

Case Report

Hypocalcaemia-induced seizures as the first manifestation of DiGeorge syndrome in a 9-year-old male child

Tao Wu^{1*}, Xiang Wang^{2*}, Kun Zhang¹, Junwen Du¹, Qiaohua Ren¹, Xin Wang¹, Subo Liu¹

¹Department of Endocrinology and Metabolism, The First Hospital of Shijiazhuang City, Shijiazhuang, China;

²Department of Endocrinology and Metabolism, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China. *Equal contributors and co-first authors.

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Abstract: DiGeorge syndrome is caused by a microdeletion of chromosome 22q11.2 and leads to the abnormal development of the third and fourth pharyngeal pouches. This syndrome is characterized by hypoparathyroidism, cellular immunodeficiency secondary to thymic hypoplasia, congenital heart disease, and dysmorphic facial features. In this case report, we describe a 9-year-old male child who was admitted to our hospital because of hypocalcaemia-induced seizures. The patient presented with hypoparathyroidism, congenital heart defects, mild facial anomalies and short stature. A computed tomography (CT) scan of the brain showed extensive symmetric bilateral calcification within the basal ganglia. A chest CT scan showed that there was no thymus. The echocardiogram assessment revealed the presence of a ventricular septal defect. The electroencephalogram showed both a spike-slow wave and a sharp-slow wave. The multiplex ligation-dependent probe amplification (MLPA) revealed that the patient had a deletion of 22q11.2. The patient was treated with vitamin D and calcitriol and achieved an acceptable response. The patient did not experience additional seizures during the follow-up period and continued calcium treatment. The patient subsequently achieved compensatory growth.

Keywords: DiGeorge syndrome, chromosome 22q11.2 deletionsyndrome, hypocalcaemia-induced seizures, hypoparathyroidism

Introduction

Chromosome 22q11.2 deletion syndrome is the most common human deletion syndrome and has an incidence of 1 in 4000 newborns [1]. Only 7% of all 22q11.2 deletion cases are inherited from a parent in an autosomal dominant manner. Thus, the majority of cases develop by de novo mutation [2, 3]. Phenotypic abnormalities that are commonly observed in patients with DiGeorge syndrome include velocardiofacial syndrome and conotruncal anomaly face syndrome [4]. The commonly deleted region of chromosome 22q11.2 includes multiple transcription factors that regulate the thymus and parathyroid development. The classical features include hypoplasia of the thymus and parathyroid glands, facial dysmorphism, congenital heart disease, palatal abnormalities, immune deficiency, and learning difficul-

ties. We report a rare case of DiGeorge syndrome presenting in childhood as hypocalcaemia-induced seizures. The patient had a chromosome 22q11 deletion that was identified using multiplex ligation-dependent probe amplification (MLPA) analysis.

Case report

The institutional review board waived the need for review and approval of this case report. A 9-year-old male child was admitted to our clinic for a sudden onset loss of consciousness lasting for one minute. During the unconscious period, the patient sustained tonic-clonic seizures that self-terminated. The patient's medical history included a learning disability and short stature. The patient had a history of congenital heart disease and cleft palate at birth. The infant had developed seizures on postnatal

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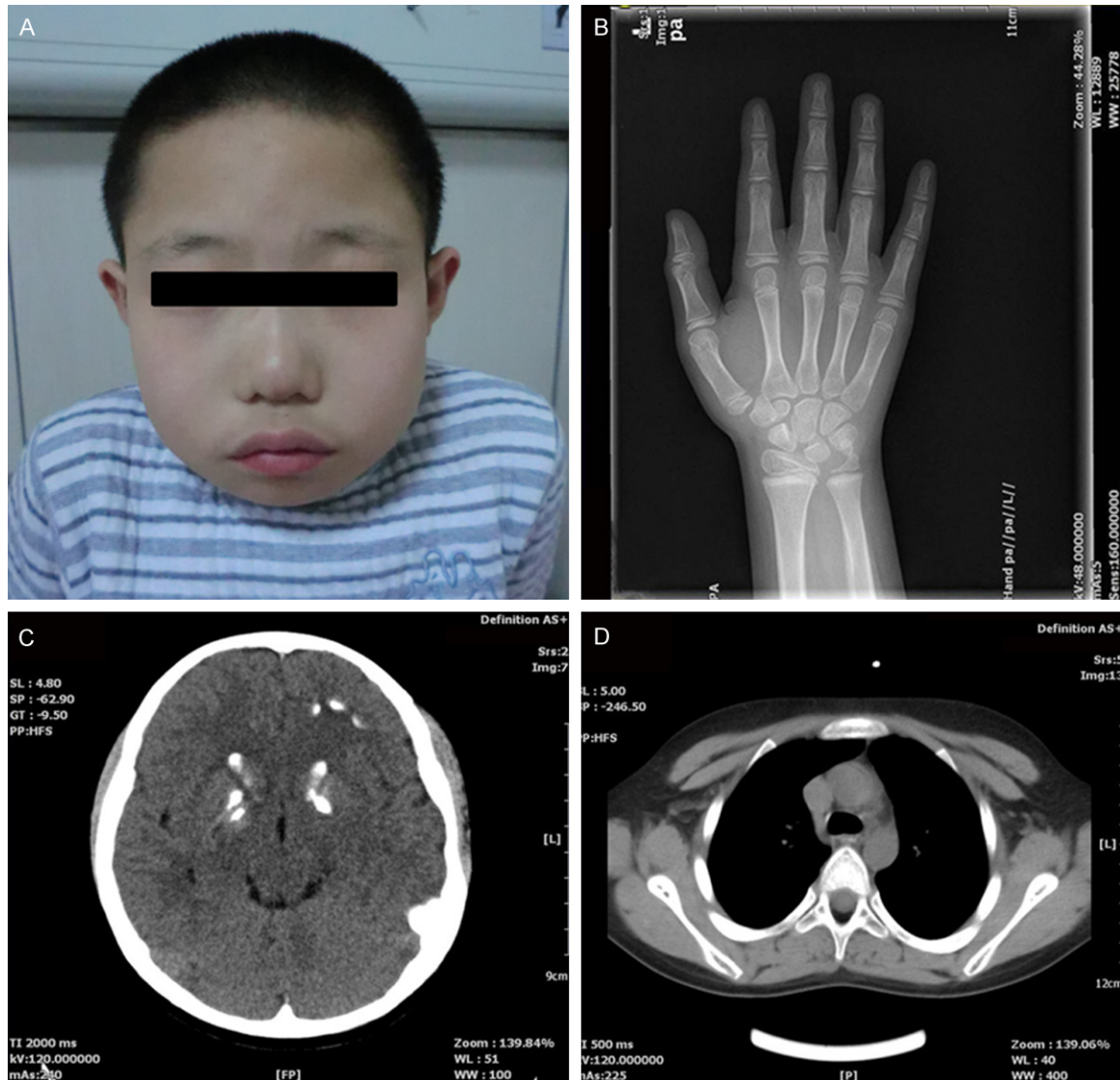


Figure 1. The physical examination results and laboratory data. A. Close-up photograph of the patient, showing small eyes, hypertelorism, a short philtrum, low set ears, short neck, and micrognathia. B. X-ray image of hand showing congenital dysplasia of the fourth and fifth metacarpals. C. Selected images from the computed tomography brain scan of the patient demonstrating basal ganglia and periventricular calcification. D. Selected images from the computed tomography chest scan of the patient demonstrating absence of the thymus.

day 17. The serum calcium concentration was 1.79 mmol/litre at the time of presentation. The patient had a history of infrequent seizures and had been treated with calcium gluconate or vitamin D. The infant received surgical cleft palate repair at 1 year of age. Additionally, the patient had recurrent chest infections as a child. The patient's mother received x-rays during the sixth week of pregnancy.

The physical examination revealed that the child had the following abnormal features:

hypertelorism, a short philtrum, low set ears, short neck, micrognathia, cleft palate, and congenital dysplasia of the fourth and fifth metacarpals (**Figure 1A, 1B**). The child weighed 55 kg, and his height was 126 cm. The chest and abdominal examination findings were unremarkable. The patient was positive for both Chvostek sign and Trousseau sign.

We obtained laboratory data at hospital admission. The serum total calcium concentration was low at 1.79 mmol/litre (normal range 2.20-

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Figure 2. Result of multiplex ligation-dependent probe amplification (MLPA) analysis using SALSA MLPA P250-B1 DiGeorge Probemix from DiGeorge syndrome critical region (CLTCL1-LZTR1). A. Sample of the patient. B. Sample of the normal person. C. Sample of the blank.

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2.70). The serum phosphorous concentration was slightly elevated at 2.03 mmol/litre (normal range 0.90-1.80). The serum PTH concentration was low at 7.62 pg/ml (normal range 15.00-65.00). The patient's 24-hour urinary calcium excretion was low at 0.78 mmol/d (normal range 2.50-7.50), and the 24-hour urinary phosphorus excretion was low at 8.03 mmol/d (normal range 10.00-42.00). The following parameters were normal: serum adrenocorticotrophic hormone (ACTH), serum growth hormone (GH), blood absolute T lymphocyte subsets, serum insulin-like growth factor-1 (IGF-1), serum prolactin (PRL), serum thyroid stimulating hormone (TSH), serum total thyroxine (T4), and 3,5,3'-triiodo-L-thyronine (T3). A computed tomography (CT) scan of the brain demonstrated extensive symmetric bilateral calcification within the periventricular and basal ganglia (**Figure 1C**). A chest CT scan showed that there was no thymus (**Figure 1D**). An echocardiogram showed the presence of a ventricular septal defect (VSD). The results of the electroencephalogram showed both a spike-slow wave and a sharp-slow wave.

We performed multiplex ligation-dependent probe amplification (MLPA) analysis to confirm the diagnosis of DiGeorge syndrome and a 22q11.2 microdeletion (**Figure 2A**).

The patient was treated with 300 mg elemental calcium in the form of calcium carbonate orally three times daily. The patient also initiated treatment with calcitriol 0.25 µg orally once daily and vitamin D 80000 units orally once weekly. A repeat laboratory evaluation showed an increase of the total serum calcium concentration to 2.0 mmol/litre and normalization of the serum phosphorus concentration. The patient did not experience additional seizures during the follow-up period and continued calcium treatment. The child also achieved compensatory growth. His current height is 152.2 cm.

Discussion

DiGeorge syndrome was originally reported in 1967 by Di George et al. and was associated with microdeletions of chromosome 22q11.2. This syndrome is the most common microdeletion syndrome in humans and has an incidence of 1 in 4000 newborns [5]. In 1972, Lischner divided DiGeorge syndrome into (a) III-IV pha-

ryngeal pouch syndrome, (b) DiGeorge syndrome characterised by thymic aplasia, and (c) partial DiGeorge syndrome characterised by thymic hypoplasia [6].

Chromosome 22q11.2 deletion syndrome is associated with immunodeficiency involving mild to moderate deficiency in peripheral blood T cells. Thymic hypoplasia or aplasia leading to defective T-cell function is one of the main features of DiGeorge syndrome. Patients can be divided into partial or complete forms of DiGeorge syndrome based on the extent of T-cell deficiency. Although immunodeficiency is found in the complete form, abnormal T-cell regulation related to aberrant T-suppressor cell function occurs in partial forms of DiGeorge syndrome [7]. The numbers of peripheral blood T-cells in may be normal in some cases [8, 9].

Hypocalcaemia most frequently manifests during the neonatal period and is considered one of the phenotypic characteristics of the DiGeorge syndrome [2]. The hypocalcaemia can be attributed to the decreased active transport of calcium from the mother to the foetus at birth and a lower intake of calcium in the first few days of life [10]. Hypocalcaemia due to hypoparathyroidism is found in 60% of patients with DiGeorge syndrome [11]. Hypocalcaemia was noted in 60% of subjects who were known to have 22q11.2 deletions, 39% of whom presented with seizures [2].

The basal ganglia calcifications found in our case report are rarely reported in the literature due to a low incidence of this phenomenon or the absence of CT studies. It is also possible that the subjects were too young to have developed this abnormality.

Short stature is defined as a standing height more than 2 standard deviations (SDs) below the mean and can be divided into three categories: chronic disease (including malnutrition genetic disorders), familial short stature, and constitutional delay of growth and development. Our patient had short stature with normal levels of GH and IGF-1. However, his bone age was consistent with his chronologic age due to the abnormal bone metabolism.

This is a rare case report of DiGeorge syndrome presenting with hypocalcaemia-induced seizures. The delayed diagnosis in this case indi-

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cates that the phenotypic characteristics of DiGeorge syndrome may not be obvious in infancy or during childhood. Seizures related to profound hypocalcaemia might be the early presentation of this deletion. The treatment is well known and can result in marked clinical improvement. Thus, we suggest that hypocalcaemia-induced seizures at any age should be considered a risk factor for DiGeorge syndrome, and the clinical absence of phenotypic characteristics of DiGeorge syndrome should not ignore this pathology.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiang Wang, Department of Endocrinology and Metabolism, The First Affiliated Hospital of Zhengzhou University, No. 1, Jianshe East Road, Zhengzhou, Henan, China. Tel: 008618336302586; E-mail: wangxiang801028@163.com; Dr. Tao Wu, Department of Endocrinology and Metabolism, The First Hospital of Shijiazhuang City, No. 36, Fan-Xi Road, Shijiazhuang, Hebei, China. Tel: 008617603119598; E-mail: 13363880021@126.com

References

- [1] Kobrynski LJ and Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes. *Lancet* 2007; 370: 1443-1452.
- [2] Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, Schuffenhauer S, Oechsler H, Belohradsky B, Prieur M, Aurias A, Raymond FL, Clayton-Smith J, Hatchwell E, McKeown C, Beemer FA, Dallapiccola B, Novelli G, Hurst JA, Ignatius J, Green AJ, Winter RM, Brueton L, Brondum-Nielsen K, Scambler PJ, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: a European collaborative study. *J Med Genet* 1997; 34: 798-804.
- [3] Smith A and Robson L. Low frequency of inherited deletions of 22q11. *Am J Med Genet* 1999; 85: 513-514.
- [4] Shprintzen RJ. Velo-cardio-facial syndrome: 30 Years of study. *Dev Disabil Res Rev* 2008; 14: 3-10.
- [5] Di George AM, Lischner HW, Dacou C and Arey JB. Absence of the thymus. *Lancet* 1967; 1: 1387.
- [6] Lischner HW. DiGeorge syndrome(s). *J Pediatr* 1972; 81: 1042-1044.
- [7] Rasmussen SA, Williams CA, Ayoub EM, Sleasman JW, Gray BA, Bent-Williams A, Stalker HJ and Zori RT. Juvenile rheumatoid arthritis in velo-cardio-facial syndrome: coincidence or unusual complication? *Am J Med Genet* 1996; 64: 546-550.
- [8] Collard HR, Boeck A, Mc Laughlin TM, Watson TJ, Schiff SE, Hale LP and Markert ML. Possible extrathymic development of nonfunctional T cells in a patient with complete DiGeorge syndrome. *Clin Immunol* 1999; 91: 156-162.
- [9] Pierdominici M, Marziali M, Giovannetti A, Oliiva A, Rosso R, Marino B, Digilio MC, Giannotti A, Novelli G, Dallapiccola B, Aiuti F and Pandolfi F. T cell receptor repertoire and function in patients with DiGeorge syndrome and velocardiofacial syndrome. *Clin Exp Immunol* 2000; 121: 127-132.
- [10] Cuneo BF, Driscoll DA, Gidding SS and Langman CB. Evolution of latent hypoparathyroidism in familial 22q11 deletion syndrome. *Am J Med Genet* 1997; 69: 50-55.
- [11] McDonald-McGinn DM, Kirschner R, Goldmuntz E, Sullivan K, Eicher P, Gerdes M, Moss E, Solot C, Wang P, Jacobs I, Handler S, Knightly C, Heher K, Wilson M, Ming JE, Grace K, Driscoll D, Pasquariello P, Randall P, Larossa D, Emanuel BS and Zackai EH. The Philadelphia story: the 22q11.2 deletion: report on 250 patients. *Genet Couns* 1999; 10: 11-24.