

# **Clinical Case Rounds in Child and Adolescent Psychiatry: Treatment resistant psychosis in an adolescent with scoliosis and a history of early feeding difficulties**

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A 17 year old young woman of borderline intellectual ability was referred to an outpatient mental health clinic from an inpatient adolescent unit following a 3 month admission. The diagnosis was of "First Episode Psychosis, possibly schizophrenia". She was described as improving on olanzapine, and ready for discharge into the community.

The Early Psychosis team made a visit to the adolescent inpatient unit to see her. She appeared a slim young woman with an unusual face. She was noted to have long slender fingers, and a thoracic scoliosis. She was gesturing and posturing, apparently responding to unseen stimuli. She was giggling to herself and appeared suspicious when not otherwise totally preoccupied. The team was informed that she needed intensive supervision to carry out any activities of daily living. Investigations including CT brain scan and EEG were normal. Genetics had not been consulted.

The admission history was as follows: She had started her primary schooling in special education but from middle school onwards had been in a regular class. Her personality had changed as she entered adolescence, becoming emotionally more distant, odd, less social, suspicious, and sometimes posturing. However she had maintained a group of friends and was said to have progressed academically though in a sheltered setting. IQ results obtained from school records indicated a possible decline in two sets of tests done mid way through primary school and later in adolescence. A traumatic event occurring a month before admission appeared to contribute to a rapid decline in her mental state. She became distressed, disorganized and paranoid and was subsequently taken to the Emergency room and then admitted.

There was no history of illicit drug use. She was the third of four children of an intact family. There was no family history of major mental illness, intellectual disability, seizure disorder or cardiac problems.

The birth and developmental history was as follows. The pregnancy was planned and of 38 weeks duration with a normal vaginal delivery and birth weight of 2340g. She was observed by a specialist for the first week after birth. There were some problems noted with breast feeding and she was bottle fed from 4 weeks onwards but continued to have feeding difficulties. Stridor, apnoeic episodes and a large para-umbilical hernia complicated the first 2 months of her life. Chromosomal studies were performed and a syndrome suspected but no diagnosis was made. Developmental milestones were stated by mother to be normal. Medically she had had a number of anaesthetics to repair the hernia and for dental procedures. Thus an undiagnosed significant cardiac anomaly was thought unlikely.

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## **Subsequent progress**

She presented with a severe psychosis which proved extremely difficult to treat. There was a pattern of initial response to atypical antipsychotics which lasted no longer than a few days before the effects diminished. Increasing the dose was of no benefit. She developed agranulocytosis on Clozapine. Some stabilization was eventually obtained on haloperidol and sodium valproate though the latter continually had to be adjusted because of thrombocytopenia. Because of her initial long admission and fear that

institutionalization would compound her difficulties, her subsequent care alternated between partial, full hospitalization and day hospital depending on her mental state. Her family was very supportive. The original discharge plan to send her back to school was clearly impractical.

She was seen by a medical geneticist but initially this yielded no new information. The diagnosis was arrived at after the location of the Velo Cardio Facial Syndrome specialist fact sheet from the Web. At least 6 of the 181 listed associated anomalies were present in spite of the fact she had neither cleft palate nor a known cardiac defect. The geneticist was contacted and asked whether velocardiofacial (VCFS) syndrome had been considered in light of the ongoing treatment resistant psychosis. A fluorescence in situ hybridization study revealed a micro deletion at band 22q 11.2 in one of her number 22 chromosomes. The geneticist advised that as long as this was a spontaneous mutation, that, as an autosomal dominant disorder, there was a 1:2 chance of the patient bearing a child with this disorder, which could be very variable in severity, should she become pregnant.

## **Discussion**

Individuals with VCFS are reported to have a characteristic behavioural phenotype, a generally below average IQ: and a high rate of behavioural and psychiatric disorder: attention deficit disorder with and without hyperactivity, anxiety, emotional instability, autism spectrum disorder, affective disorder in childhood, and psychotic disorders, in adulthood (Murphy, 2005). Papolos et al (1996) found that 64% of an unselected series of patients with VCFS met the DSM criteria for bipolar disorder. Shprintzen et al (1992) suggested that around 10% of his sample of VCFS children and adults followed into adulthood developed psychiatric disorders that mostly resembled chronic schizophrenia with paranoid delusions. However the patient did not have either a known cardiac defect or a cleft palate though on further education may have some of the described facial features of the syndrome. Meinecke et al (1986) described considerable clinical variation in the expression of the disorder. This is certainly well illustrated by scanning the VCFS Specialist Fact Sheet. Cleft palate clinics and clinics dealing with conotruncal heart abnormalities sometimes screen for VCFS. Morava et al (2002) evaluated 20 patients with scoliosis and connective tissue anomalies and as a result of their findings suggested that 22q11.2 deletion should be considered in patients with unexplained scoliosis and developmental delay. Mc-Donald McGinn et al (2001) looked at 30 individuals identified following diagnosis in a relative. Sixty percent of those had no visceral anomalies and only 32% of the adults and 55% of the children had major findings that would have brought them to medical attention. Swillen et al (1997) reported wide variability in intelligence with a mean IQ around 70 so it is possible to find individuals with the microdeletion with normal IQ. Arnold et al (2001) noted that the VCFS affected father of one of their VCFS cohort was a university graduate. As deletion of chromosome 22q 11 is thought to represent one of the highest known risk factors for schizophrenia with the exception of being the off-spring of dual mating or the monozygotic co-twin of an affected individual( Murphy et al 2001), it may be that questions should be asked about anatomical abnormalities in relatives of early psychoses patients and those with unexplained behavioural difficulties and particular attention given to early feeding difficulties which might indicate subtle velo-palatal difficulty. Families where there is a history of psychosis in close relatives would be of special interest. Practically there may be considerable reluctance by patients' parents to seek a genetic consultation whilst the clinician may see it as a possible opportunity for primary prevention and early intervention. A close working relationship with parents as well as between community adolescent psychiatrist, pediatrician and geneticist is

essential to outcome. Costs for genetic testing may also be a deterrent.

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- Velo Cardio Facial Syndrome Specialist Fact Sheet Velo Cardio Facial Educational Foundation; [www.vcfs.org](http://www.vcfs.org).

#### Learning objective

To consider VCFS in the differential diagnosis of a child or adolescent with early onset psychosis even in the absence of obvious “core” symptomatology.

## Clinical Case Rounds in Child and Adolescent Psychiatry: Commentary

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This case highlights the importance of recognizing 22q11 Deletion syndrome (22q11DS) in clinical psychiatric practice. Psychotic disorders are highly prevalent (25-30%) in patients with 22q11DS (Pulver et al. 1994; Murphy et al. 1999), and psychotic symptoms are even more common (26-48%) (Baker and Skuse 2005; Debbane et al. 2006; Vorstman et al. 2006). Among randomly selected patients with schizophrenia there is evidence of an increased prevalence of 22q11 deletions compared with the general population (2% versus 0.025 %, respectively) (Karayiorgou et al. 1995). However, when individuals with schizophrenia are screened for the presence of clinical features consistent with 22q11DS, like in the current report, a much higher prevalence (14-53%) is found (Gothelf et al. 1997; Bassett et al. 1998). It is important to recognize that the phenotypic features of 22q11DS are highly variable and a diagnosis may be elusive during infancy, this is especially true for cases of the syndrome in which there is later onset of findings such as speech abnormalities, thrombocytopenia, osteopenia, and behavioral problems. In this regard there are three previously published cases in addition to the current report of psychotic symptoms leading to cytogenetic diagnosis of 22q11 microdeletion (Sieberer et al. 2005; Sieberer et al. 2006).

Clozapine in the treatment of psychosis in patients with 22q11DS has been

previously suggested (Gothelf et al. 1999) in spite of the risk of agranulocytosis; however, it is not known whether there is a greater risk for this adverse event in 22q11DS. Poor response to conventional anti-psychotic medications - such as haloperidol used in the current report after the development of agranulocytosis - has been previously reported (Gothelf et al. 1999) ; yet others (Murphy et al. 1999; Bassett et al. 2003) published that response to anti-psychotics is similar in 22q11 deleted and non-deleted psychotic individuals. There is a need for systematic evaluation of the efficacy of anti-psychotics in large cohorts of 22q11DS.

Clinicians must have a high index of suspicion for 22q11DS among psychotic patients, especially when at least one of the following is present: learning disabilities, facial dysmorphology, palate anomalies, congenital heart disease, or hypocalcaemia.

Diagnosing this chromosomal abnormality has important implications for patient management, early recognition of conditions associated with 22q11DS such as hypocalcaemia or hyperparathyroidism allow for improved treatment. In addition, it is an important consideration for family members who may be at risk given the 50% risk of transmitting the deletion to the next generation.

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