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CASE REPORT

Delayed diagnosis of 22q11.2 deletion syndrome in a child with symptomatic hypocalcemia: case report

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22q11 Deletion syndrome, Hypocalcemia, Hypoparathyroidism.

Abstract

22q11.2 Deletion Syndrome is the commonest microdeletion syndrome in humans and has a wide spec-trum of clinical manifestations, such as craniofacial dysmorphism, airway malformations, heart disease, renal malformations, hypoparathyroidism, neurological and behavioral disorders, immunodeficiencies and anomalies of the thymus. The broad phenotype spectrum makes the diagnosis more challenging, and an early identification allows not only the evaluation of comorbidities and interventions, but also adequate genetic counseling. Hypoparathyroidism manifested by symptomatic hypocalcemia is one of the clinical presentations of 22q11.2 Deletion Syndrome. This clinical case shows the diagnosis of 22q11.2 Deletion Syndrome in an 11-year-old child with symptomatic hypocalcemia and emphasizes the possibility of a late diagnosis of 22q11.2 Deletion Syndrome.

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INTRODUCTION

The microdeletion in region 11.2 on the long arm of chromosome 22, called 22q11.2, is the most common gene deletion mutation, with an estimated incidence of one in 4,000 live births[1-3].Spontaneous mutations occur in 90% of the cases, and only 6% to 10% of the cases have a documented family inheritance pattern.[4,5] About 30 to 50 genes are represented in the area most commonly affected by the 22q11.2 deletion. More than 180 distinct clinical manifestations have been described, including physical and behavioral abnormalities.[6,7] The wide phenotypic variability connects this deletion to several presentations, including DiGeorge syndrome, velocardiofacial syndrome (Shprintzen-Goldberg syndrome), Cayler cardiofacial syndrome and Opitz G/BBB syndrome.[8,9]

DiGeorge Syndrome was first described in 1965, from reports about three children with severe immunodeficiency, thymus aplasia and neonatal hypocalcemia. Advancements in genetic testing allowed researcher to find in 90% of the cases the syndrome was caused by 22q11.2.4 deletion.[4,10] Clinical presentations include oligosymptomatic and difficult-to-identify cases, to cases with multiple organ involvement, and cardiac, palatal, endocrine, genitourinary, gastrointestinal, neurological and psychiatric anomalies.[4,8]

This article describes the case of a patient diagnosed with 22q11.2 deletion syndrome at the age of eleven, with symptomatic hypocalcemia and without other associated anomalies.

CASE REPORT

A female patient aged 11 years was admitted to a tertiary hospital in southern Brazil with vomiting and seizures. She was brought to the emergency unit due to a 30-second paroxysmal event with eyelid tremor and bilateral hand stiffness (clawing), without loss of consciousness or relaxation of sphincter muscles. During treatment, the patient complained of stiffness in her hands (Figures 1A and 1B). When asked about comorbid conditions, her mother said that when the patient was 10 years old, she had her first paroxysmal event, described as a tonic-clonic seizure by a neurologist, who initially prescribed clonazepam and added carbamazepine two months ago. She was not followed up and did not have a history of repeated infections.

In terms of her gestational and obstetric history, the mother said the patient was born full-term from an uneventful vaginal delivery, and that she took the measles, mumps and rubella (MMR) vaccine in the first trimester of pregnancy.

Regarding global development, the mother reported the patient had borderline motor development and adequate language development according to the Denver II scale[11], having sat without support at eight months, walked without support at 15 months, spoken her first words at 12 months, and combined two words at 24 months of age. However, her mother also said that since as early as the preschool years the patient has had learning difficulties, with literacy achieved only at the age of 10 years. She is currently a third grader.

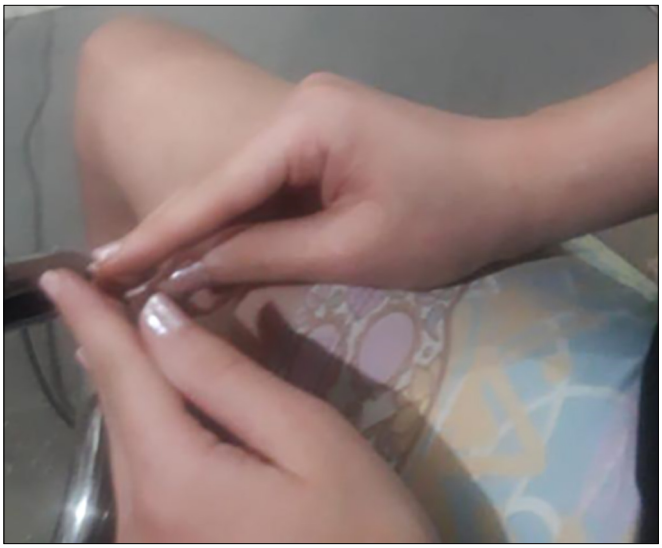


Figure 1. A: Patient's hands showing stiffness.



Figure 1. B: Patient's right hand showing stiffness.

Physical examination revealed a rounded face, thick lips with an everted upper lip, and almond-shaped eyes. She appeared communicative and oriented, with mild discomfort upon palpation of the hypogastrium, without peritoneal irritation. Neurological examination showed symmetrical and preserved strength, cranial nerves without changes, hands flexed and fingers extended, with preserved mobility and strength. Chvostek's and Trousseau signs were present.

Laboratory tests performed upon admission revealed she had hypocalcemia, hypomagnesemia, hyperphosphatemia, PTH below the reference value and borderline vitamin D levels (Table 1). Other tests, such as complete ultrasound of the abdomen, ultrasound of the kidneys and urinary tract, echocardiogram, chest x-ray, ultrasound of the thyroid and parathyroid glands, were normal.

Table 1. Lab test results at different times.

Lab test Ionized calcium (mmol/L)	Results on admission	Results after six days of treatment	Results after 23 days of treatment	Reference values
Ionized calcium (mmol/L)	0.49	0.67	1.10	1.15 to 1.32
Total Calcium (mg/dL)	4.0	5.3	8.9	8.7 to 10.4
Phosphorus (mg/dL)	9.6	7.5	7.1	3.7 to 5.6
Magnesium (mg/dL)	1.3	1.9	1.7	1.7 to 2.3
PTH (pg/mL)	6	7	-	12 to 88
Vitamin D (ng/mL)	17.5	17	-	20 to 60

Clinical and workup findings substantiated a tentative diagnosis of 22q11.2 deletion syndrome based on the association of intellectual disability, subtle craniofacial dysmorphia, and symptomatic hypocalcemia leading to tetany.

Treatment with calcium carbonate, magnesium and calcitriol was initiated and resulted in improvement of symptoms and cessation of stiffness and tremors. Laboratory tests performed six and 23 days after the initiation of treatment showed an increase in serum calcium and magnesium levels, as well as a decrease in phosphorus levels (Table 1). Comparative Genomic Hybridization (CGH) testing found an interstitial microdeletion of approximately 2.8 Mb in band 22q11.2, from the region of Chr22:18,142,191 to Chr22:21,109,441 and confirmed the diagnosis of 22q11.2 deletion syndrome. The patient was discharged without symptoms. She continued to take the prescribed medications and was referred for follow-up with the endocrinology, neurology and genetics services. The patient was also referred for immunodeficiency investigation on an outpatient basis.

DISCUSSION

22q11.2 deletion syndrome, a complex condition with significant phenotypic variability, has been associated with a number of clinical signs and symptoms.[6,8] The broad clinical spectrum of the syndrome is reflected in the different names it is known for, such as DiGeorge syndrome and velocardiofacial syndrome, which convey the erroneous impression that these are different conditions related to 22q11.2 deletion instead of different phenotypic representations of the same condition.[9] Of the more than 180 clinical findings described, none is pathognomonic or obligatory, which makes diagnosis difficult.[3,7] The most common clinical manifestations include craniofacial dysmorphia, heart disease, hypoparathyroidism, neurological alterations, and immunodeficiency.[8,12] Presentation ranges from mild and oligosymptomatic to severe, which can be easily recognized at birth.[4,7]

Hypoparathyroidism due to parathyroid agenesis or hypoplasia in 22q11.2 deletion syndrome occurs in an estimated 49-80% of the cases and usually becomes apparent in neonatal life. It is a rare finding in adults, although it may appear at any age.[5,13] A plausible explanation for late-onset symptomatic hypocalcemia is inadequate parathyroid reserve, in which PTH secretion may be sufficient to maintain normal calcium levels under usual conditions, but unable to create an adequate response in situations of stress such as surgery, infection or pregnancy.[1,13]

Late diagnosis of the syndrome in adults based on hypocalcemia, as in the case reported herein, is uncommon and has rarely been described in the literature. Our patient did not have heart disease or classic dysmorphia as seen in individuals with DiGeorge syndrome, which include a long face, hypertelorism, retrognathia or micrognathia, narrow palpebral fissures, a small mouth with an everted upper lip, and dysmorphic low-set ears.[8] Our patient was diagnosed with 22q11.2 deletion syndrome at 11 years of age based on a finding of acute symptomatic hypocalcemia.

The authors of a review including 12 cases of late diagnosis of DiGeorge syndrome found that eight sought care for symptomatic hypocalcemia, and only two had a documented history of neonatal hypocalcemia. Half of the patients had no cardiac abnormalities, suggesting that diagnosis may be delayed when patients do not develop neonatal symptomatic hypocalcemia or cardiac abnormalities.[14]

In 2005, a Swedish study enrolling 100 children with 22q11.2 deletion syndrome described the ages at which diagnosis was rendered, which according to age groups were as follows: 26% in neonatal life; 17% between 2-5 years; 41% between 6-12 years; and 16% in adolescence. The mean age at diagnosis was 6.7 years.[15] The authors also demonstrated that the most common characteristics that led to the diagnosis in children under two years of age were heart defects, absent or hypoplastic thymus, hypocalcemia and dysmorphia. Meanwhile, in children over two years of age, the characteristics that most suggested the presence of the syndrome were heart defects, recurrent infections, delayed speech development, and dysmorphia, with hypocalcemia as a secondary and uncommon diagnostic finding in this age group.[15]

When 22q11.2 deletion syndrome is suspected, diagnosis is generally performed with the aid of fluorescent in situ hybridization (FISH), which is the method of choice for detecting chromosomal deletions. This test is highly accurate and reliable, and can be used in antenatal diagnosis.[2] Currently, other molecular tests are used to detect microdeletions, such as array CGH,[3] the test performed in our patient.

Given its wide phenotypic variability, 22q11.2 deletion syndrome should be considered even in oligosymptomatic cases and patients with predominant manifestations of hypoparathyroidism, as in our patient. Early identification of 22q11.2 deletion is important, given the varied presentations in multiple systems and the risk of neurodevelopmental disorders. Early diagnosis not only allows assessment of comorbidities and interventions, but also appropriate family counseling.

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