Hypocalcemic Seizure Mistaken for Idiopathic Epilepsy in Two Cases of DiGeorge Syndrome (Chromosome 22q11 Deletion Syndrome)

Pei-Lin Tsai¹, Li-Ming Lian¹,², and Wei-Hung Chen¹,²

Abstract—The chromosome 22q11 deletion syndrome, which is synonymous with DiGeorge syndrome, is a congenital anomaly characterized by abnormal facies, congenital heart defects, hypoparathyroidism with hypocalcemia, and immunodeficiency. Neurological manifestations of the chromosome 22q11 deletion syndrome are variable, and include mental deficiency, speech disturbances, learning difficulties, attention deficit hyperactivity disorder, and epilepsy. Hypoparathyroidism and hypocalcemia cause recurrent seizures if patients are not properly treated. We present two patients with poorly controlled epileptic seizures that turned out to be caused by DiGeorge syndrome with hypocalcemia. For such patients, the definitive treatment of seizures depends on recognition of this syndrome and correction of the hypocalcemic state, rather than the use of anticonvulsants.

Key Words: Hypocalcemia, Hypoparathyroidism, DiGeorge syndrome, Chromosome 22q11 deletion syndrome, Seizure

INTRODUCTION

The DiGeorge syndrome comprises features of dysmorphic facies, conotruncal cardiac defects, hypocalcemic hypoparathyroidism, T cell-mediated immune deficiency, and palate abnormalities. Most cases result from a deletion of chromosome 22q11.2 (the DiGeorge syndrome chromosome region, or DGCR). Several genes are lost including the putative transcription factor TUPLE1 which is expressed in an appropriate distribution. This deletion may present with a variety of phenotypes: velocardiofacial syndrome (VCFS or Shprintzen syndrome); conotruncal anomaly face syndrome (or Takao syndrome); and isolated outflow tract defects of the heart including tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch. A collective acronym, CATCH22 (Cardiac disease, Abnormal facies, Thymic hypoplasia, Cleft palate, and Hypocalcemia with chromosome 22 deletion), has been proposed to encompass the clinical spectrum. A small number of the DiGeorge syndrome patients have defects in other chromosomes, most notably 10p13. The microdeletion of...
22q11 is readily detected in both the prenatal and postnatal periods by commercially available fluorescent in situ hybridization (FISH) probes. The symptoms of hypocalcemia in the DiGeorge syndrome are variable and may often be overlooked. Here we report two cases of hypocalcemia-related seizures that were mistaken for idiopathic epilepsy until the final diagnosis of the DiGeorge syndrome was made.

**CASE REPORTS**

**Case 1**

A 44-year-old housewife was admitted because of confusion and an unsteady gait. She had had seizures since age 14. The seizures manifested as adhesive seizures with secondary generalization. She was treated with various anticonvulsants including phenobarbital, phenytoin, and primidone, but her seizures were not well controlled, occurring at least once a month. She was mentally retarded and barely graduated from an elementary school. At age 35, she suffered from a head injury which resulted in cerebral contusional hemorrhage and she was admitted for craniotomy. During hospitalization, she was found to have hypocalcemia (iCa: 2.54 mg/dL; normal range: 3.68-5.6 mg/dL); a subsequent examination led to a diagnosis of primary hypoparathyroidism (intact PTH: 3.1 pg/mL; normal range: 15-65 pg/mL). The patient was subsequently treated with calcium supplements and calcitriol, and her seizures were well controlled with phenytoin 200 mg and valproic acid 1800 mg per day. Afterwards, she had only one attack during the following years until 2 months prior to admission when another seizure occurred. At that time her serum level of phenytoin was low (2.5 µg/mL; normal range: 10-20 µg/mL). Therefore, phenytoin was increased to 400 mg daily. Ten days prior to this admission she started to have an unsteady gait and frequent falls. Five days later, she was unable to stand and suffered from vertigo, dysarthria, and impaired responsiveness. Laboratory tests revealed an overdose of phenytoin (30.57 µg/mL), and hypocalcemia (iCa: 2.84 mg/dL). The complete blood counts (CBC) showed normal white cells and differential counts. Her thyroid function was normal with thyroid stimulating hormone (TSH) was 1.25 uU/mL (normal range: 0.4-5.0 uU/mL). The electroencephalogram (EEG) showed intermittent diffuse theta waves. The results of brain computed tomography (CT) were unremarkable. The electrocardiography (EKG) showed sinus tachycardia and bi-atrial enlargement but the echocardiogram disclosed no congenital abnormality. On physical examination, the patient was dull in response, short in stature (body height of 146 cm and body weight of 56 Kg, BMI=26.2), and had a dysmorphic face, including prominent forehead, hypertelorism, flat nasal bridge, small palpebral fissures, and short philtrum with a fish-mouth appearance (Fig. A). Taking all these features into consideration, we arranged for a FISH analysis, which disclosed a submicroscopic deletion on chromosome 22q11.2 compatible with the DiGeorge syn-

![Figure](A) Case 1, a 44-year-old woman with the DiGeorge syndrome has a characteristic dysmorphic face, including prominent forehead, hypertelorism, flat nasal bridge, small palpebral fissures, and short philtrum with a fish-mouth appearance. (B) Fluorescent in situ hybridization detects the absence of red fluorescence hybridized to the loci within the DiGeorge critical region in one of the chromosome 22 copies (Del 22).
drome (Fig. B). The patient was then treated with calcitriol and calcium supplements. Her anticonvulsants were subsequently discontinued without recurrence of seizures.

Case 2

A 19-year-old girl had had seizures since age 2. For the past 7 years, she had taken valproic acid 200 mg twice a day. However, her seizures were poorly controlled, having a frequency of about one attack per month. Two years previously, she was admitted for a recurrent generalized seizure and was found to have hypocalcemia (iCa: 2.8 mg/dL) and hypoparathyroidism (intact PTH: 2.3 pg/mL). Although she was referred to an endocrinologist for treatment, she rarely visited the clinic. Four months before admission she had another seizure and hypocalcemia (iCa: 3.29 mg/dL), hyperphosphatemia (P: 7.4 mg/dL), and a low serum level of valproate (21.57 ug/dL) were found again. The results of CBC and thyroid function tests were within normal ranges (TSH: 2.18 uU/mL). The EEG showed intermittent diffuse theta waves without epileptiform discharge. Her head CT disclosed calcification in the bilateral basal ganglia. The cardiac evaluation showed no abnormal findings. On examination, the patient was alert with normal mentality. However, she was small in stature (body height of 150cm and body weight of 60 Kg, BMI=26.7) and had a characteristic dysmorphic face, which was very similar to the findings on examination of case 1. We checked her chromosomes with FISH analysis, which revealed chromosome 22q11 deletion and confirmed the diagnosis of the DiGeorge syndrome. The patient was treated with calcitriol and calcium supplements and her seizures have not recurred.

DISCUSSION

The neuropsychiatric symptoms of hypocalcemia are variable, and may include seizures, altered mental status, delusions, hallucinations, psychosis, depression, mental retardation, dementia, pseudotumor cerebri, chorea, and parkinsonism. Hypocalcemia can manifest as epileptic seizures, which occur in 20-25% of patients with acute hypocalcemia as a medical emergency and in 30-70% of patients with symptomatic hypoparathyroidism. The mainstay of treatment is correction of hypocalcemia, and underlying causes of hypocalcemia should be sought. If physicians fail to recognize hypocalcemia as the cause of seizures, they may prescribe anticonvulsants. However, anticonvulsants such as phenytoin, phenobarbital, and carbamazepine are known to aggravate hypocalcemia, which would further exacerbate the seizures. The mechanisms of anticonvulsant-related hypocalcemia include increased vitamin D inactivation by hepatic enzymes, pregnant X receptor activation, and decreased intestinal absorption of calcium.

One of the most important causes of hypocalcemia is hypoparathyroidism. The causes of hypoparathyroidism are the following: iatrogenic, autoimmune, congenital, and idiopathic. Congenital hypoparathyroidism is most often a component of the chromosome 22q11 deletion syndrome. The chromosome 22q11 deletion syndrome was first described in 1968 by DiGeorge in young children with the triad of hypoparathyroidism, thymic hypoplasia, and recurrent infections, and was initially termed the DiGeorge syndrome. Microdeletion in region 22q11 of one copy of chromosome 22 is found in the majority of cases. As a consequence of the microdeletion, there is congenital failure in the development of the derivatives of various pharyngeal arches and pouches. The DiGeorge syndrome is due to the failure of the third and fourth pharyngeal pouches differentiating into the thymus and parathyroid glands, respectively. The facial abnormalities result primarily from abnormal development of the first pharyngeal arch components because neural crest contribution is lacking. Deletion of this critical region is estimated to affect approximately 1 in 4000 live births. This microdeletion typically occurs de novo, although it is inherited in about 10-20% of cases.

The neurological manifestations of the chromosome 22q11 deletion include mental deficiency, speech disturbances, learning difficulties, attention deficit hyperactivity disorder, oppositional defiant disorder, autism, and epilepsy. Epilepsy is an uncommon manifestation and was present in less than 5% of the chromosome 22q11 deletion syndrome.
deletion patients in the European collaborative study\(^\text{6}\)). In another retrospective cohort study, the histories of 348 patients with the chromosome 22q11 deletion were reviewed and it was found that 81 patients (23%) had seizures of various etiologies\(^\text{6}\)). Among the 81 patients with seizures, 27 (33%) apparently had unprovoked seizures. The prevalence of a single unprovoked seizure was 7.7%, which was clearly higher than that in the general population\(^\text{6}\)). Among the patients with unprovoked seizures, 8 had primary generalized epilepsy, 8 had idiopathic partial epilepsy, and 8 had symptomatic partial epilepsy\(^\text{6}\)). The results suggest that the increased risk of seizures in patients with the chromosome 22q11 deletion is at least partly attributable to the primary defects of the syndrome\(^\text{6}\)). Hypoparathyroidism and related hypocalcemia are responsible for the development of seizures.

In the DiGeorge syndrome, the symptoms of hypoparathyroidism-related hypocalcemia usually manifest during the neonatal period\(^\text{7}\)). However, symptomatic hypocalcemia may develop in adolescence and adulthood\(^\text{1,2,3,10}\). Kao et al.\(^\text{9}\) reported a 16-year-old girl with the 22q11 deletion syndrome who developed generalized myoclonic epilepsy at 15 years of age and Maalouf et al.\(^\text{7}\) reported a male patient who had seizures at 14 years of age. In the present report, case 1 developed her seizures at age 14, however, the diagnosis of hypoparathyroidism was not made until she reached age 35. In patients with seizures associated with hypocalcemia, the possibility of a genetic cause or congenital disease should be considered despite the late age of onset. Furthermore, if patients with hypoparathyroidism also present with subtle dysmorphic facial anomalies, short stature, and mental subnormality, the chromosome 22q11 deletion syndrome is highly suspected\(^\text{1,9}\).

In conclusion, we presented two patients with poorly controlled epileptic seizures that had the underlying cause of the DiGeorge syndrome with hypocalcemia. For these patients, the definitive treatment of seizures is correction of the hypocalcemic state rather than the use of anticonvulsants. Anticonvulsants should be used prudently because many anticonvulsants aggravate hypocalcemia, which further exacerbates the seizures. For treatment of these patients, non-enzyme-inducing anticonvulsants are preferred.

**REFERENCES**