (VSD) at age 3, cobbler's chest at age 11, and chronic sinusitis at age 16. She easily suffered from the common cold after birth. Her mental development was normal.

In December 1996, she had numbness of both hands and general fatigue. In January 1997, when she visited our hospital with symptoms of common cold, she had tachycardia and finger tremor. Elevated free-T3 (20.20 pg/ml) and decreased TSH levels (0.01 μ U/ml) were observed with increasing titer of microsome test ($\times 400$). She was diagnosed

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Fig. 1. Anomaly face: Size of auriculas is small and the position of ear pipe is low rank.

as Graves' disease and prescribed 200 mg of propylthiouracil. Because of continued fatigue and numbness of hands, she was admitted to our hospital on March 17th.

On physical examination, her height was 148 cm, weight 48 kg, blood pressure 128/86 mmHg, and pulse rate 79 beats/min. The size of her auriculas was small and the position of her ears was low as shown in Fig. 1. Diffuse and enlarged thyroid glands (grade I, category of Shichijo [19]) were palpable. She had VSD operation scar on her chest. Trousseau's sign was observed when she was being checked for blood pressure.

Laboratory findings showed severe hypocalcemia (5.4 mg/dl) and hyperphosphatemia (8.1 mg/dl)

Table 1. Laboratory Findings

	Normal range	Laboratory findings
Complete blood count		
RBC ($\times 10^6/\text{mm}^3$)	4.5~9.0	5.2
Hemoglobin (g/dl)	11.9~15.0	14.2
WBC ($\times 10^3/\text{mm}^3$)	4.5~9.0	5.2
Neutrophil (%)	46.1~63.3	46.0
Eosinophil (%)	0.8~5.0	4.0
Basophil (%)	0.2~1.3	0.4
Lymphocyte (%)	27.5~43.1	38.6
Monocyte (%)	3.8~6.2	8.0
Plt ($\times 10^3/\text{mm}^3$)	132~380	131
Biochemistry		
Na (mEq/l)	137~149	142
K (mEq/l)	3.7~5.0	4.4
Cl (mEq/l)	98~109	101
Ca (mg/dl)	8.6~11.0	5.4
P (mg/dl)	2.5~4.5	8.1
Uric acid (mg/dl)	3.0~5.5	2.6
Urea nitrogen (mg/dl)	8~15	15
Creatinine (mg/dl)	0.57~0.87	0.44
Serum immunoglobulins		
IgG (mg/dl)	870~1700	2180
IgA (mg/dl)	110~410	160
IgM (mg/dl)	33~190	117
Endocrinological		
Serum c-PTH (ng/ml)	1.3~	0.3
Serum high sensitive PTH (pg/ml)	74~273	50
free T_3 (pg/ml)	3.9~5.5	4.3
free T_4 (ng/ml)	1.1~1.9	1.2
TSH ($\mu\text{U}/\text{ml}$)	0.48~4.82	0.07
Thyroid test	0	$\times 6400$
Mycrosome test	0	$\times 6400$
TBII (%)	-10.0~10.0	2.7
%TRP (%)	85~95	97.8

Fig. 2. Ellsworth-Howard test: changes in urinary excretion of inorganic phosphate (Pi) and cyclic AMP (c-AMP) increased in response to intravenous infusion of PTH (100u).

Fig. 3. Chromosome test: Deletion of the 22nd chromosome length arm (22q11.2) is recognized in FISH (fluorescence in situ hybridization).

(Table 1). Urinary calcium excretion decreased to 0.045 mg/day. QTc was extended to 0.49 second on electrocardiogram. We recognized calcification in right base nucleus and left caudate nucleus in head CT. The plasma level of parathyroid hormone was low (c-PTH 0.3 ng/ml, high sensitive PTH 50 pg/ml). Liver function tests were within normal limits. Urinary excretion of phosphate increased to 67.8 mg/2 hr and cyclic AMP increased to 6.31 μ mol/hr after intravenous injection of human PTH (Fig. 2). Weakly positive tuberculin reaction (8 $\times$ 8 mm) revealed decreased T cell immunity and decreased T cell series was observed in lymphocyte subset (Table 2). We recognized the deletion of the 22nd chromosome length arm (22q11.2) in chromosome by fluorescence in situ hybridization (FISH) (Fig. 3).

Table 2. Lymphocyte subsets

Subjects			
CD3+19-	65.1%	(68~83)	Tcell
CD3-19+	17.0%	(5~15)	Bcell
CD16+3-	16.0%	(10~20)	NKcell
CD16-3+	49.3%	(68~82)	Tcell
CD3+4+	26.7%	(35~55)	CD4 Tcell
CD3+8+	17.7%	(18~35)	CD8 Tcell
CD3-8+	7.8%	(3~18)	Part of NKcell

This case was diagnosed as DiGeorge syndrome, because she had a history of VSD operation, hypoparathyroidism, decreased lymphocytes of T cell series in peripheral blood, deletion of the 22nd chromosome long arm (22q11.2) and characteristic faces.

She was treated with 1.0 μ g/day of alfacalcidol. One month later, when the serum calcium level increased to 9.0 mg/dl and the level of serum phosphorus decreased to 4.2 mg/dl, her tetany disappeared. She continued medication with propylthiouracil for Graves' disease because serum TSH level was still low (0.07 μ U/ml).

Discussion

Most patients with DiGeorge syndrome show tetany due to hypocalcemia within 24–48 hours after birth, because of aplasia or hypoplasia of the parathyroid glands. This patient had no history of tetany until age 18. Hyperventilation due to hypermetabolism with hyperthyroidism and mental irritation complicated with Graves' disease may induce tetany. Since the degree of hypoplasia of parathyroid glands in this case was incomplete, it was considered to be partial DiGeorge syndrome.

The thymus plays an important role in the maturation of T cells. Aplasia or hypoplasia of thymus in DiGeorge syndrome causes a decrease in the T cell series that makes a person prone to recurrent infection [20–22]. But the disturbance of cellular im-

munity in partial DiGeorge syndrome shows a heterogeneity corresponding to the degree of defect of the thymus tissue [23–25]. In the case of thymus aplasia with complete DiGeorge syndrome, the transplantation of thymus of embryo must be considered [26–28]. Although she easily suffered from common cold and had a history of chronic sinusitis, she was able to prevent from severe infection because the decrease of her T cell series was mild.

Recent investigation has pointed out the possibility that the genetic defect of DiGeorge syndrome is located in the 22nd chromosome length arm (22q11.2), which might be DNA binding protein [14]. Deletion of the 22nd chromosome long arm (22q11.2) was also identified by FISH in this case.

DiGeorge syndrome presents certain facial characteristics such as hypertelorism, microgenia and low ear position. In this case, her auriculae were small and the position of her ears was low, but the other characteristic features were not recognized.

The interesting points of this case are not only long-term survival, but also complication by Graves' disease. As discussed above, DiGeorge syndrome involves thymic dysfunction that influences the maturity of T cells, and might influence the occurrence of auto-immune disease. Adachi *et al.* reported that idiopathic thrombocytopenic purpura (ITP) complicated by DiGeorge syndrome [18]. It also

appears reasonable that such patients are predisposed to auto-immune disease as a result of thymic dysfunction. In our case, weakly positive tuberculin reaction revealed decreased T cell immunity and decreased T cell series observed in the lymphocyte subset, indicating the superiority of Th2. Patients with DiGeorge syndrome may show a shift to a more Th2-generated cytokine pattern. Thus, the unbalance of Th1/Th2 in patients with DiGeorge syndrome might trigger the onset of auto-immune disease such as Graves' disease or ITP. However, TSH receptor antibody was negative in this case. Thus, there is the possibility of complication by DiGeorge syndrome with hyperthyroidism due to non-auto-immune mechanisms such as somatic mutation causing constitutive activation of TSH receptor [29]. However, cases of DiGeorge syndrome with Graves' disease are quite rare, and only two cases have been reported to date [17, 18]. Further studies are necessary to investigate the relation between these two disease.

The leading cause of death is cardiovascular problems in the neonatal period or infancy. In our case, the patient had treatment for intraventricular septal defect. Since the defects in immunity were incomplete, complicating Graves' disease, these points may have contributed to her long-term survival.

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