Impact of cardiac anomalies in the prognosis of patients with velo-cardio-facial syndrome

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ABSTRACT

One of the most common multiple anomaly syndromes in human is the velo-cardio-facial syndrome (VCFS). A very important step in managing a patient with a 22q11.2 deletion is to identify the exact phenotypic manifestations so that appropriate counseling and anticipatory care can be provided. Patients with VCFS have a 25 times higher rate of psychosis than general population. Therefore, it is almost certain that a genomic factor or factors in the deleted region influence brain development and/or function. Childhood psychiatric manifestations of VCFS include mood dysregulation, anxiety disorders, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders. VCFS is the most commonly

known genetic risk factor for schizophrenia. The 25% risk of developing schizophrenia is a great concern of the patients and their families given its gravity and social stigma. Regarding the psychopharmacological treatment, the therapies need to be carefully chosen, taking into account literature data on tolerability and efficacy. Thus, it is particularly important to know the features and symptoms of the disease in order to a good evaluation and monitoring of the patient. A multidisciplinary approach is fundamental to ensure that the patient will be able to attain his or her maximal potential.

KEYWORDS:

Velo-cardio-facial syndrome, cardiac malformations, schizophrenia

INTRODUCTION

One of the most common multiple anomaly syndromes in human is the velo-cardio-facial syndrome (VCFS). Other names as DiGeorge sequence, 22q11 deletion syndrome, CATCH 22, conotruncal anomalies face syndrome and Sedláčková syndrome have all been given to the same disorder (1,2). Approximately 6–10% of cases are familial, while most occur de novo. Nearly 75% of patients with a 22q11.2 deletion have a congenital heart malformation, as well as aortic arch anomalies (1).

VCFS syndrome has an extensive phenotype with more than 180 clinical features. It basically involves every organ and system. Early recognition of the deletion is important, so that the treatment of the involved organ anomalies can be initiated, screening for associated malformations performed and prevention of neuropsychological problems provided. A multidisciplinary approach is fundamental to ensure that the patient will be able to attain his or her maximal potential. Psychiatrists are an important part of the team that evaluate and treat these patients who frequently present a number of common psychiatric illnesses and phenotypic features including attention deficit disorder, schizophrenia or bipolar disorder. The psychiatric manifestations are highly variable, some individuals being essentially normal or at the mildest end of the spectrum, or some

with most severe cases having life-threatening and life-impairing problems.

MOLECULAR CHARACTERISTICS AND INHERITANCE PATTERN

The 22q11.2 locus is flanked by chromosome specific, low copy repeats that share more than 97% sequence homology. This fact causes the region to be prone to misalignment of reduced copy repeats during meiosis. Therefore, deletion or duplication of the region can occur due to nonallelic homologous recombination events. Nearly 90% of patients with a deletion share a common 3-Mb deletion, 8% have a smaller deletion (1.5-Mb) and very rare cases have an even smaller one within the disease locus, called „nested deletion”. The highly variable clinical presentation is not yet explained by the deletion size, therefore other undefined mechanisms must be involved (3, 4).

Most of the genes that lack in this disease have not been well characterized. Shorter deletions in the same region (contiguous gene deletion syndrome) appear in a small percentage of the affected individuals. However, the loss of a particular gene on chromosome 22, *TBX1*, is probably responsible for most of the syndrome's characteristic signs (distinctive facial features, heart defects, hearing loss, low calcium levels and also behavioral problems). The increased risk of developing psychiatric and behavioral

problems can also be explained by the loss of COMT gene, in the same region of chromosome 22 (5). However, some of the patients with classical features of the syndrome have smaller deletions that do not include TBX1, so the question remains as to whether other genes in the region contribute to the phenotype. Efforts to identify potential genetic modifiers of the cardiac phenotype are also underway (6, 7).

A person with a chromosome deletion has a 50% chance of transmitting the affection to their child (autosomal dominant transmission) (8). Yet, about 90% of the cases with a 22q11.2 deletion occur randomly during fertilization or fetal development, therefore, most of them are *de novo* (9).

MANAGEMENT

The most important step in managing a patient with a 22q11.2 deletion is to identify the exact phenotypic manifestations so that appropriate counseling and anticipatory care can be provided. Given the highly variable phenotype, the clinical evaluation will vary both in extent and by age. The International 22q11.2 Deletion Consortium provided guidelines on the management of the patients with VCFS (10).

NEUROPSYCHIATRIC DISORDERS

So far, it is not clear the biologic basis of mental illness in VCFS. However, the syndrome represents an excellent model for understanding psychiatric disorders, especially psychosis, in humans. Patients with VCFS have a 25 times higher rate of psychosis than general population. Therefore, it is almost certain that a genomic factor or factors in the deleted region influence brain development and/or function.

Childhood psychiatric manifestations of VCFS include mood dysregulation, anxiety

disorders, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (11). Attention deficit hyperactivity disorder (ADHD) was the most frequent disorder in children (37.10%) and was overrepresented in males. Anxiety disorders were more prevalent than mood disorders at all ages, but especially in children and adolescents. In approximately 32% of individuals with VCFS, chronic psychosis presents between late adolescence and early adulthood, and most of these cases meet the criteria for schizophrenia. Anxiety and unipolar mood disorders were overrepresented in females. Psychotic disorders were present in 41% of adults over age 25. Males did not predominate in psychotic or autism spectrum disorders. Moreover, the adults show minimal resolution of psychiatric symptoms (12).

VCFS is the most commonly known genetic risk factor for schizophrenia. The 25% risk of developing schizophrenia is a great concern of the patients and their families given its gravity, social stigma and impact on functioning (13, 14, 15, 16). The schizophrenia associated with VCFS accounts for 0.5–1% of schizophrenia in the general population. There is no difference between this and other forms of schizophrenia regarding prodrome, age at onset, the core signs and symptoms, cognitive profile, except overall lower average IQ and the absence of gender differences (17, 18, 19). Symptoms include delusions, hallucinations, disorganized thinking, emotional expression and/or behavior, as well as blunted affect, reduced speech, social withdrawal and motor disturbances (20, 21).

In the general population, psychiatric disorders such as anxiety disorders, schizophrenia and other psychotic disorders are effectively treated with both

pharmacological and non-pharmacological therapies. For anxiety the latter can include cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT). These recommendations are documented in the guidelines by the American Psychiatric Association (APA, United States of America) and the National Institute for Health and Care Excellence (NICE, United Kingdom). Clinicians may wonder if standard treatment strategies are feasible and effective in 22q11.2DS and if adaptations to treatment guidelines are required. For example, individuals with 22q11.2DS may need more time to establish a trusting relationship with clinicians, to process information, or may have difficulties understanding abstract information due to intellectual disabilities and deficits in socialization (17, 22).

Regarding the psychopharmacological treatment, the therapies need to be carefully chosen, taking into account literature data on tolerability and efficacy. Moreover, they seem to have a higher susceptibility to side effects than subjects with psychotic disorders (without VCFS). The antipsychotic medications have the potential to induce, exacerbate, or, interestingly, diminish pre-existing movement disorders in some cases (23). Studies suggest an increased vulnerability to antipsychotic-related movement disorders in VCFS that may include drug-induced parkinsonism, dystonia and non-epileptic myoclonus (24, 25, 26). Other psychotropic medications commonly used in VCFS such as antidepressants and anticonvulsants can also cause adverse motor effects (27).

SPEECH AND LANGUAGE IMPAIRMENT

Studies report that 70 to 90% of the patients with VCFS present hypernasal speech, severe articulation impairment (28). Speech onset is

usually mildly delayed and receptive language abilities exceed expressive. Some of them are related to unintelligible speech and incorrect management of these disorders in childhood (29). However, remediation of these problems has led to excellent prognosis in the large majority of cases.

CONGENITAL HEART DISEASE

Recent studies estimate that approximately 75–80% of patients with a 22q11.2 deletion have congenital heart disease. These studies may overestimate the prevalence of cardiac defects in the deleted population given that children and adults without significant heart disease may escape diagnosis (30, 31).

The most common cardiac defects seen in the 22q11.2 deletion syndrome include a subset of conotruncal defects such as tetralogy of Fallot (26%), interrupted aortic arch (10%) or truncus arteriosus (10%), pulmonary atresia with ventricular septal defect (24%) and less commonly atrial septal defects (30, 32). The full range of aortic arch anomalies, including cervical aortic arch, double aortic arch, right-sided aortic arch and abnormal origin of the subclavian arteries (both aberrant and isolated subclavian arteries) have been observed (33). In addition to cardiovascular malformations, a subset of patients with the 22q11.2 deletion syndrome develops aortic root dilation over time, suggesting that this feature may be progressive. However, the clinical significance of this finding remains to be determined as there are no reports of aortic root dissection (34).

These diseases can be observed after a clinical examination to which are added paraclinical investigations: ECG, echocardiography, stress test, CT angiography, cardiac MRI. These cardiac diseases are compatible with life but require supervision and eventually surgical treatment.

CRANIOFACIAL DYSMORPHIA

Patients with VCFS have a long face with a prominent upper jaw and an underdeveloped lower jaw, prominent nose with narrow nasal passages, long thin upper lip and a down-slanting mouth. They also present flattening of the cheeks (4). However, the presence of these features as well as other facial findings is variable. Results from a prospective evaluation for ocular abnormalities in 33 patients with VCFS revealed hooding of the upper lids (41%), ptosis (9%), hooding of the lower lids (6%), epicanthal folds (3%) and distichiasis (abnormal growth of lashes from the orifices of the meibomian glands) (3%). Strabismus was observed in 13% and amblyopia in 6% of the individuals (3, 6). The incidence of astigmatism, myopia and hyperopia was comparable to that in the general population. Ear abnormalities include overfolded or squared off helices, cupped, microtic and protuberant ears, also narrow external auditory meati.

VELOPHARYNGEAL DYSFUNCTION

Palatal anomalies are also common among children with VCFS, especially submucous cleft palate and occult submucous cleft palate (35). These clefts can be very difficult to identify without a nasopharyngoscopy. That is why several reports have significantly underestimated the frequency of clefting (36). It is for this reason that reports suggest that individuals with VCFS have “short palates” or hypernasal speech. More specifically, occult submucous cleft palate is an identifiable anomaly that is a form of cleft palate that often goes undetected because it requires endoscopic examination of the nasal surface of the velum (35). Stridor resulting from vascular ring, laryngomalacia and laryngeal web, laryngeal atresia and subglottic stenosis can also be found in these patients.

IMMUNE DEFICIT

Approximately 80% cases demonstrate some level of immunologic abnormality with most manifesting mild-to-moderate decrements in T-cell numbers due to thymic hypoplasia and only a very rare minority (0.5%) manifesting severe immunodeficiency that requires immediate medical attention. Patients may also experience humoral defects (26%) and IgA deficiency (6%) (37). In most of the cases, early childhood is marked by frequent respiratory infections, middle ear effusions and sinusitis. In the more severe cases, pneumonia and bronchitis may appear through childhood (28).

HYPOCALCEMIA

At least half of the infants with VCFS manifest hypocalcemia, which can result in hypocalcemic seizures if not recognized and treated appropriately. The hypocalcemia usually resolves by 1 year of age, but can reappear or present as isolated hypoparathyroidism for the first time at later ages (38).

DIAGNOSIS

The molecular diagnosis of a 22q11.2 deletion was previously made using fluorescence in situ hybridization of test probes from the 22q11.2 locus hybridized with metaphase chromosomes. While this approach reliably identified the typical 3-Mb deletion and some smaller deletions, it failed to detect the less common ‘nested’ or atypical deletions (3, 4, 39). Newer methods including MLPA and microarrays now identify both the common and atypical deletions in the region and are now the preferred methods of interrogation (40, 41).

CLINICAL OUTCOME

It is particularly important to know that features and symptoms, such as calcium homeostasis and neuropsychiatric issues, may

evolve over time and must be periodically reevaluated. Likewise, it is critical to screen parents for the 22q11.2 deletion in order to identify the previously undiagnosed adult as they have a 50% risk of recurrence in subsequent offspring and require clinical counseling to address their own clinical and neuropsychiatric needs.

Early reports revealed a high rate of mortality for patients with VCFS on account of inoperable cardiac malformations and severe infections. With medical and surgical advances, survival has significantly improved for all patients with congenital heart disease, but numerous studies suggest that cases with a malformation syndrome suffer worse clinical

outcomes than those with apparently isolated congenital heart disease (31). To date, the management of the associated congenital heart malformations follows standard approaches, but as our understanding of the 22q11.2-deleted patients specific clinical challenges improve, care may soon be tailored to their specific needs (personalized, or genotype-specific, clinical management) (10, 31).

The multidisciplinary approach (geneticist, psychiatrist, cardiologist) is essential for the positive evolution of the patient with velocardiofacial syndrome. The patient requires periodic evaluation (at every 6 months) for monitoring and reassessment.

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