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CLINICAL CASE

Early onset intellectual disability in chromosome 22q11.2 deletion syndrome☆

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Abstract Chromosome 22q11.2 deletion syndrome, or DiGeorge syndrome, or velocardiofacial syndrome, is one of the most common multiple anomaly syndromes in humans. This syndrome is commonly caused by a microdelection from chromosome 22 at band q11.2. Although this genetic disorder may reflect several clinical abnormalities and different degrees of organ commitment, the clinical features that have driven the greatest amount of attention are behavioral and developmental features, because individuals with 22q11.2 deletion syndrome have a 30-fold risk of developing schizophrenia. There are differing opinions about the cognitive development, and commonly a cognitive decline rather than an early onset intellectual disability has been observed. We report a case of 22q11.2 deletion syndrome with both early assessment of mild intellectual disabilities and tetralogy of Fallot as the only physic manifestation.
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PALABRAS CLAVE
Síndrome de DiGeorge;
Síndrome velocardiofacial;
Síndrome de microdeleción;

Inicio temprano de discapacidad intelectual en el Síndrome de deleción del cromosoma 22q11.2

Resumen El síndrome del cromosoma 22q11.2, también conocido como supresión o síndrome de DiGeorge o síndrome velocardiofacial, es uno de los síndromes más comunes de anomalías múltiples en los seres humanos. Este síndrome es comúnmente causado por una microdeleción del cromosoma 22 en q11.2 banda. Aunque este trastorno genético muestra varias anomalías clínicas y diferentes grados de compromiso orgánico, las características clínicas que han atraído

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Síndrome de deleción 22q11;
Tetralogía de Fallot;
Deterioro cognitivo;
Trastornos de discapacidad intelectual

la mayor atención son el comportamiento y el desarrollo, porque las personas con síndrome de deleción 22q11.2 tienen un riesgo 30 veces mayor de desarrollar esquizofrenia. Hay diferentes opiniones sobre el desarrollo cognitivo, y comúnmente se se ha observado un deterioro cognitivo en lugar de un inicio temprano de discapacidad intelectual. Presentamos un caso de síndrome de deleción 22q11.2 tanto con la evaluación temprana de discapacidades intelectuales leves como con la tetralogía de Fallot como única manifestación física.
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Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS), previously also known as DiGeorge syndrome or velocardiofacial syndrome, is a complex genomic disorder caused in most cases by a hemizygous 3-megabase microdeletion from chromosome 22 at band q11.2. The 22q11DS can shows several clinical abnormalities and different degrees of organ commitment.[1] More than 180 clinical features, have been described, not only physical but behavioral and psychiatric, too.[2] Children and adults with 22q11DS have high rates of behavioral, psychiatric, and communication disorders. In children, these include attention deficit/hyperactivity disorder, anxiety, and affective disorders. Adults have a high rate of psychotic disorders, particularly schizophrenia.[3] Population 22q11DS usually have a below-borderline normal intelligence quotient (IQ), with most individuals having higher scores in the verbal than the nonverbal domains. Some are able to attend normal schools, while others are homeschooled or in special classes. The severity of hypocalcemia early in childhood is associated with autism-like behavioral difficulties.[4] The objective of this study was to report a case of 22q11DS with both early assessment of mild intellectual disabilities (ID) and tetralogy of Fallot (TOF) as only clinical manifestation.

Case report

A 13 years old Caucasian male is followed by our infantile neuropsychiatry team, since he was 3 years old. He came to our observation for both severely expressive language deficits and motor dysfunction. The personal anamnesis showed the intrauterine diagnosis of TOF, however at birth there were no perinatal asphyxia (APGAR score was 8 at 1 min and 9 at 5 min). He was born with labor at term via spontaneous vaginal delivery, weighing 3017 g. TOF was managed with a two-stage repair strategy with an initial palliation (systemic-to-pulmonary shunt operation at the age of 2 months) followed by later repair (transanular repair at the age of 18 months). Family history was non-contributory. Because of the presence of this heart defect, testing for the 22q11DS was performed. A 22q11.2 FISH genetic analysis with LSI DiGeorge N25(D22S75) and LSI DiGeorge/VCFS (Vysis) probes showed a microdeletion from chromosome 22 at band q11.2. At the age of 4 years old the child showed difficulties of acquiring vocabulary and formulating a spoken language. His motor dysfunction consisted in performance of motor coordination, significantly below the expected level for his age (developmental coordination disorder). At first, full-scale IQ was assessed by using Wechsler Preschool and Primary Scale of Intelligence (WPPSI). This test showed an IQ of 54, suggestive for a mild ID, confirmed with both the Raven Progressive Matrices at the age of 7 years old, and the Wechsler Intelligence Scale for Children (WISC-R = 51) at the age of 10 years old. The last IQ test administered (WISC IV = 52 at the age of 12 years old), further confirmed the degree of the intellectual development disorder (ICD-11), with deficits in sustained attention, working memory, executive function, verbal learning, and visual–spatial processing. The parents had a good educational level (high school) showing a normal IQ (WAIS-III). TOF was the only physic manifestation of 22q11DS. There were no other features such as facial dysmorphisms and immunodeficiency, as well as hypocalcemia, gastroesophageal reflux and atopy. Furthermore, the nasopharyngoscopy did not show any palate anomalies. The child received educational services with psychomotor education until he was 7 years old and logopedy until the age of 10 years old; furthermore at this age he started a program of occupational therapy.

Discussion

Chromosome 22q11DS is one of the most common multiple anomaly syndromes in humans with a population prevalence ranging from approximately 12,000 to 16,000.[5] Although a large number of clinical features have been reported in association with 22q11DS, the anomalies that have attracted the greatest amount of attention are the behavioral and developmental. While Shprintzen et al.[6] described at first psychiatric disorders in 22q11DS, a lot of researchers studied 22q11.2 resided genes, influencing psychiatric phenotypes.[7,8] According to Shprintzen it is not yet clear what biologic basis of mental illness in 22q11DS, however the syndrome is an clinical model for understanding psychiatric disorders, especially psychosis, in humans.[9] People with 22q11DS have a 30-fold risk of developing schizophrenia, suggesting that the 22q11.2 deletion can be considered the highest known genetic risk factor for schizophrenia.[10,11] The neurocognitive profile is also highly variable, both between individuals and during the course of development.[12] It is well known that schizophrenia phenotype includes a cognitive deficit and a decline in academic performance preceding the first episode of psychosis.[12] Duijff et al.[13] studying the cognitive development in children with 22q11DS, suggested that the finding of cognitive decline can be only partly explained as the result

of 'growing into deficit'; indeed in their study about a third of children with the syndrome showed an absolute loss of cognitive faculties previously acquired.[13] Recently, results from the International Consortium on Brain and Behavior in 22q11DS have been published.[14] This study confirms previous findings that this syndrome is one of the most important risk factors for psychosis, because the authors report an high prevalence of schizophrenia spectrum disorders; indeed attention deficit hyperactivity disorder (ADHD) as well as mood and anxiety disorders were also prevalent. Severe cognitive impairment was associated with schizophrenia spectrum disorders,[14] however this result can be detected in both 22q11DS patients and general population. The association of developmental delays (particularly in language) are very common in patients with 22q11DS. While our patient did not present any psychiatric disorders, nevertheless he was last assessed at age 12 years, so subsequent development of psychosis cannot be excluded; indeed according to Vorstman et al.,[15] the early cognitive decline is a strong indicator of the risk of developing psychosis and our commitment will be to follow the patient in years. The real peculiarity was the early ID rather than a more specific cognitive decline. A lot of studies demonstrated that cognitive impairments are common in individuals with 22q11DS with a mean IQ of 75,[16–18] suggesting that other factors contribute to adaptive functioning in this population, such as poorer socialization and communication skills.[19] Our patient showed a cognitive deficit with both early onset and IQ less than commonly observed in 22q11DS. Tarsitano et al.[20] described a case of 22q11DS associated with ID, however in their case there were evident dysmorphic features and an additional genomic disorder (duplication in 8q22.1). Dysmorphic facial features with attention disorder and learning difficulties were present in two cases described in literature, however in this double report there were not information about the degree of intellectual development disorder assessed with any full-scale IQ.[21] In our case there were not neonatal hypocalcemia and/or seizures. This is another particularity of our case, because according to Cheung et al.[22] both two conditions are associated with the severity of ID. The results of several studies confirm that palate anomalies are very common in this syndrome[23,24]; so these features require recognition and treatment and may impact cognitive evaluation. Although the palate anomalies such as submucous cleft palate and velopharyngeal insufficiency are common, and these conditions if underdiagnosed can contribute to speech and language delays, however in our patient the nasopharyngoscopy did not show any sign of palate anomalies.

Conclusion

Chromosome 22q11DS is relatively common and this diagnosis should be considered in patients who have TOF features accompanied by psychiatric and behavioral disorders. It is important that we remain open to the more subtle manifestations of 22q11DS because this syndrome remains undiagnosed in many children. Our case is a particular report of 22q11DS for the early mild intellectual disabilities with an early ID rather than a more specific cognitive decline.[13] The guidelines also state clearly that dysmorphic features can be subtle in some children with 22q11DS.[25] However, to our knowledge, the combination of early onset mild ID with no other features such as facial dysmorphisms, palate anomalies, immunodeficiency, hypocalcemia, gastroesophageal reflux and atopy is an unusual clinical manifestation of 22q11DS.

Conflict of interest

This article meets all requirements about informed consent/acknowledgement, ethics committee, funding, animal research and lack conflict of interest, as appropriate.

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