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CASE REPORT

Multiple terms for a complex phenotype: contribution of two clinical cases for the recognition of 22q11.2 deletion syndrome

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22q11 deletion syndrome, DiGeorge syndrome, tetralogy of Fallot, heart defects, congenital.

Abstract

22q11.2 microdeletion is the most common microdeletion syndrome in humans and occurs with a frequency of 1 in 2,000-6,000 live births. Its main clinical features are associated with a failure to form derivatives of the third and fourth branchial arches during embryonic development. The phenotype includes heart outflow tract defects, craniofacial dysmorphisms (prominent and bulbous tip, external ears malformations, and posterior cleft palate) and endocrinological and immune system dysfunctions, as well as neurological and psychiatric disorders. Patients with this syndrome received different names, such as DiGeorge syndrome and velocardiofacial syndrome, since the recognition was based on the phenotype. Recently, molecular and genomic techniques have shown that this syndrome has great phenotypic heterogeneity. Two children with quite distinct phenotypes from this microdeletion syndrome are described in order to review the most common clinical manifestations and highlight that the great clinical heterogeneity can complicate its recognition by pediatricians.

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INTRODUCTION

Genetic syndromes may present different etiologies including chromosome alterations, monogenic conditions, teratogenicity, and the more recently recognized syndromes involving deletions (losses) or duplications (gains) in specific regions of the genome. These submicroscopic alterations, recognized as the main cause of congenital malformations and intellectual disability, are not detected by conventional cytogenetic tests, since their resolution resides between 5-10 megabases (Mb). The development of cytomolecular diagnostic techniques such as fluorescence in situ hybridization (FISH) and cytogenomic approaches such as array comparative genomic hybridization (aCGH) has enabled the recognition of new syndromes. FISH uses specific DNA probes labeled with fluorophores to identify target-regions in the genome. For this reason, the test is known for its low sensitivity, since it relies on the level of suspicion for each alteration. By its turn, aCGH scans through the whole genome and detects minor imbalanced alterations. Its higher resolution also allows for greater sensitivity. aCGH is considered the initial diagnostic tool for individuals with developmental delay, intellectual disability, and/or autism spectrum disorders associated with craniofacial dysmorphism.[1-3]

Recurrent 1.5-3Mb deletions in the long arm of chromosome 22, more specifically in the 22q11.2 region, result in the most common microdeletion syndrome in humans, with an incidence of 1:2.000-6.000 live births. In this syndrome, approximately 50 genes are deleted, the most important of which is T-Box Transcription Factor 1 (*TBX1*). TBX1 haploinsufficiency leads to failed embryogenesis involving derivatives of the third and fourth branchial arches, resulting in a variety of malformations including complex congenital heart diseases, thymic or parathyroid hypoplasia/agenesis palatine malformations, and craniofacial dysmorphism.[4-6]

Several names have been given to this condition since the advent of cytogenomics. In the 1960s, pediatric endocrinologist Ângelo DiGeorge described the cases of children with hypocalcemia, congenital heart disease, and immunodeficiency, a triad of symptoms called DiGeorge Syndrome seen in 35-90% of the patients with deletions in the 22q11.2 region. In the 1970s, Dr. Robert Shprintzen used the term velocardiofacial syndrome (VCFS) to describe patients with a posterior cleft palate, nasal speech, learning difficulties, and congenital heart disease associated with ventricular septum defects. About 80-100% of these patients present deletions in the same region of chromosome 22. The term conotruncal anomaly face syndrome was adopted in Japan in the 19702 to differentiate the flow-related heart disease of VCFS from the conotruncal heart disease in the "new" syndrome. In the 1990s, it became clear that all such terms referred to 22q11.2 microdeletion syndrome and that the different names reflected the heterogeneity of the phenotypes associated with the condition.[7-10]

This report describes the cases of two patients with distinctive manifestations tied to 22q11.2 microdeletion syndrome with the purpose of reviewing clinical phenotypes and underlining the heterogeneity of clinical signs and phenotypes that has led to the assignment of different names to this condition and to potential diagnostic difficulties.

CASE REPORTS

Patient 1 (P1) is a female only child of a young non-consanguineous couple without a family history of recognized genetic syndromes. Her mother denied experiencing complications in the prenatal period, taking medication, or smoking or drinking during pregnancy. The child was born full term after 39 weeks of pregnancy; she was small for gestational age [weight 2375g (-3 < z < -2); length: 46cm (-2 < z < 0); head circumference: 32cm (-2 < z < -1); APGAR score: 8/10] and had central cyanosis, which improved after oxygen supplementation. Two weeks later, during a visit with a pediatrician, the infant was found to have dyspnea, tachycardia, cyanosis, and a murmur. She was referred to a tertiary hospital for further evaluation.

In the pediatric intensive care unit, an echocardiogram found signs of tetralogy of Fallot associated with pulmonary atresia and a sub-aortic interventricular communication measuring 8.5 mm, with a left to right shunt, which, when considered with craniofacial dysmorphism, is indicative of DiGeorge syndrome. The patient was referred to an assessment by the Clinical Genetics team. Examination of dysmorphisms found the patient had small, low-set ears; narrow palpebral fissures (blepharophimosis); a prominent nose with a bulbous tip; a small posterior cleft palate; and retrognathia (Figures 1A and 1B). A diagnosis of 22q11.2 microdeletion syndrome was considered. Tests ordered to assess thyroid and parathyroid function found the patient had primary hypothyroidism [TSH: 13.3 mUI/L; T4L 1.18 ng/dL; thyroid peroxidase (TPO) and thyroglobulin (Tg) antibody tests were negative] and hypoparathyroidism with transient hypocalcemia [total Ca^{2+}: 8.37 mg/dL (RV: 8.5-10.2 mg/dL); ionized Ca^{2+}: 0.85 (RV: 1.1-1.35) and PTH: 14.80pg/mL (RV:15-65)]; abdomen ultrasound examination found the patient had bilateral renal hypoplasia. Fluorescence in situ hybridization (FISH) confirmed clinical suspicions, with tests showing 46,XX,ish del(22)(q11.2q11.2) (Figure 1C).

P1 underwent palliative heart surgery with the placement of a Blalock-Taussig shunt when she was aged 30 days, during which she was found to have thymic hypoplasia. Two months after the procedure, the patient had tachypnea with persistent low oxygen saturation and cyanosis. She was diagnosed with increased pulmonary blood flow and was prescribed surgery. The patient improved clinically and hemodynamically after the second procedure, although she still failed to thrive and suffered with incoordination of swallowing, mild global developmental delay, and repetition upper airway infections without signs indicative of immunodeficiency.

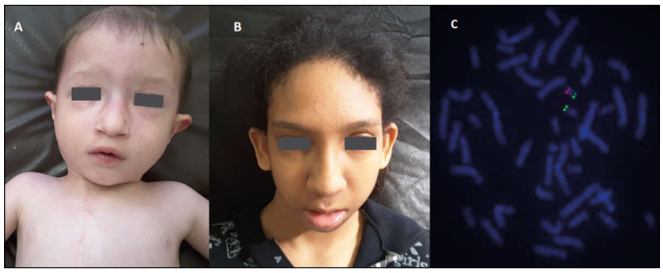


Figure 1. A. and 1B. show the craniofacial dysmorphisms seen in P1 and P2, respectively. Some of the most important findings are the prominent nose with a square bridge and a bulbous tip, and "hooded" eyes with a trend towards having a narrower palpebral fissure (blepharophimosis); C. shows the result of the fluorescence in situ hybridization (FISH) test for patient P1 using a specific probe (Cytocell, LPU-004). In the analyzed metaphase, note the presence of two green signs (control probes in 22q13.3) and the presence of only one red sign that confirms a deletion in region 22q11.2.

Patient 2 (P2) is a 12-year-old girl referred to treatment from the Pediatric Neurology unit with a history of global developmental delay that developed into mild to moderate intellectual disability associated with behavioral disorders and mild craniofacial dysmorphism. She is the oldest daughter of a young non-consanguineous couple without comorbidities during pre- and post-natal life. Her mother could not recall and did not keep records of the child's anthropometric data at birth, although she noticed the child had a speech developmental delay, since she was only able to form simple sentences from the age of three years. The child grew to develop a behavioral disorder characterized as attention deficit and hyperactivity disorder (ADHD) and was being followed at the Pediatric Endocrinology unit for autoimmune thyroiditis with normal thyroid function [TSH: 3.91mUI/L; T4L: 1.45 ng/dL; TPO antibodies: 60.01 UI/mL (RV: < 35 UI/mL) and Tg antibodies: 317.6 UI/mL (RV: <116 UI/mL)] and at the Hematology unit for chronic thrombocytopenia (platelet counts ranging between 60,000-90,000).

Genetic and clinical assessment found the patient had brachycephaly; ears with hypoplastic helices; a prominent nose with a broad tip; retrognathia; a hypoplastic uvula; distal joint laxity; and nasal speech. Skull MRI scans showed hypoplasia of the posterior horn of the corpus callosum, while abdominal ultrasound images, echocardiograms, and karyotyping were normal. Examination by a speech and hearing therapist revealed the patient had velopharyngeal insufficiency. A diagnosis of velocardiofacial syndrome was suggested and FISH tests confirmed 22q11.2 microdeletion syndrome.

DISCUSSION

22q11.2 is the most common microdeletion syndrome in humans. It has been associated with a wide range of phenotypes, which may include severe malformations associated with significant morbimortality. The heterogeneity of phenotypes has hampered the identification of the syndrome and the adoption of specific follow-up measures. This report presents the cases of two patients with different phenotypes and the same sub-microscopic alteration. Patient P1 had a complex congenital heart disease, transitory hypocalcemia, and thymic hypoplasia, but she did not present with immunodeficiency, a characteristic sign of DiGeorge syndrome. Patient P2 had velopharyngeal insufficiency, intellectual disability associated with behavioural disorder, and mild craniofacial dysmorphism consistent with velocardiofacial syndrome.[7,11]

22q11.2 deletion is characterized by multisystem manifestations that are not yet fully comprehended, except for malformations resulting from failed embryogenesis involving derivatives of the third and fourth branchial arches stemmed from TBX1 haploinsufficiency. The TBX1 gene belongs to a family of transcription factors that regulate the formation and/or remodelling of the pharyngeal arch arteries, which by their turn may alter the formation of the pharynx, the vessels of the base of the heart, and thyroid and parathyroid gland development. The frequency of occurrence of the main clinical traits described in 22q11.2 deletion and the findings seen in the two patients are described in Table 1.[12]

Neurocognitive findings in this disease vary and present a negative correlation with age. Therefore, as patients get older, there is a more intense decline in verbal when compared to non-verbal communication. Severe intellectual disability is not a common finding, unless an atypical deletion greater than 3Mb occurs and involves genes associated with neurodevelopment. About two thirds of the patients have an IQ ranging between 55-85, and an average IQ of 70. For example, P1 had a developmental delay in language acquisition, while P2 had an intellectual disability that led to impaired verbal communication.[13-14]

Various candidate genes expressed in the brain may explain the neuropsychiatric phenotype. The catechol-O--methyltransferase (COMT) gene is involved in the metabolism of catecholamines such as dopamine. Non-pathogenic genetic variants (polymorphisms) of this gene have been tied to schizophrenia. By its turn, the RAN Binding Protein 1 (RANBP1) gene involved in the formation of cortical circuits has been associated with attention deficit and hyperactivity disorder (ADHD) and autism spectrum disorders (ASD). P1 did not present behavioral alterations, while P2 was referred to our unit, among other things, for having ADHD. None of the patients had seizures – often seen in ASD – or a personal or family history of schizophrenia.[15]

Except for microcephaly, seen in half of the patients[6], all other cranial dysmorphisms were observed in the patients. However, the two had different findings. P1 had small, low-set ears, and a cleft palate that was only detected once she was suspected for 22q11.2 microdeletion. On the other hand, P2 had protruding ears with hypoplastic helices; although she did not have a cleft palate, the patient had a hypoplastic uvula and a nasal voice.

Tabela 1. Descrição da frequência dos achados clínicos da síndrome de deleção 22q11.2 e a sua comparação com as pacientes descritas.

Achados clínicos		Frequência[5,9]	P1	P2
Neurológicos ou Psiquiátricos	DI grave	10%	-	-
	DI leve	30%	NA	+
	TDAH	50%	NA	+
	Crises convulsivas	15%	-	-
	TEA	20%	-	-
	Esquizofrenia	15%	-	-
Craniofaciais	Microcefalia	50%	-	-
	Olhos "encapusados" com tendência à fenda palpebral pequena	70%	+	+
	Nariz proeminente com ponte nasal quadrada e ponta bulbosa	95%	+	+
	Alteração de orelha externa	80%	+	+
	Fenda palatina posterior/úvula bífida/insuficiência velofaríngea	75%	+	+
	Retrognatia	20%	+	+
Malformações cardíacas (80%)	Conotruncal	90%	+	-
	Não-conotruncal	10%	-	-
Endocrinológicas	Hipotireoidismo	10%	+	+
	Hipocalcemia	70%	+	-
	Baixa estatura pós-natal	10%	+	-
Sistema imune	Disfunção celular	50%	-	-
	Disfunção humoral	20%	-	-
	Doenças autoimunes	10%	-	+
Gastrointestinais	Refluxo gastroesofágico	30%	+	-
	Constipação	35%	+	+
Genitourinário	Anomalias renais	30%	+	-
	Criptorquidia/ hipospádia	8%	NA	NA
Musculoesquelético	Escoliose	50%	-	+
	Anomalias cervicais	20%	-	-

Legenda: P1: Paciente 1; P2: Paciente 2; DI: Deficiência intelectual; TDAH: Transtorno do déficit de atenção e hiperatividade; NA: Não se aplica; TEA: Transtorno do espectro autista; (+): Presente; (-): Ausente.

About 80% of the patients with 22q11.2 deletion present with congenital heart disease, mostly of the conotruncal kind. This was the warning sign and the reason why P1 was referred to a tertiary hospital, which further reinforces the need for pediatricians to find whether congenital heart disease is occurring in isolation or as part of a syndrome, since each possibility carries distinctive clinical repercussions. Although a significant portion of patients (80%) have symptoms, some individuals with 22q11.2 deletion might experience asymptomatic congenital heart disease. An echocardiogram was ordered for P2 since this malformation had not been found. Cardiovascular diseases still rank as the main cause of death in this group of subjects, including patients without congenital heart disease.[16]

Low stature is not a frequent finding in this microdeletion syndrome. Only 10% of the patients present this trait in childhood, but it tends to normalize during adolescence. Heart disease and parental stature appear as more significant factors in low stature. P1 had heart disease and low stature. Hypothyroidism is not a frequent finding either (10%) and has been associated with thyroid structural (hypoplasia) and functional (autoimmune thyroid disease) alterations. Both patients had thyroid alterations. P1 had primary hypothyroidism with negative antibody tests, while P2 had autoimmune thyroid disease. 22q11.2 deletion is also characterized by inter- and intra-individual variations (throughout their lives) in parathyroid function with hypocalcemia as a telltale sign. It is the most frequent endocrinopathy and is usually associated with heart disease, although it occurs in a transient manner during periods in which demand for PTH is greater, such as in surgery, acute diseases, and puberty. Symptoms may be severe and might include tetany and seizures or more subtle events such as hyporexia and fatigue. Only P1, the patient with tetralogy of Fallot, had hypocalcemia. However, the two patients might experience calcium metabolism disorders in other periods of their lives.[17-18]

22q11.2 microdeletion is also characterized by significant clinical variability in terms of immune deficiency disorders. Cellular immunodeficiency is the most frequent finding, followed by humoral alterations (predominantly IgA deficiency) and autoimmune disease such as idiopathic thrombocytopenic purpura and juvenile idiopathic arthritis. Deregulated development of T cells in the thymus is apparently the underlying mechanism in these conditions. Thymic hypoplasia and hypoparathyroidism have been considered as indicators of severity of immunodeficiency for lack of a better marker. None of the patients developed immunodeficiency.[19]

Platelet alterations are the main hematologic manifestations in patients with 22q11.2 microdeletion. This group of alterations includes asymptomatic macrothrombocytopenia and Bernard-Soulier syndrome, a rare hemorrhagic disorder associated with glycoprotein Ib-V-IX complex deficiency or disorder, a membrane receptor involved in the adhesion of platelets in vascular injury sites. Platelet disorders have been associated with variations on the GPIb*β* gene located in region 22q11.1 that encodes one of the four subunits that constitute the glycoprotein Ib-V-IX complex. P2 is being followed at the Hematology unit for presenting platelet counts below normal

levels associated with volume increases, although she has not had hemorrhage episodes.[20]

Genitourinary and musculoskeletal alterations are more uncommon[8], but our patients had renal hypoplasia (P1) and mild kyphoscoliosis (P2).

Given the broad phenotype variation in individuals with 22q11.2 deletion syndrome, the description of two cases with different manifestations may help pediatricians identify this condition and intervene earlier.

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