Deletion 22q11

A Newly Recognized Cause of Behavioral and Psychiatric Disorders

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Background: Chromosome 22q11 deletion (del22q11), the most common microdeletion syndrome, causes a wide spectrum of clinical disorders. Recent studies have suggested that significant psychiatric and behavioral disturbances occur in up to 60% of these individuals.

Objective: To illustrate the spectrum of behavioral and psychiatric abnormalities associated with del22q11 and the subtle nature of its associated physical findings.

Patients and Methods: Case series describing psychiatric and behavioral findings in 3 patients with del22q11.

RESULTS AND CONCLUSIONS: Behavioral and psychiatric problems are common in patients with del22q11 syndrome. Because the physical manifestations of the disorder are so variable and may be subtle, the behavioral and psychiatric manifestations may be the presenting problem. Providers must therefore consider del22q11 as a potential diagnosis in children and adults with behavioral and psychiatric problems. Furthermore, behavioral and psychiatric problems need to be looked for when caring for children and adolescents with a known diagnosis of del22q11.


CHROMOSOME 22q11 deletion (del22q11) is the most common microdeletion syndrome, with an incidence estimated at 1 in 2000 to 4000.1 It causes a spectrum of well-described clinical syndromes, which includes DiGeorge syndrome (conotruncal heart defect, hypocalcemia, and thymic hypoplasia)2; velocardiofacial syndrome (VCFS) (cleft palate or velopharyngeal insufficiency, hypernasal speech, learning disabilities, heart defects, and characteristic facial findings)2; and conotruncal anomaly face syndrome (conotruncal heart defects and typical facial appearance).3 Chromosome 22q11 deletion has been found in 11% to 16% of cases of nonsyndromic congenital conotruncal heart disease,5,6 and has been reported to present as apparently isolated neonatal hypocalcemia7 or learning problems.8 Furthermore, some individuals manifest only mild facial abnormalities.9,10 The availability of molecular cytogenetic testing by fluorescence in situ hybridization (FISH) has led to an appreciation of both the high incidence of del22q11 and the wide variety of clinical presentations that can be seen even within a single family.9

However, because there is no single, easily recognizable “del22q11 syndrome” phenotype, this important cause of disease easily can be overlooked. This fact is of even greater concern because of recent reports that show significant psychiatric and behavioral disturbances occurring in up to 60% of patients with del22q11.11-13 Here we describe 3 persons with del22q11, a mother and son and a sporadic case, illustrating the effect that the associated behavioral and psychiatric problems have on patients and families with del22q11.

REPORT OF PATIENTS

PATIENT 1

A 16-year-old boy was first evaluated for genetic abnormalities in the craniofacial clinic. The medical history was remarkable for cleft palate repair, ventriculoseptal defect repair, tonsillectomy and adenoidectomy, and pharyngeal flap surgery for correction of velopharyngeal insufficiency. Bilateral myringotomy tube placement was performed after multiple episodes of otitis media and persistent middle ear effusion.

School records note that he was “anxious” and “withdrawn.” He was described...
as restless and easily distracted, was often found daydreaming or disturbing other children, and required frequent reminders to stay on task. Work was not completed at home or school. He had difficulty with peer relationships.

Wechsler Intelligence Scale for Children scores were verbal, 87 and 92; performance, 78 and 78; and full-scale, 81 and 84 at ages 8 and 12 years, respectively. During these years his classroom performance steadily declined, as documented by a drop in his total battery scores on the California Achievement Test from 80 in 1990 to 26 in 1992. His teachers’ observations confirm this trend.

Physical examination showed mild midfacial flattening, mild micognathia, small and simple ears, long nose with square nasal tip, and long tapered fingers (Figure 1). These physical findings as well as the history of learning difficulties suggested the diagnosis of VCFS. Chromosome analysis at a resolution of 600 bands showed a male karyotype with deletion of chromosome 22q11, confirmed by FISH with a DNA probe (D22S75, Oncor, Gaithersburg, Md) specific for the DiGeorge critical region.

PATIENT 2
This 48-year-old woman is the mother of patient 1. Her medical history was significant for a cleft palate repaired in early childhood. Developmental history was not known, although her father stated that she had learning disabilities. She had a speech defect but had never had speech therapy. There was no history of hypocalcemia or congenital heart disease.

After high school, she was able to live independently only with ongoing support from her parents. She developed alcohol dependence, compulsive eating patterns that led to clinical obesity, and recurrent episodes of depression. Her son (patient 1) went to live with her parents during his first year of life owing to her inability to care for him.

During her son’s initial genetic evaluation, she was admitted to the psychiatric unit of another hospital, following a suicide attempt, with a diagnosis of major depression. At that time, her chromosome analysis at a resolution of 550 bands showed a normal female karyotype, but del22q11 was demonstrated by FISH using a DNA probe (D22S75, Oncor) specific for the DiGeorge critical region.

Physical examination revealed an obese woman of low-normal height. She had hypernasal speech with an articulation defect. The face was notable for small ears, mild midfacial hypoplasia, and a long nose with a squared-off nasal tip (Figure 2). Her fingers were long and tapered.

PATIENT 3
The patient is a 12-year-old boy who was born at full term by spontaneous vaginal delivery to a healthy primigravida female following an uncomplicated pregnancy. He was well throughout early childhood, with normal developmental milestones during the first year of life. By age 3 years, however, he was noted to have both receptive and expressive language delays. There was a hypernasal quality to his speech. His hearing was normal. Videofluoroscopy revealed velopharyngeal dysfunction, and he underwent a pharyngeal flap procedure at age 4 years. He had no evidence of congenital heart disease or hypocalcemia.

He was noted to have difficulty in school caused by the combination of his limited intellectual capacity and attention-deficit/hyperactivity disorder (ADHD). Some improvement was seen with methylphenidate therapy for the ADHD. His mother described him as always having been reserved and having difficulty with social interactions, at one point offering money to a classmate to be his friend. These observations were confirmed repeatedly by his school teachers. At age 11 years, his Wechsler Intelligence Scale for Children scores were verbal, 59; performance, 70; and full-scale, 62. These scores represented a small but significant decline from his scores at age 4 years.

Physical examination revealed normal stature, weight, and head circumference for age. The ears were small and cupped, there was malar flattening, and the nasal tip was squared off (Figure 3). The palate was high and arched. The fingers were long and tapered. Findings from the remainder of the examination were normal. High-resolution chromosome analysis at the 650-band level was normal, but del22q11 was confirmed by FISH using a DNA probe (D22S75, Oncor) specific for the DiGeorge critical region.
A characteristic personality has been described in children with VCFS, marked by an expressionless face, monotonous speech, flattened affect, and abnormal social interactions. Behavior can range from withdrawn to socially uninhibited and impulsive. They also have poor motor coordination and deficits in numerical understanding. In older children, difficulty with abstract reasoning can lead to increasingly poor performance in school, as seen in patients 1 and 3. During the past 5 years, a variety of behavioral and psychiatric diagnoses have been described in patients with VCFS, including ADHD, oppositional defiant disorder, personality disorders, schizoaffective disorder, bipolar disorder (particularly a rapid-cycling variety), schizophrenia, obsessive-compulsive disorder, and others. To our knowledge there have been no large, prospectively designed studies to determine the incidence of these types of disorders in patients with del22q11.

Pulver et al12 studied 14 patients older than 15 years with a known diagnosis of VCFS who agreed to undergo a psychiatric evaluation. Four (30%) were diagnosed with schizophrenia or schizoaffective disorder. Three others were diagnosed with personality disorders. Alcohol abuse or dependence, social phobias, or adjustment disorders were seen in 7 (50%), either as the only diagnosis or comorbidly with other psychiatric diagnoses. While there may have been selection bias for patients who were already suspected or known by their families to have mental illness, 12 (86%) of the 14 had a Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition Axis I (clinically defined psychiatric disorder or developmental disorder of childhood) or Axis II (personality disorder or mental retardation) diagnosis. Additionally, 12 of families that agreed to provide family history, 3 had other family members with psychoses. While the deletion status of those family members was not described, it is provocative that their findings reflect the estimated 25% familial incidence of del22q11.9

In 2 later studies,13,16 the authors characterized the size of the chromosome 22q11 deletion in 18 (14 of whom were described in a previous study) and 26 patients, respectively. They showed that the deletions seen in the patients with schizophrenia are similar in size to the deletions seen in previously reported patients with DiGeorge syndrome and VCFS. In 2 patients no deletion could be identified.16 This suggests that most, if not all, patients with del22q11 are at risk of psychiatric disturbance, as are patients with VCFS without deletions.

In a study looking for genetic associations with schizophrenia, 2 (2%) of 100 schizophrenic patients were found to have del22q11.15 Both patients had facial findings suggestive of VCFS, but neither had other congenital anomalies typical of VCFS. A recent study ascertained patients from a population with schizophrenia, selecting those with suggestive facial findings for testing. Ten (59%) of 17 patients tested had del22q11. Not surprisingly, this group, ascertained because of mental illness, had a significantly lower incidence of of cardiac disease or cleft palate than did previously reported groups ascertained because of other presenting characteristics of VCFS.17 psychiatric problems, therefore, may be the primary finding in patients with del22q11, and the absence of other major anomalies should not preclude consideration of the diagnosis. To our knowledge, no similar study has looked at patients with bipolar spectrum disorders, a group that is likely to yield more patients with del22q11 as the bipolar disorders seem to be more common than schizophrenia among patients with known chromosome 22q11 deletions.13

Papolos et al13 identified bipolar spectrum conditions in 16 (64%) of 25 patients with del22q11, and ADHD was diagnosed in 4 (all 17 years old or younger). They also noted that many of the older patients diagnosed with bipolar disorders had had findings consistent with ADHD at a younger age. Furthermore, they noted an apparent drift in symptoms in these patients as they aged, so that patients who initially seemed to have ADHD progressed to bipolar disorders. This apparent progression has been observed previously in early-onset bipolar disorder.18-20 These data also suggest that the earlier perception that del22q11 is associated with schizophrenia may be due to difficulty with diagnosis, particularly in young patients. In younger patients, bipolar disorders more often present with psychotic symptoms. Also, the behavioral phenotype associated with del22q11, including the flattened affect and tendency toward concrete thought processes, might contribute to incorrect classification of these patients' psychiatric disturbance.

Catechol-O-methyltransferase (COMT) has been implicated in the neuropsychiatric disorders found in VCFS. Coded on the segment of chromosome 22q11 that is commonly deleted in affected patients,21 COMT inactivates several psychoactive catecholamines, including dopamine. The enzyme is expressed ubiquitously, including in liver and in brain. A single base-pair substitution in this gene, causing substitution of methionine for valine at codon 138 (COMT138Val→Met), leads to heat lability and decreased activity of the enzyme. In their study of patients with VCFS and psychiatric diagnoses, Lachman et al21 compared the allele frequency for the low-activity COMT138Met in patients with VCFS and psychiatric diagnoses with controls. There was a trend toward an increased frequency of the low-activity allele that did not reach statistical significance for the whole VCFS group. However, in the subgroup of patients with bipolar spectrum disorders, schizoaffective disorders, or cyclothymia, there was a significantly higher frequency of the low-activity
COMT158Met allele compared with controls. Further, the authors noted that the control population used had a somewhat higher frequency of the COMT158Met allele than did a group of parents of the patients with VCFS in the study. The parents may better represent the background frequency for this polymorphism, as there is a known ethnic variation. Thus, use of this control group may have underestimated the true difference.

In the same study, 2 other patients clinically diagnosed with VCFS but without demonstrable deletions were homozygous for COMT158Met. Most impressive was the fact that 100% (8/8) of patients with VCFS and the rapid-cycling form of bipolar disorder carried the COMT158Met allele (7 of these with deletions, and 1 without deletion but homozygous for the COMT158Met allele)—significantly different from the expected 3 of 8 (P < .05). The deletion may be unmasking a recessive trait carried on the undeleted allele. A recent report found no relationship between the COMT158Met allele and psychiatric disorders in 40 patients with del22q11; however, the authors did not report an analysis of the subgroup of patients with bipolar spectrum disorders. It should be remembered, however, that mental illness is likely inherited in a complex pattern, and that multiple factors may be involved in a given patient. The deleted region of chromosome 22q11 therefore probably contains 1 or more major determinants for mental illness.

The finding of a low-activity COMT variant in some patients raises an important therapeutic issue regarding the use of methylphenidate for ADHD in patients with del22q11. Several patients with del22q11 developed manic symptoms, including pressured speech, flight of ideas, increased psychomotor activity, hypersexuality, anxiety, and sleep disturbances while using methylphenidate for ADHD. Methylphenidate causes the release and blocks the reuptake of dopamine and other catecholamines in presynaptic vesicles in the central nervous system. While it is not thought to be important in deactivation of neurotransmitters at the level of the synapse, COMT deficiency may potentiate the action of methylphenidate by reducing the rate of metabolism of catecholamines in presynaptic vesicles in the central nervous system. While it is not thought to be important in deactivation of neurotransmitters at the level of the synapse, COMT deficiency may potentiate the action of methylphenidate by reducing the rate of metabolism of catecholamines in presynaptic vesicles in the central nervous system. Specifically, the action of methylphenidate may be altered in patients with del22q11.

The patients described herein highlight the spectrum of behavioral and psychiatric abnormalities associated with del22q11, and the accompanying figures demonstrate the subtle nature of the associated physical findings. While the true incidence of these problems is yet to be determined, early studies from one center that ascertained patients primarily through a craniofacial clinic suggest that as many as 60% of patients with del22q11 will manifest psychiatric and/or behavioral problems. In some patients this may be the presenting problem, so providers must consider this possibility and actively search for associated findings when evaluating patients with ADHD, affective disorders, and other behavioral and psychiatric disorders of childhood. Alternatively, when caring for young children with del22q11 ascertained because of congenital malformations, providers must specifically look for psychiatric problems during health supervision visits, as early recognition and intervention is crucial in preventing the long-term morbidity commonly encountered with psychiatric and behavioral disorders of childhood.

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REFERENCES