The 22q11.2 Deletion in Children: High Rate of Autistic Disorders and Early Onset of Psychotic Symptoms

JACOB A.S. VORSTMAN, M.D., MONIQUE E.J. MORCUS, M.Sc., SASJA N. DUIJFF, M.Sc., PETRA W.J. KLAASSEN, M.Sc., JOSIEN A. HEINEMAN-DE BOER, M.Sc., Ph.D.,† FRITS A. BEEMER, M.D., Ph.D., HANNA SWAAB, M.Sc., Ph.D., RENÉ S. KAHN, M.D., Ph.D., AND HERMAN VAN ENGELAND, M.D., Ph.D.

ABSTRACT

Objective: To examine psychopathology and influence of intelligence level on psychiatric symptoms in children with the 22q11.2 deletion syndrome (22q11DS). **Method:** Sixty patients, ages 9 through 18 years, were evaluated. Assessments followed standard protocols, including structured and semistructured interviews of parents, videotaped psychiatric interview, and intelligence assessment of the child. Intelligence level, psychiatric symptoms, and classification provided the main outcome. **Results:** High rates of autism spectrum disorders (30 of 60, 50.0%) and psychotic symptoms (16 of 60, 26.7%) were found in this sample. In 7 of 60 (11.7%), the psychotic symptoms interfered with behavior and caused considerable distress. In these cases, the diagnosis of a psychotic disorder was applied. The average age of the children with psychotic symptoms at time of assessment was 14.2 years. Although it is likely that the high rate of psychopathology in this sample is to some extent associated with the lower level of cognitive function, a major effect of the degree of cognitive impairment on psychiatric morbidity was not found. **Conclusion:** Autism spectrum disorders and subthreshold autistic symptomatology are common in children with 22q11DS. Furthermore, a high rate of psychosis and psychotic symptoms is found in this childhood sample, suggesting an early onset of psychosis in 22q11DS patients. Autistic and psychotic disorders should be considered to be main elements of the behavioral phenotype of 22q11DS children. *J. Am. Acad. Child Adolesc. Psychiatry*, 2006;45(9):1104–1113. **Key Words:** 22q11 deletion syndrome, velocardiofacial syndrome, autism, psychosis, behavioral phenotype.

Accepted April 16, 2006.

Drs. Vorstman, Swaab, and van Engeland and Ms. Morcus are with the Department of Child and Adolescent Psychiatry; Dr. Heineman-de Boer, Ms. Duijff, and Ms. Klaassen are with the Department of Pediatric Psychology; Dr. Beemer is with the Department of Medical Genetics; Dr. Kahn is with the Department of Psychiatry, University Medical Centre, Utrecht, The Netherlands. Drs. Vorstman, Swaab, Kahn, and van Engeland and Ms. Morcus are also with the Rudolf Magnus Institute of Neurosciences, Utrecht, The Netherlands.

†*Deceased.*

This study was sponsored in part by a research grant from the Hersenstichting Nederland (Dutch Brain Foundation). The authors thank W.G. Staal, M.D., Ph.D., F.E. Scheepers, M.D., Ph.D., and R.S. Simons, M.Sc., for their assistance in the child psychiatry clinic and E.P. Martens, M.Sc., for statistical advice.

Reprint requests to Dr. Jacob A.S. Vorstman, Division of Human Genetics and Molecular Biology, The Children's Hospital of Philadelphia, Abramson Research Center, Room 1002, 3615 Civic Center Blvd., Philadelphia, PA 19104-4318; e-mail: J.A.S.Vorstman@umcutrecht.nl.

0890-8567/06/4509-1104©2006 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/01.chi.0000228131.56956.c1

The 22q11.2 deletion syndrome (22q11DS) is a congenital multisystem disorder with an estimated prevalence at birth of approximately 1 in 4,000, equally affecting male and female individuals (Goodship et al., 1998; Oskarsdottir et al., 2004; Tezenas Du Montcel et al., 1996). Velocardiofacial syndrome and several other syndromes such as DiGeorge syndrome and Cayler syndrome can be caused by this genetic abnormality, characterized by a deletion of a small region (1.2–3 megabases) on the long arm of chromosome 22 (Edelmann et al., 1999; Shaikh et al., 2000).

Characteristic physical manifestations include characteristic facial appearance, anatomical and/or functional abnormalities of the palatal shelves such as cleft palate and velopharyngeal insufficiency, lymphoid tissue hypoplasia, and conotruncal heart defects. In the earliest

descriptions of the phenotype, learning disabilities were also mentioned as a common feature (Goldberg et al., 1993; Golding-Kushner et al., 1985; Shprintzen et al., 1978). In 1992, Shprintzen et al. reported a high prevalence of psychiatric disorders in patients with the 22q11DS, the most frequent diagnosis in their cohort being schizophrenia (Shprintzen et al., 1992).

Since then, a growing number of studies on the psychopathology in 22q11DS patients have been published. Most of these studies were undertaken in samples of adult 22q11DS patients and some in samples including both children and adult patients. To date, a limited number of clinical studies specifically report on the psychiatric profile of 22q11DS children (Arnold et al., 2001; Feinstein et al., 2002). Recently, a study involving 25 adolescents and young adults with 22q11DS (age range 13–25 years) was published (Baker and Skuse, 2005).

In several studies of adults with 22q11DS, a high rate (20%–30%) of psychotic disorders is reported (Murphy et al., 1999; Pulver et al., 1994). In addition, 22q11DS patients, including patients without psychosis, were found to exhibit significantly more schizotypic traits in comparison to their first-degree relatives and a healthy nonrelated control group, suggesting an increased predisposition to psychosis associated with the presence of the deletion (Murphy et al., 1999).

Reports on the prevalence of mood disorders (major depressive disorder and dysthymia) in 22q11DS patients (children and adults) range from 11.5% to 40% (Arnold et al., 2001; Carlson et al., 1997; Murphy et al., 1999; Papolos et al., 1996). High prevalence rates of attention-deficit/hyperactivity disorder (ADHD) are also reported, ranging from 35% to 46% (Feinstein et al., 2002; Niklasson et al., 2001; Papolos et al., 1996). Obsessive-compulsive disorder (OCD) has been described in several studies, with rates ranging from 8% to 33% (Gothelf et al., 2004; Papolos et al., 1996).

Observation of autistic-like behavior is mentioned in several studies. Gerdes et al. (2001) describe self-directed behavior, preference for independent play, diminished motivation by external appreciation, non-compliance, high activity, and poor social skills. One clinical study (Niklasson et al., 2001) specifically included assessment of autism spectrum disorders (ASDs) and established a prevalence of ASDs of ≈30% in a sample of 32 22q11DS patients. Moreover, >50% of the subjects who did not meet sufficient criteria for ASDs were nevertheless found to exhibit symptoms in the three core domains of autism (communication, social interaction, stereotypical behavior). In another recent study by Fine et al. (2005), the question of whether social and communicative deficits in this population qualify for the diagnosis of an ASD was further evaluated. A standardized screening interview by phone was performed in a subset of 22q11DS children (n = 20) who fulfilled strict diagnostic criteria for ASD based on scores from an initial mailed questionnaire survey (N = 98, age range, 2–12 years). This study found a prevalence of ASDs among 22q11DS children of ≈14%.

Summarizing the results of psychiatric studies in 22q11DS patients, a high prevalence of psychosis (20%–30%) among adults with 22q11DS appears to be the most consistent result across the different reports, whereas "psychosis-like" symptoms are reported in adolescents and young adults (age range 13–25 years; Baker and Skuse, 2005). In children, variable rates of a range of psychiatric disorders are reported, including affective disorders, attention-deficit disorders, and ASDs, but not psychosis. The question that surfaces from these findings is whether the psychiatric disorders reported in children with 22q11DS should be considered as independent phenomena or, alternatively, as markers of an increased vulnerability for schizophrenia in adulthood. The present study was set up as a prospective longitudinal study to address this question.

In this article, we report the cross-sectional psychiatric findings in a sample of 60 children with 22q11DS, using appropriate assessment tools to encompass a broad range of psychiatric disorders, including autism and psychosis. A second question that is addressed concerns the extent to which psychiatric morbidity is associated with the level of cognitive functioning within this population.

METHOD

Subjects

All children (N = 60, inclusion criterion age 9–20 years) were presented by their parents through publicity on the Web site and a newsletter of the parents' network of 22q11DS children in The Netherlands. An estimated 40% to 50% of Dutch parents with school-age children with 22q11DS is affiliated with this association. Furthermore, the information on the Web site is accessible to everyone. To further minimize the effect of selection bias, the information provided to the parents stated that children were invited to participate regardless of the presence of behavioral problems.