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증 례

A DiGeorge Syndrome with both Basal Ganglia Calcification with 22q11.2 Deletion

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DiGeorge syndrome is a disorder caused by microdeletion in chromosome 22q11.2 with various abnormalities including cardiac anomaly, facial dysmorphism, thymic and parathyroid hypoplasia, cleft palate and immune dysfunction. The frequency of hypocalcemia caused by hypoparathyroidism is known to be approximately 60% of DiGeorge syndrome. It is known that the disorder mostly occurs in the neonatal period and the symptoms are improved afterwards. Herein we report a case of DiGeorge syndrome only accompanied by hypocalcemia caused by hypoparathyroidism without other abnormalities. She was first diagnosed only at the age of 22 with basal ganglia calcification that had been discovered in brain CT (Computed tomography).

Key words: DiGeorge syndrome, 22q11.2 Microdeletion, Hypocalcemia, Hypoparathyroidism, Basal ganglia calcification

Introduction

DiGeorge syndrome presents multi-systemic clinical manifestations such as cardiac anomaly, facial dysmorphism, immune deficiency due to thymic hypoplasia, hypocalcemic tetany due to parathyroid hypoplasia, and cleft palate. DiGeorge syndrome results from microdeletion of chromosome 22q11.2[1]. Among them, it is reported that hypocalcemia and hypocalcemic tetany caused by hypoparathyroidism appears mostly during the neonatal period and the symptoms improve with age[2]. The incidence of DiGeorge syndrome is one in 3,000-4,000 infants[1]. Only a few cases are reported about adult onset DiGeorge syndrome. Without typical features of DiGeorge syndrome, it is hard to make diagnosis. We experienced a case of DiGeorge syndrome diagnosed at the age of 22. She has been in relatively good health without history of seizure or tetany since the neonatal period. Since two years ago, she has been suffered from intermittent headache and dizziness and multiple basal ganglia calcification discovered on brain CT (Computed tomography). Consequently, she was diagnosed with DiGeorge syndrome with 22q11.2 microdeletion. We hereby report a case of DiGeorge syndrome that presented with hypocalcemia and calcification of basal ganglia without other clinical manifestation of DiGeorge syndrome.

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Case Report

A 22-year-old woman was referred to our hospital due to the brain CT finding of calcification of both basal ganglia (Fig. 1). On Past medical history, she has been suffered from intermittent headache and dizziness for two years. But there were no history of tetany or seizure. On Family history there were also no specific findings. On developmental history, the patient spent her school days mostly in South America and Vietnam, and her school grades were maintained above average. She attained low average level IQ (Intelligence quotient 86) in Korean Wechsler Adult Intelligence Scale (K-WAIS) performed in our hospital.

On physical Examination, her weight and height were 56.3 kg (50-60 percentile) and 152 cm (below 5 percentile). Her maxilla was shown to be more protruded compared to the mandible (Fig. 2). Heart murmur was not noted on heart auscultation, and the Trousseau sign and Chvostek sign did not appear on neurological examination. Her muscular strength was normal.

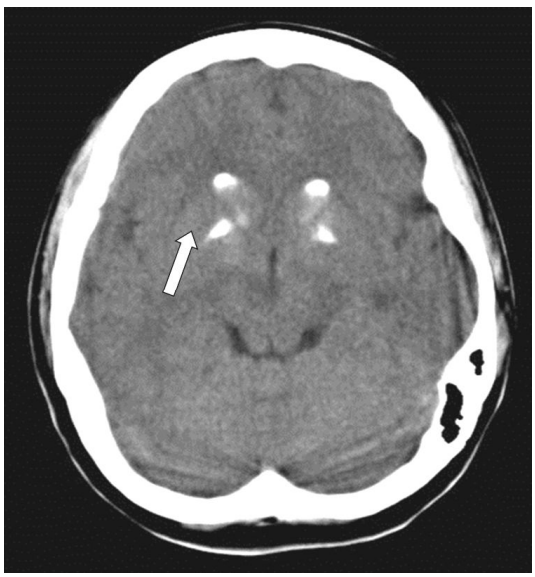

Fig. 1. The computed tomography (CT) of brain showed multiple calcification of bilateral basal ganglia.

On laboratory findings, the results of peripheral blood test are as follows (Table 1); white blood cell 4.790 k/mm^3 (normal range 4-10 k/mm^3), hemoglobin 9.4 g/dL (normal range 11-16 g/dL), platelet 165 k/mm^3 (normal range 130-380 k/mm^3), ionized calcium 0.88 mmol/L (normal range 1.09-1.3 mmoL), total calcium 5.4 mg/dL (normal range 8.4-10.2 mg/dL), phosphorus 5.6 mg/dL (normal range 2.6-4.6 mg/dL), parathyroid hormone 6.7 pg/mL (normal range 14-72 pg/mL) and 1,25(OH)$_2$Vitamin D3 19.8 pg/mL (normal range 25.1-66.1 pg/mL). iron 18 ug/dL (normal range 29-164 ug/dL), TIBC (total iron binding

Table 1. Peripheral Blood Test

		Min	Max	Unit
WBC count	4.79	4.0	10.0	$\times10^3$/uL
Hemoglobin	9.4	11	16	g/dL
Hct (Hematocrit)	30.8	37	47	%
Platelet count	165	130	380	$\times10^3$/uL
Glucose	101	70	110	mg/dL
Calcium total	5.4	8.4	10.2	mg/dL
Phosphorus	5.6	2.6	4.6	mg/dL
BUN	10.7	10.0	26.0	mg/dL
Creatinine	0.7	0.6	1.2	mg/dL
AST	16	8	39	IU/L
ALT	20	5	45	IU/L
Na	144	135	145	mmol/L
K	3.8	3.6	5.5	mmol/L
Cl	99	96	108	mmol/L
1,25(OH)$_2$ VitaminD3	19.8	25	66	Pg/mL
iCa (Calcium, ionized)	0.88	1.09	1.3	mmol/L
Iron	18	29	164	ug/dL
Ferritin	<1.0	4.63	204	ng/mL
PTH	6.7	14	72	pg/mL
calcitonin	<1.0	1.0	4.8	pg/mL
T cell	56	53.8	81.8	%
Th cell	35	29	55.4	%
Ts cell	20	12.2	35	%
B cell	15	6.2	22.7	%

capacity) 395 ug/dL (normal range 250–400 ug/dL), ferritin <1.0 ng/mL (normal range 4.63–204 ng/mL). QTc interval was prolonged to 496 ms (normal range <440 ms) in electrocardiogram, and cardiac anomaly was not found in 2D echocardiography. Bone age was shown to be normal on plain left hand radiography. The cell-mediated and humoral immunities were also found to be normal (Table 1). Both basal ganglia calcification was clearly observed in brain CT (Fig. 1). Parathyroid hypoplasia was not found in parathyroid scan.

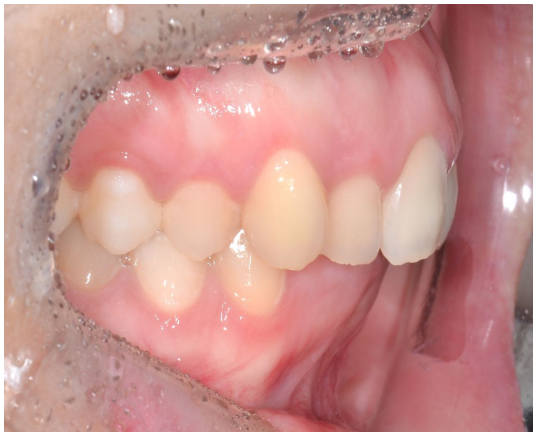

Fig. 2. Her maxilla is protrused compared to the mandible. And she is wearing braces.

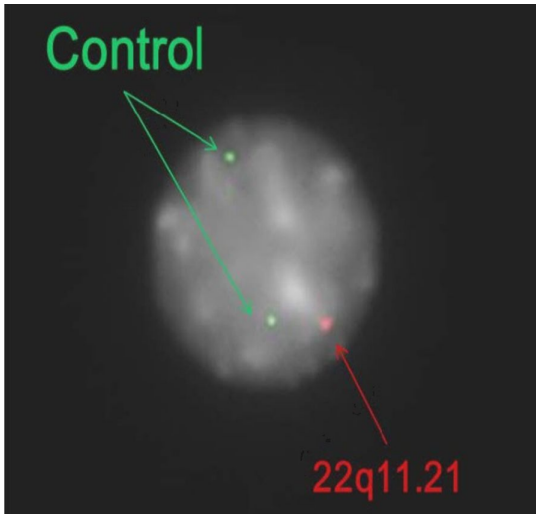

Fig. 3. Fluorescence in situ hybridization (FISH) test revealed 22q11.2 microdeletion compared to control group.

22q11.2 microdeletion was identified in fluorescence in situ hybridization (FISH) test (Fig. 3), accordingly she was finally diagnosed with DiGeorge syndrome. And iron deficiency anemia is discovered incidentally. Calcium carbonate and alfacalcidol were administered for hypocalcemia, aluminum hydroxide was for hyperphosphatemia, and ferrous sulfate was for iron deficiency anemia. After 2 months of medication, calcium, phosphorus concentrations and hemoglobin were improved and subjective symptoms of headache and dizziness improved markedly.

Discussion

DiGeorge syndrome is usually diagnosed in early childhood in the presence of a typical facial appearance, congenital heart defects, palatal cleft and early-onset hypocalcemic tetany. In contrast, our patient was first diagnosed at 22 years of age with hypocalcemia casused by hypoparathyroidism. Pathophysiologically, in DiGeorge syndrome, 22q 11 monosomy occurs due to microdeletion at the position 11.2 of 22q chromosome and it occurs most frequently among all autosomal deletion syndromes. A total of 30–50 genes are present within the commonly deleted region of chromosome 22q11.2 that includes multiple transcription factors regulating thymus and parathyroid development[3].

It was reported to affect one in 4,000 infants in the United States, and one in 3,000 worldwide [4]. Clinical features of DiGeorge syndrome vary depending on patient age. During infantile and childhood, the organ malformations such as con-

genital heart disease, malfunctioning parathyroid glands and hypoplastic thymus dominate. Later, psychiatric illnesses such as schizophrenia appear and dominate[5]. Clinical manifestations of DiGeorge syndrome include congenital heart disease (50-75%), immunodeficiency (35-40%), hypocalcemia/hypoparathyroidism (>60%), learning disabilities/developmental disabilities (>90%), palatal defects (75%) and characteristic facial features (>90%)[6, 7]. For congenital heart disease, It include truncus arteriosus, interrupted aortic arch, aorta dominance, Fallot's tetralogy and ventricular septal defect. The spectrum of immune disorder is various ranging from lowered humoral immunity to severe immunodeficiency[8].

It is known that basal ganglia calcification occurs generally in patients with chronic hypocalcemia[9]. But it was described that the symptom was rare in patients with DiGeorge syndrome[10], which was presumed to be due to persistent hyperphosphatemia[4]. Hypocalcemia may occur in approximately 60% of DiGeorge syndrome. And it is known to occur mostly during the neonatal period[2]. Hypocalcemia usually improves over the first year of life because of parathyroid gland hypertrophy and dietary calcium intake. However, in some cases, hypocalcemia does not always occur in the neonatal period, and there have been a few rare cases that was first diagnosed only at adolescence or adulthood[11-13]. Late-onset appearance of symptomatic hypocalcemia can be caused by hypocalcemic stress. When calcium requirements are increased during adolescence, pregnancy, surgery or infection, PTH (parathyroid hormone) secretion can be inadequate, leading to hypocalcemia[14]. In 1983, Winter et al.[15] reviewed 135 cases and found that only 12 patients were older than 2 years of age. In Korea, a 13 year old child has been diagnosed with the DiGeorge syndrome due to hypocalcemic seizure and since then, additional cases have been continuously reported[16, 17]. Similar to the case of our patient, basal ganglia calcification was found in 2 cases in Korea before. But there was no seizure caused by hypocalcemia in the case of our patient. It is the difference between our case and 2 cases reported in Korea.

At adulthood of these patients, there are another problems about neuropsychological disease. Some researches have shown that these patients IQ scores are lower than normal and they have a mild developmental delay[18]. And attention-deficit disorder is also described with Digeorge syndrome, So most of these patients need educational supports and consultations with neuropsychologist[19].

In this case, most of clinical manifestations of DiGeorge syndrome such as congenital cardiac anomaly, immune dysfunction, learning disability and cleft palate were not found. Only hypocalcemia due to hypoparathyroidism and basal ganglia calcification were detected. But the patient had no clinical manifestation of hypocalcemic seizure. She has been confirmed to have 22q11.2 microdeletion with FISH. In a patient with basal ganglia calcification and hypocalcemia, DiGeorge syndrome should be included in differential diagnosis, whether the patient have other clinical manifestation of DiGeorge syndrome such as cardiac anomaly, facial dysmorphism, immune deficiency due to thymic hypoplasia, hypocalcemic tetany due to parathyroid hypoplasia, and cleft palate or not.

Summary

We report here a mild case of DiGeorge syndrome that showed only basal ganglia calcification, hypocalcemia caused by hypoparathyroidism, and

hyperphosphatemia in a 22 year old woman. But there were no abnormal findings of cardiac abnormality, immune dysfunction, learning disability and cleft palate. So we intend to report the case of DiGeorge syndrome with literature review.

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