An Adult Case of 22q11.2 Deletion Syndrome Diagnosed in a 36-year-old Woman with Hypocalcemia Caused by Hypoparathyroidism and Hashimoto’s Thyroiditis

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Abstract

22q11.2 Deletion syndrome is recognized to be a major cause of congenital hypoparathyroidism, and affected patients exhibit a range of autoimmune characteristics. The syndrome becomes apparent in early childhood and is rarely diagnosed in adulthood. This report describes an adult case of 22q11.2 deletion syndrome first diagnosed in a 36-year-old woman with hypocalcemia caused by hypoparathyroidism and Hashimoto’s thyroiditis. It is important to diagnose 22q11.2 deletion syndrome in adults because such patients are still at high risk for developing treatable diseases, such as hypocalcemia and autoimmune diseases.

Key words: 22q11.2 deletion, autoimmune disease, hypocalcemia, thyroiditis

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Introduction

Congenital hypoparathyroidism typically manifests with hypocalcemia (1), with 22q11.2 deletion syndrome being recognized as its major cause (2). This syndrome, which includes DiGeorge syndrome and velocardiofacial syndrome, is caused by microdeletion of chromosome region 22q11.2 (3). It is associated with a typical facial appearance and clinical symptoms and findings such as congenital heart defects, immune deficiency caused by thymic hypoplasia, palatal cleft and mental retardation (2, 4, 5). In addition, autoimmunity is more common in affected patients than in the general population (6).

A range of autoimmune features associated with 22q11.2 deletion syndrome have been described, including cytopenia and disorders of systemic autoimmunity, particularly rheumatoid arthritis and autoimmune thyroid disease (6). This syndrome typically becomes apparent in early childhood and is rarely diagnosed in adulthood (7-9). To our knowledge, there are no reports in the English literature of adult cases of this syndrome with hypocalcemia caused by hypoparathyroidism in Japan. We herein report an adult case of 22q11.2 deletion syndrome diagnosed in a 36-year-old Japanese woman with hypocalcemia caused by hypoparathyroidism and Hashimoto’s thyroiditis.

Case Report

Clinical summary

In July 2012, a 36-year-old woman was taken to a nearby hospital due to clouding of consciousness. An examination revealed hypocalcemia (serum calcium: 7.0 mg/dL; albumin: 4.3 mg/dL). She was referred to our department for further evaluation and treatment of hypocalcemia. Her height was 162.5 cm, her body weight was 67.2 kg, her blood pressure was 130/73 mmHg and her pulse was 80 beats per min. She had been suffering from occasional convulsions and clouding of consciousness since 33 years of age. Her previous medical history included surgery for tetralogy of Fallot at 5 years of age and patellar dislocation at 8 and 32 years of age. At 13 years of age, she developed hearing loss. She was diagnosed with type 2 diabetes mellitus at 20 years of age.

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age and Hashimoto’s thyroiditis at 33 years of age. She also experienced a mild learning disability. For these ailments, she was prescribed metildigoxin, verapamil hydrochloride, voglibose, metformin hydrochloride, nateglinide, pioglitazone hydrochloride and levothyroxine sodium.

A physical examination revealed swollen eyelids with blepharophimosis and lower and lateral displacement of both auricles (Fig. 1); however, no palatal anomalies were observed. The patient’s nose was wide and flat, and her mouth was small. Her thyroid was diffusely enlarged. Chvostek’s sign was negative. Biochemical analyses performed on admission to our hospital showed a low level of serum calcium (8.3 mg/dL), normal albumin levels (4.4 g/dL) and a normal level of phosphorus (4.4 mg/dL) under treatment with an intravenous drip of calcium gluconate (3.9 mEq/day) for one week. The urinary calcium excretion level (25 mg/day) and the creatinine clearance rate (111.7 mL/min) over 24 hours were within the normal limits. The serum intact parathyroid hormone (PTH) levels (17 pg/mL) were inappropriately low. The serum levels of thyroid-stimulating hormone (7.78 μIU/mL) were increased, while the free triiodothyronine (2.48 pg/mL) and free thyroxine (1.4 ng/dL) levels were within the normal ranges under treatment with 12.5 μg/day of levothyroxine sodium. The antithyroglobulin antibody levels (236 IU/mL) were positive; however, other autoantibodies, including antithyroid peroxidase antibodies (<6 U/mL), anti-glutamic acid decarboxylase antibodies (<0.3 U/mL), rheumatoid factor (<3 IU/mL) and antinuclear antibodies (<×40), were negative. The plasma glucose (fasting) level was 134 mg/dL and the HbA1c (NGSP) level was 8.2%.

22q11.2 deletion syndrome was suspected based on the findings of hypoparathyroidism, Hashimoto’s thyroiditis, a typical facial appearance and a previous history of tetralogy of Fallot. A fluorescence in-situ hybridization analysis using the TUPLE1 (22q11.2) probe demonstrated a microdeletion within the chromosome 22q11.2 region (Fig. 1). The patient had no history of severe infections. A T-cell subset analysis showed slightly lower levels of CD8 (13%; normal range: 17-44%) and normal levels of CD4 (34%; normal range: 30-55%), while a lymphocyte stimulation test revealed a normal T-cell function. The patient was administered a daily dose of 6 g of calcium lactate and 1 μg of calcitriol, and her serum calcium levels gradually increased to the normal ranges.

**Discussion**

22q11.2 deletion syndrome is usually diagnosed in early childhood in the presence of a typical facial appearance, congenital heart defects, palatal cleft and early-onset hypocalcemia. In contrast, our patient was first diagnosed at 36 years of age with hypocalcemia caused by hypoparathyroidism.

The clinical features of 22q11.2 deletion syndrome vary depending on patient age (10) but commonly include two or more of the standard findings: structural heart disease (50-75%), hypocalcemia/hypoparathyroidism (>60%), learning disabilities/developmental disabilities (>90%), palatal defects (75%), immunodeficiency (35-40%) and characteristic facial features (>90%) (11, 12). In addition, both common and rare multisystem features can be useful for making a diagnosis (12), such as sensorineural/conductive hearing loss, obesity, dysphagia, cholelithiasis, strabismus, scoliosis, thrombocytopenia, autoimmune thyroid diseases and schizophrenia and other psychotic disorders. Because our patient had tetralogy of Fallot, patellar dislocation, minor facial anomalies and presumably hearing loss during childhood, these findings were considered to be associated with 22q11.2 deletion syndrome.

The phenotype of adults with this syndrome can differ from that of children (4). In one study, adults with 22q11.2 deletion syndrome were found to have lower rates of congenital heart defects and higher rates of palate anomalies and learning disabilities/mental retardation compared with a
large group of predominantly pediatric patients (4). In adults, the identification of manifestations not observed at birth, such as minor palate anomalies and learning disabilities, may explain these differences. It is also possible that severe complications increase infant mortality, while findings that appear after infancy may not be reported as often in pediatric cases (4).

Hypocalcemia in patients with this syndrome frequently manifests during the neonatal period, while hypoparathyroidism caused by congenital agenesis or hypoplasia of the parathyroid glands is typically a rare finding in adults (7-9). Although it is unclear why symptomatic hypocalcemia appeared in an adult in our case, a spectrum of parathyroid gland dysfunctions have previously been reported to be associated with this syndrome (2, 13, 14) and may develop gradually with individual differences. Alternatively, a late-onset appearance of symptomatic hypocalcemia can be caused by hypocalcemic stress (15, 16). PTH secretion is sufficient to maintain the blood calcium levels under basal conditions; however, when calcium requirements are increased during adolescence, pregnancy, surgery or infection, PTH secretion can be inadequate, leading to hypocalcemia. It is also possible that late-onset hypocalcemia is caused by autoantibodies against calcium-sensing receptors (17).

A variety of autoimmune diseases often complicate this syndrome. Indeed, Genny et al. reported autoimmune disorders or detectable autoantibodies in 33% of children with 22q11.2 deletion syndrome (18), while Lima et al. observed autoimmune thyroid disease in three of 10 patients above 17 years of age, which is higher than the incidence observed in the general population in Norway (6). Although there are differences between races, for example Choi et al. showed that autoimmune thyroid diseases occurred in only two (3.3%) of 66 patients with 22q11.2 deletion syndrome in Korea (19), these results suggest that the incidence of autoimmune thyroid disease in adults with this syndrome is higher than that observed in the general adult population.

In conclusion, we herein reported an adult case of 22q11.2 deletion syndrome with hypocalcemia and Hashimoto’s thyroiditis. It is important to diagnose 22q11.2 deletion syndrome in adults because such patients are still at high risk for developing treatable medical diseases, such as hypocalcemia and autoimmune diseases.

The authors state that they have no Conflict of Interest (COI).

References