CLINICAL CASE ROUNDS IN CHILD AND ADOLESCENT PSYCHIATRY

Anxiety Disorders and Perceptual Disturbances in Adolescents with 22q11.2 Deletion Syndrome Treated with SSRI: A Case Series

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Abstract

Introduction: Psychotic symptoms are highly prevalent in adolescents with 22q11.2 Deletion Syndrome (22qDS), with as many as half reporting transient psychotic symptoms. Anxiety is also commonly seen in this population, and patients frequently report both psychotic symptoms and anxiety. **Objective:** To describe the psychiatric presentation, course and management of primary anxiety disorders in patients with 22qDS who also presented with isolated perceptual disturbances. **Method:** This report describes a 24-month clinical follow-up of three patients with 22qDS who were seen in the Medical Psychiatry clinic at the Hospital for Sick Children (Toronto, Canada). **Results:** Patients presented with primary anxiety disorders and perceptual disturbances. Patients were placed on selective serotonin reuptake inhibitor only, with improvement of both anxiety and perceptual disturbances being noted. **Conclusions:** Some patients with 22qDS who present with psychotic symptoms do not develop a psychotic disorder; therefore, the use of antipsychotics for every child or adolescent with 22qDS who experience psychotic symptoms is debatable. Long-term follow-up, phenomenological and treatment efficacy studies in larger samples are needed to determine optimal treatment of psychotic symptoms in children and adolescents with 22qDS.

Key words: *22q11.2 Deletion Syndrome, adolescents, anxiety disorders, psychotic symptoms, pharmacological management*

Résumé

Introduction: Les symptômes psychotiques sont fréquents chez les adolescents qui souffrent du syndrome de délétion 22q11.2: cinquante pour cent de ces sujets présentent des troubles psychotiques transitoires. Les troubles anxieux sont également courants dans cette population qui déclare souffrir fréquemment à la fois de troubles psychotiques et de troubles anxieux. **Objectifs:** Décrire les symptômes psychiatriques, l'évolution et le traitement de l'anxiété primaire chez des patients souffrant du syndrome de délétion 22q11.2 et de troubles isolés de la perception. **Méthodologie:** Suivi clinique de trois patients de la clinique psychiatrique de l'*Hospital for Sick Children* de Toronto (Canada) pendant 24 mois. **Résultats:** Les patients présentaient de l'anxiété primaire et des troubles de la perception; ils ont reçu uniquement un inhibiteur sélectif de recapture de la sérotonine (ISRS) qui a diminué l'anxiété et les troubles de la perception. **Conclusion:** Certains patients atteints de délétion 22qDS peuvent présenter des symptômes psychotiques sans développer de psychose. C'est pourquoi prescrire un antipsychotique à tous les enfants ou adolescents souffrant du syndrome 22qDS qui présentent des symptômes psychotiques est discutable. Un suivi à long terme, des études phénoménologiques et une étude de l'efficacité du traitement sur un plus large échantillonnage s'imposent afin de mettre au point un traitement optimal des symptômes psychotiques chez les enfants et adolescents atteints de délétion 22qDS.

Mots clés: *syndrome de délétion 22q11.2, adolescents, troubles anxieux, symptômes psychotiques, traitement pharmacologique*

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Introduction

The 22q11.2 Deletion Syndrome (22qDS) is a genetic syndrome associated with a microdeletion on the long arm of chromosome 22 first described by Strong (Strong, 1968) and Shprintzen (Shprintzen et al., 1978). Incidence of 22qDS in the general population is approximately 1 in 4000 live births (0.025%) (Devriendt, Fryns, Mortier, van Thienen, & Keymolen, 1998; Driscoll et al., 1993); however, it is seen in 1-2% of patients with adult-onset psychosis (Karayiorgou et al., 1995; Pawlowska et al., 2007), and in 5-6% with early-onset psychosis (Sporn et al., 2004; Usiskin et al., 1999).

The 22qDS phenotype is broad, with psychiatric symptoms being amongst the most common (Shprintzen, 2000). Twenty-five to thirty percent of adults with 22qDS meet diagnostic criteria for a psychotic disorder (Bassett et al., 2003; Murphy, Jones, & Owen, 1999). Psychotic symptoms appear even more commonly in 22qDS during childhood and adolescence (Baker & Skuse, 2005; Debbane, Glaser, David, Feinstein, & Eliez, 2006; Gothelf et al., 2007; Jolin et al., 2009a; Stoddard, Niendam, Hendren, Carter, & Simon, 2010; Vorstman et al., 2006). Up to half of the adolescents with this genetic syndrome have been found to develop brief positive psychotic symptoms that are not perceived as highly distressing (Baker & Skuse, 2005), or attenuated positive psychotic symptoms (Stoddard et al., 2010). Further, cases of psychosis with onset in childhood or adolescence have been described in adults with 22qDS who received the diagnosis of "atypical psychosis" or psychotic disorder not otherwise specified (Goldberg, Motzkin, Marion, Scambler, & Shprintzen, 1993; Krahn, Maraganore, & Michels, 1998; Pinquier et al., 2001). Some of these cases were reported to be successfully managed by medications other than antipsychotics (Carandang & Scholten, 2007; Graf et al., 2001). The "atypical" psychotic presentations in 22qDS are being studied further and this is resulting in an improved understanding of the breadth of psychiatric presentations that include psychotic symptoms. For instance, anxiety symptoms and anxiety disorders are also known to commonly occur in patients with 22qDS (14-54%) (Arnold, Siegel-Bartelt, Cytrynbaum, Teshima, & Schachar, 2001; Baker & Skuse, 2005; Feinstein, Eliez, Blasey, & Reiss, 2002; Jolin et al., 2009a; Pulver et al., 1994; Stoddard et al., 2010), and a trend for psychotic symptoms to be associated with two or more anxiety disorders has been reported (Jolin et al., 2009a).

The best management of psychotic symptoms in adolescents with 22qDS, especially in cases that do not fulfill criteria for a primary psychotic disorder, remains unresolved. Thus, further longitudinal examination of adolescents with 22qDS who present with psychotic symptoms can enhance the understanding of the clinical profile and strategies for management.

This report describes a 24-month follow-up of three adolescents with molecular diagnostic confirmation of 22qDS who were referred to the Medical Psychiatry clinic at the Hospital for Sick Children (Toronto, Canada) in 2007 and who were noted to have anxiety disorders as well as perceptual disturbances. Additional clinical information is compiled in Table 1. Data were collected from a retrospective medical chart review of several interviews with patients and parents and diagnoses were based on DSM-IV criteria. Research Ethics Board approval and written consents from patients and parents were obtained.

Case Reports

Case 1

Case 1 is a 16 year-old intellectually disabled boy with Separation Anxiety Disorder and Generalized Anxiety Disorder who had a history of hallucinations. At age nine, he reported seeing and sometimes feeling snakes on him, on a daily basis, for two months. At age 11, lasting eight weeks, he described seeing a "half-man/half-monkey" (human face and body of a monkey) and seeing monkeys that would talk to him, saying things like "make a railroad". At the time, his parents told him that they were not real, but despite this, he would not believe them and remained scared. Six months prior to the assessment he had visual and auditory hallucinations of a similar nature, occurring several times per month, and mostly when he was alone. At the assessment, he endorsed hearing voices that were perceived to be outside of his head. The hallucinations appeared to be exacerbated by being scared when alone or by his guilt at some perceived wrong-doing (e.g. not completing homework). The hallucinations affected his ability to shower by himself, stay home and sleep alone. Although he could describe the hallucinations, he had difficulty with time frame. Of note, he had a delusional interpretation of the hallucinations.

Investigations (bloodwork, ECG, EEG and structural brain MRI) were ordered to rule out physical causes for the psychiatric symptoms and to establish baseline measures prior to starting psychotropics. Abnormal results included a low vitamin B12, elevated CPK, elevated tyrosine, low calcium and prolonged QTc interval on ECG.

Antipsychotic medication was discussed; however, Cardiology advised against it given a prolonged QTc interval and non-adherence to calcium supplementation. In follow-up from April to July (2007) similar brief episodes of visual and auditory hallucinations continued to be reported and his anxiety remained elevated. He reported nightmares, waking up several times per night and requiring the lights and radio on when home alone during the day. Given these symptoms, sertraline was started at 25mg and titrated to 50mg/day (July 2007). Although he tolerated sertraline well and

Table 1: Clinical Summary of Three Adolescents with 22qDS

	Case 1	Case 2	Case 3
Age at first assessment by Medical Psychiatry (date)	14 (Apr 2007)	10 (Aug 2007)	12 (Mar 2007)
Primary Psychiatric Diagnoses	SAD, GAD	SAD, GAD, Simple Phobias	SAD, GAD, Simple Phobias
Past Medical History	Failure to thrive as an infant, recurrent upper respiratory tract and ear infections, mild conductive hearing loss requiring a hearing aid, pharyngeal flap surgery at age 7, low calcium and low iron requiring supplementation.	Tetralogy of Fallot repair at 18 months of age, hypothyroidism with L-thyroxine supplementation, recurrent upper respiratory tract infections, seborrheic dermatitis.	Laryngomalacia, patent ductus arteriosus, mild scoliosis, recurrent ear infections requiring tubes, and obstructive sleep apnea.
Neurocognitive Testing (FSIQ)	3rd percentile (at age 8)[1] <1st percentile (at age 16)[3]	3rd percentile (at age 7)[2]	<0.1 percentile (at age 8)[2]
Past Psychiatric History	Assessed at age 9 for hallucinations – no follow-up. Assessed at age 14: SSRI plus antipsychotic were prescribed but not taken.	Never seen by a psychiatrist. No history of psychiatric medication.	Assessed at age 9 for anxiety symptoms – no follow-up. Assessed at age 12: olanzapine was prescribed but not taken.
Family History	Maternal grandmother and aunt on antidepressants. Paternal uncle possibly had schizophrenia. Father has a learning disability; suspected (but never tested) for 22qDS.	Patient adopted at 7 weeks. Biological mother diagnosed with depression. Biological mother and maternal uncle diagnosed with 22qDS.	Mother and brother on antidepressants. Father has reading and spelling difficulties. Mother's cousin diagnosed with bipolar disorder.

Abbreviations: GAD, Generalized Anxiety Disorder; SAD, Separation Anxiety Disorder; 22qDS, 22q11.2 Deletion Syndrome; SSRI, Selective Serotonin Reuptake Inhibitor; FSIQ, Full Scale Intelligence Quotient; [1]FSIQ based on Wechsler Intelligence Scale for Children – Third Edition (WISC-III); [2] FSIQ based on Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV); [3] FSIQ based on Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV)

had no side effects, there were concerns with adherence. As a result, to reduce the risks related to abrupt cessation of medication by the patient, sertraline was switched to fluoxetine 10mg/day (February 2008). Follow-up of 24 months revealed improvement of his anxiety and functioning: he was able to shower by himself and stay home alone. No disturbances of perception were reported following the introduction of the SSRI.

Case 2

Case 2 is a 12 year-old girl with Separation Anxiety Disorder, Generalized Anxiety Disorder, Simple Phobias and a borderline IQ, who had a history of auditory hallucinations. She described a 2-year history of hearing her name being called by a female voice. The voice would also say things such as "how about you go outside?" or "throw a water balloon". During various sessions, she endorsed hearing a voice that was perceived to be outside of her head and which did not belong to an imaginary friend, however, it was sometimes unclear whether her endorsement was due to wanting to please or to a true psychotic experience.

Investigations revealed an elevated TSH but normal free T4 and T3 (August 2007). In December (2007), fluoxetine 2.5 mg/day was started and titrated to 5mg/day. Follow-up of 24 months showed that her anxiety improved, including fewer complaints of stomach aches, less worrying at night, and being more positive about going to school and making new friends. Reports of perceptual disturbances became much less frequent: she reported seeing the dresser "floating" at night and being scared (May 2008), and that sometimes while alone she would hear a female voice (August 2008).

Case 3

Case 3 is a 14 year-old intellectually disabled girl with Separation Anxiety Disorder, Generalized Anxiety Disorder, and Simple Phobias, who had a history of perceptual disturbances. She described seeing a poodle that no one else could see during the day and at night from ages 3 to 6, which stopped after her parents told her "they killed the poodle." From age 12, she would recurrently see "black shadows looking like people" and hear noises including footsteps and "scruffing" noises. She would ask her mother to say "you are dead, go away" in a ritualized way in order to feel better. The perceptual abnormalities seemed to be in the context of heightened anxiety, but loss of reality testing was noted in relation to these symptoms.

Investigations revealed no abnormal results. Fluoxetine 2.5mg/day was started and titrated to 3mg/day (March 2007). No visual or auditory hallucinations were reported after May 2007. Follow-up of 24 months revealed significant improvement of her anxiety, with fewer complaints of stomach aches, improvement in sleep, less worrying at night and no school refusal. By 2008, she was noted to be much more independent socially and academically.

Discussion

This report describes three adolescents with 22qDS who present with primary anxiety disorders and perceptual disturbances that ameliorated after treatment with SSRI. The psychiatric phenotype observed in our 22qDS cases is concordant with the previously reported common association between psychotic symptoms and two or more comorbid anxiety disorders in adolescents with 22qDS (Jolin et al., 2009a; Jolin, Weller, & Weller, 2009b). Early antipsychotic drug intervention has been proposed for the management of psychotic symptoms in children and adolescents with 22qDS (Vorstman et al., 2006). This recommendation is well justified for a number of 22qDS patients who experience psychotic symptoms early in life and convert to a full-blown psychotic disorder (25-30%). While antipsychotics are the first-line treatment for psychotic symptoms as part of a psychotic disorder, our cases and others in the literature (Baker & Skuse, 2005; Jolin et al., 2009a; Jolin et al., 2009b; Stoddard et al., 2010) have shown that psychotic symptoms in 22qDS can also be of short duration, attenuated, not impairing, or comorbid with primary anxiety disorders. Psychotic symptoms and anxiety disorders have been reported in the 22qDS population (Jolin et al., 2009a) and also in patients without a 22q11.2 deletion (Cassano, Pini, Saettoni, & Dell'Osso, 1999; Galynker, Ieronimo, Perez-Acquino, Lee, & Winston, 1996; Hlastala & McClellan, 2005; Sievers, Sato, Moller, & Bottlender, 2005; Ulloa et al., 2000; Veras, do-Nascimento, Rodrigues, Guimaraes, & Nardi, 2011). The first case also serves to highlight that the presence of a prolonged QTc interval may caution against the use of antipsychotics, highlighting the need to review the ECG at baseline. Given the multisystemic nature of the syndrome, psychiatric management needs to be done in collaboration with an interdisciplinary team (Bassett et al., 2011).

Of note, although we described the anxiety disorders as "primary," these disorders form part of the 22qDS phenotype and as such, may be more appropriately viewed as "secondary to 22qDS." As well, the medical conditions associated with 22qDS such as calcium abnormalities and thyroid abnormalities may also contribute to the biological risk for developing anxiety disorders and psychotic symptoms if patients are non-adherent with the treatment for such (Heinrich & Grahm, 2003; Levine & Gaoni, 1990). Treating the anxiety disorders may have led to improved adherence with calcium supplementation for instance and in turn, may have ameliorated the perceptual disturbances.

Cognitive difficulties are very common in patients with 22qDS, and can affect their ability to express their ideas and experiences, making psychiatric assessment challenging. Similar to our experience, others have observed the difficulty in obtaining an accurate time frame and in differentiating hallucinations from fears, both commonly observed in 22qDS subjects (Arnold et al., 2001; Chow, Bassett, & Weksberg, 1994; Feinstein et al., 2002; Reif, Fallgatter, Ehlis, & Lesch, 2004).

A possibility remains that the cases presented here may subsequently develop a psychotic disorder; however, our follow-up period covered the average time from onset of psychotic symptoms to expected conversion to a psychotic disorder making this conversion less likely (Hafner & Maurer, 2006). Nonetheless, due to the high prevalence of psychotic disorders in 22qDS (Bassett et al., 2003; Murphy et al., 1999), continuous close follow-up is still warranted in our patients. Close psychiatric follow-up in this population will be necessary until biological markers and/or specific clinical features can be used to predict whether patients will convert to a psychotic disorder. Efforts in this regard are seen from longitudinal studies in 22qDS. One study reported an association between baseline sub-threshold psychotic symptoms, anxiety, depressive symptoms, lower verbal IQ and COMT Val allele with severity of psychotic disorders at follow-up evaluation in adolescents (Gothelf et al., 2007). Another study reported that weaker executive functioning and verbal abilities, high levels of odd/eccentric and anxious behaviours in childhood predicted prodromal psychotic symptoms in adolescents, but found no difference between the Val or Met COMT allele (Antshel et al., 2010). A subsequent study on a sample drawn from the previously published study by Antshel and colleagues suggested that decreases in temporal lobe grey matter volumes increase the risk for prodromal psychotic symptoms in patients with 22qDS (Kates et al., 2011). However, at the current time, no genetic or endophenotypic markers can accurately predict conversion to a psychotic disorder and more research is needed.

The well-known complications of exposure to antipsychotics and stigma need to be considered when encountering adolescents who are at risk, but who do not meet criteria for a psychotic disorder (Corcoran, Malaspina, & Hercher, 2005). Such precautions are of particular relevance to patients with 22qDS as the literature shows that not every adolescent with 22qDS who presents with psychotic symptoms will develop a chronic psychotic disorder. Hence, the use of medications other than antipsychotics has been proposed for treatment of psychotic symptoms in patients with 22qDS (Carandang & Scholten, 2007; Graf et al., 2001). In

the cases reported here, anxiety symptoms had the greatest perceived negative impact on their lives, while perceptual disturbances were brief and less distressing. Consequently, management integrated SSRI treatment of the anxiety disorders with close monitoring of perceptual disturbances.

The cases are highlighted to bring attention to adolescents with 22qDS who present with primary anxiety disorders and perceptual disturbances. It is important that clinicians be cognizant of the full range of psychiatric presentations that may occur in adolescents with 22qDS. We propose that primary anxiety disorders - which are very common and which can present with psychotic symptoms in a young 22qDS population - may be best managed initially with anti-anxiety medications (SSRIs) without antipsychotics. Larger longitudinal studies investigating similar 22qDS cases will add much to our understanding of the best psychiatric management of adolescents with 22qDS.

Acknowledgements / Conflicts of Interest

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