22q11.2 microdeletion in two adolescent patients who presented with convulsion

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Abstract

22q11.2 microdeletion which involves DiGeorge syndrome, velo-cardiofacial syndrome and conotruncal anomaly face syndrome occurs as a result of a deletion in the short segment of the long arm of the 22th chromosome. Patients with this syndrome have a wide clinical spectrum

including learning difficulty, dysmorphic face, cardiac anomalies, hypocalcemia, hypoparathyroidism, cleft palate, thymus anomalies, immune failure and speech and feeding problems. The number of clinical characteristics which have been reported to be related with this syndrome is higher than 180. All anomalies may not be present in all patients. In this article, a 12-year old female patient who was found to have 22q11.2 microdeletion with mild mental retardation and dysmorphic face and who presented to our hospital because of convulsion and a 13-year old male patient who was found to have 22q11.2 microdeletion with hypocalcemia, hypoparathyroidism, dysmorphic face and mental retardation and who presented to our hospital because of convulsion (it was learned from his history that he was being followed up in another center because of autism) were presented. (Türk Ped Arş 2014; 49: 70-3)

Key words: Hypocalcemia, convulsion, autism, mental retardation, 22q11.2 microdeletion

Introduction

22q11.2 microdeletion syndrome is the most common genetic syndrome in the population and it is observed in one of 4 000 live births (1, 2). The incidence of the syndrome gradually increases as the awareness increases. For example, in a study performed in USA, it was reported that the incidence was higher; the prevalence was 1:2 000 (3). This microdeletion was shown in some patients with DiGeorge syndrome, velo-cardiofacial syndrome and conotruncal anomaly face syndrome (2). These diseases which were previously thought to have different genetic origins have been named as 'CATCH-22 PHENOTYPE' (cardiac anomalies, abnormal facial appearance, thymic hypoplasia, cleft palate, hypocalcemia, 22q11.2 microdeletion) (4, 5). Hypocalcemia determined in any period of life may be the first finding of this microdeletion. Dysmorphic findings and mental-motor development should be examined in detail especially in patients with a history of neonatal hypocalcemia. In the literature, patients with 22q11.2 syndrome who were diagnosed in the adulthood because of accompanying dysmorphic facial findings during investigation of hypocalcemia have been reported (6-8). In this article, two patients who were found to have 22q11.2 microdeletion in the adolescence were presented.

Cases

Case 1

A 13-year old male patient presented to our hospital with a complaint of extensive tonic-clonic seizure. In his history, it was learned that he was born from parents who had no consanguinity and the pregnancy was normal. Hypocalcemia was found for the first time in the hospital which he was referred to because of a seizure in the neonatal period and he received calcium therapy, further investigations for hypocalcemia were not performed. He was followed up by child psychiatry when he was diagnosed with autism at the age of 2 years and the patient who had motor and mental retardation had no convulsion until the age of 13. On physical examination, he was found to have a body weight of 72 kg (>97p) and a height of 168 cm (90-97p). The patient had a dysmorphic face, short palpebral fissures, retrognathia, micrognathia and angular nose (Figure 1). Laboratory tests were as follows: serum calcium level: 5.8 mg/dL (N:8.4-10.2 mg/dL), phosphorous: 7.1 mg/dL (N: 2.7-4.5 mg/dL), parathormon (PTH) level: 7.1 pg/mL (N:10-70 pg/mL). Serum electrolytes, complete blood count and calcium/creatinine ratio in spot urine were found to be normal. The patient was thought to have

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hypoparathyroidism. On cranial tomography, a focal calcification area was found in the anterior part of the basal ganglia on the right side (Figure 2). Leukocyte count was found to be normal in the patient who had no history of recurrent infection. On cranial magnetic resonance imaging of the patient who had normal abdominal ultrasonographic examination, an interpeduncular cysterna lipoma was found accidentally. Echocardiography and electroencephalography were found to be normal. Intravenous 10% calcium gluconate was administered primarily and oral elementary calcium and vitamin D (1.25(OH)2D3) treatment was given subsequently. Sodium valproate treatment was started to control seizures. Fluorescent in situ hybridization (FISH) study which was performed using LSI TUPLE1 (HIRA) probe and LSI ARSA control probe revealed 22q11.2 microdeletion in the patient who had dysmorphic findings, severe mental retardation and autism.

Case 2

A 12-year old female patient presented to our hospital with a complaint of extensive tonic-clonic seizure. In her history, it was learned that she was born from parents who had no consanguineous marriage as the third child by cesarean section with a birth weight of 3500 g, afebrile seizures started at the age of three for the first time, she received sodium valproate treatment with a diagnosis of epilepsy in an external center, she had no seizures after treatment, her motor development stages were compatible with her age, her mental development was slightly retarded and she attended a normal school, but her academic performance was not well. On physical examination her body weight was found to be 35 kg (10-25p) and her height was found to be 146 cm (10-25p). She had a marked dysmorphic face with short palpebral fissures, retrognathia, angular nose and small ears (Figure 3a, b). A 1/6 systolic murmur which was best heard at the apex was found on auscultation. Laboratory tests revealed that her serum electrolytes and complete blood count were normal. Sodium valproate level was found to be low (20.6 ug/ mL (N:50-100)). Leukocyte count, lymphocyte subgroups and immunoglobulin levels which were measured in terms of immune failure in the patient who had a history of recurrent lower respiratory infections were found to be normal. Secundum type atrial septal disorder was found on echocardiography. On ophthalmoscopic examination, no pathology was found except for herpetic keratitis sequela in the right eye. Hyperventilation-induced epileptic disorder was found on electroencephalogram in the patient who had normal abdominal ultrasonographic examination. Mild conduction type hearing deficit was found in both ears on hearing test performed by otolaryngology. Metabolic screening tests performed in terms of metabolic diseases were found to be normal. Mild mental retardation was found using WISC (Wechsler Intelligence Scale for Children Revised). Fluorescent in situ hybridization (FISH) study which was performed using LSI TUPLE1 (HIRA) probe and LSI ARSA control probe revealed 22q11.2 microdeletion in the patient who was thought to have 22q11.2 microdeletion with these findings. The patient whose antiepileptic treatment was adjusted and whose seizures were controlled was started to be followed up after giving genetic counseling to the family.

Figure 1. Short palpebral fissures, retrognathia, micrognathia and angular nose structure in the patient who had a dysmorphic face

Figure 2. Excessively intensive areas compatible with calcsification in the frontal part of the main ganglia on the right side on non-contrast axial brain tomography sections

Figure 3. a, b. Dismorphic face characterized with short palpebral fissures, retrognathia, angular nose structure and small ears in our patient

Discussion

22q11.2 microdeletion syndrome includes DiGeorge syndrome, velo-cardiofacial syndrome and conotruncal anomaly face syndrome. Interstitial microdeletions in the 22q11 chromosome have been shown with a rate of 94% in patients with DiGeorge syndrome, with a rate of 83% in patients with velo-cardiofacial syndrome and with a rate of 15% in patients with conotruncal heart defect alone (9, 10). The syndrome has more than 180 clinical findings and the most important findings include marked facial appearance, cleft palate, heart defects, hypocalcemia, hypoparathyroidism, renal anomalies, learning problems, immunological problems, musculoskeletal anomalies and speech and feeding problems (5, 10). Short stature, anal atresia, inguinal hernia, hypospadias, scoliosis, facial nerve paralysis and thrombocytopenia may accompany the syndrome (5). In most patients, microdeletion occurs de novo and 8% shows an autosomal dominant inheritance (4). The patients have a notable facial appearance. The most common characteristics include narrow palpebral fissure, edematous palpebras, hypoplastic mandibula, depressed nasal bridge, square nose, dysmorphic earlobe and small mouth (5, 10). In our patient, short palpebral fissure, retrognathia, micrognathia, angular nose and small ears were the findings which indicated the diagnosis.

Learning difficulty, developmental retardation, speech disorder and psychiatric disorders are observed commonly in 22q11.2 microdeletion syndrome. Severe mental retardation is observed rarely, but mild mental retardation is observed more commonly (5). Among psychiatric diseases, association with attention deficit hyperactivity disorder and schizophrenia has been emphasized most commonly and association with autism, anxiety disorders and mood disorder has also been mentioned additionally (2). In the literature, psychiatric disorders including mainly schizophre-

nia have been reported in 10-30% of the patients with 22q11.2 microdeletion, autism has been reported in 15-45% and speech and articulation disorders have been reported in approximately 75% (2, 3). Our first patient had been followed up with a diagnosis of unexplained autism in an external center for years. Our second patient was being followed up with a diagnosis of mild mental retardation and learning difficulty in an external center. In this syndrome in which clinical findings show considerable variance, patients may present with cardiac problems or cleft palate alone or with mild mental retardation and dysmorphic face as in our second patient.

In this syndrome, endocrinological disorders including hypocalcemia, hypoparathyroidism, thyroid dysfunction and short stature may also be observed. Choi et al. (11) examined 61 patients who were diagnosed with 22q11.2 microdeletion in 2005 and found hypocalcemia in 20 patients and hypoparathyroidism in 8 of these patients, Graves in one patient, Hashimoto thyroiditis in one patient and short stature in 10 patients. In the study performed by Hiéronimus and McDonald-McGinn (1, 12), hypoparathyroidism and hypocalcemia were observed in 49-50% of the patients who were diagnosed with 22q11.2 microdeletion. In another study, 22q11.2 microdeletion was found in 10 of 14 patients who were diagnosed with hypoparathyroidism and only dysmorphic face and mild mental retardation were found in one patient similar to in our second patient. In this study, the age at the time of diagnosis ranged between 9 days and 13 years (13). In patients with 22q11.2 microdeletion, hypocalcemia may occur at any time of life and severe neonatal hypocalcemia may be the first sign of this microdeletion. In one study, hypocalcemia was found in the neonatal period in 60% of the patients who were diagnosed with 22q11.2 microdeletion and at the age of 18 years in one patient (14). In the neonatal period, patients may present with hypocalcemia due to hypoparathyroidism, seizures,

tremor or tetany. In addition, patients may also present at more advanced ages with complaints arising from hypocalcemia. For example, Philip et al. (7) made a diagnosis of 22q11.2 microdeletion in a 29-year old female patient who presented with numbness in the hands and feet, who had a history of hypocalcemia in the neonatal period and was completely asymptomatic in the interval period with findings of dysmorphic face and hypocalcemia. Van et al. (6) found 22q11.2 microdeletion in a 43-year old female patient who presented because of diarrhea and had been operated because of ventricular septal defect and cleft palate with findings of accompanying atypical face, hypocalcemia and hypoparathyroidism. In the majority of patients, hypocalcemia improves in the first one year, but hypocalcemia may be observed again in surgical interventions where calcium requirement is high because of subtle hypoparathyroidism, in infectious diseases, infancy, adolescence and pregnancy (15). In the history of our 13-year old male patient, it was learned that he was hospitalized in another center because of hypocalcemic seizure, his findings improved after calcium treatment, but no further investigations were made. In our patient who had dysmorphic face, mental retardation and unexplained autism, hypocalcemia and hypoparathyroidism were found when he presented because of seizure. With the present findings 22q11.2 microdeletion was considered and a diagnosis of 22q11.2 microdeletion was made with FISH method. Therefore, patients who are diagnosed with hypoparathyroidism and hypocalcemia like our first patient should be evaluated carefully especially in terms of dysmorphic findings and 22q11.2 microdeletion should be studied.

Conclusion

Clinical characteristics of the patients with 22q11.2 microdeletion are considerably variable. Patients who are diagnosed with hypoparathyroidism in the childhood should be absolutely investigated in terms of 22q11.2 microdeletion when dysmorphic findings are present. It should be kept in mind that patients with this microdeletion may present with dysmorphic face and mental retardation alone without any other systemic involvement.

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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