



## Brief Report: Major Depressive Disorder with Psychotic Features in Williams Syndrome: A Case Series

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### Abstract

Descriptions of individuals with Williams syndrome (WS) and co-morbid major depressive disorder (MDD) with psychotic features have not appeared in the literature. In addition to reviewing previous reports of psychotic symptoms in persons with WS, this paper introduces clinical histories and therapeutic management strategies for three previously unreported adults with WS diagnosed with co-morbid MDD with psychotic features. Co-morbid medical disorders common in WS are highlighted with regard to safe and appropriate pharmacological treatment. The importance of assessment for co-morbid MDD with psychotic features in individuals with WS is emphasized.

**Keywords** Williams syndrome · Major depressive disorder · Psychosis · Co-morbidity · Psychopharmacology

Williams syndrome (WS) is a neurodevelopmental disorder caused by a hemizygous microdeletion (only one copy present) in chromosome 7 at 7q11.23. The estimated prevalence of WS is between 1/7500 and 1/10,000 (Strømme et al. 2002). Williams syndrome is characterized by distinctive facial features. In young children, these include flat nasal bridge, short upturned nose, periorbital puffiness, long philtrum, and delicate chin. Older patients have slightly coarse features with full lips, wide smile, and full nasal tip. Other findings can include vascular stenoses, such as supra-aortic stenosis, hypercalcemia and other endocrine abnormalities, sensorineural hearing loss, structural renal anomalies, and growth deficiency. The neuropsychological profile can include mild to moderate intellectual disability with relative strengths in language skills as compared to other cognitive domains. Patients with WS often

demonstrate an endearing, friendly personality that can confer vulnerability to inappropriate advances (Pober 2010).

Previous studies have attempted to characterize the associated psychopathology among patients with WS. Reports have shown high rates of anxiety disorders (48–65%) including generalized anxiety disorder (GAD) (12–25%), specific phobias (30–54%), and agoraphobia (24%) as well as attention-deficit/hyperactivity disorder (ADHD) (20–64.7%). Much less commonly reported are depressive disorders (3–25%), obsessive–compulsive disorder (2–5%), and psychotic symptoms (5–6%) (Dodd and Porter 2009; Dykens 2003; Leyfer et al. 2006).

Only a limited number of reports of patients with WS and psychotic symptoms appear in the literature. Bradley and Udwin (1989) reported the case of a 43-year-old man with WS who, after the death of his mother, presented with profound depression and regressed behavior associated with confabulation, flight of ideas, and ideas of reference. The patient was diagnosed with bipolar affective disorder. His depressive symptoms did not improve with adequate trials of three antidepressant medications, one “unspecified,” the second a tricyclic antidepressant, and the third a monoamine oxidase inhibitor. An “unspecified” antipsychotic medication resulted in “some improvement in his behaviors.” The authors concluded that it is possible that the psychotic aspects were more related to the patient’s confabulation, against a background of increased anxiety, rather

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than to a psychotic illness (Bradley and Udwin 1989). Savoja and Vicari (2010) described a 22-year-old-man with WS and severe intellectual disability (IQ = 36) who developed “psychotic-like symptoms and aggressiveness,” without co-morbid mood symptoms, that responded to risperidone 0.5 mg/day. The symptoms of psychosis recurred when risperidone was discontinued after 3 years due to an adverse event (Savoja and Vicari 2010). Salgado and Martins-Correia (2014) described a 23-year-old woman with WS who presented with persecutory delusions, auditory and visual hallucinations, and self-dialoguing. The patient was hospitalized on a psychiatric unit and treated with risperidone 1.5 mg daily with complete resolution of psychotic symptoms. No concurrent mood symptoms were identified as part of her presentation (Salgado and Martins-Correia 2014). Finally, Pineiro and colleagues (2014) described a 19-year-old woman with WS who developed psychotic symptoms in the context of propofol-induced mania following a gastrointestinal procedure (Pineiro et al. 2014).

The prevalence of psychotic disorders in WS is unclear. Results from two studies of psychopathology in WS have described the occurrence of psychotic disorders in 2/92 and 3/50 subjects, respectively (Dodd and Porter 2009; Stinton et al. 2010). The patients with psychosis in the studies had diagnoses of schizophrenia ( $n = 3$ ), schizoaffective disorder ( $n = 1$ ) or undifferentiated psychosis ( $n = 1$ ). Another study compared the neuropsychiatric phenotype in two micro-deletion syndromes, velocardiofacial syndrome (22q11.2 deletion) and WS (Zarchi et al. 2014), respectively. In this investigation of adolescents and young adults, 7/39 subjects with velocardiofacial syndrome (29.2%) versus 1/24 subjects with WS (5.6%) had a psychotic disorder. Such relatively low rates of occurrence may indicate that psychosis is a rare event in WS. Some authors have suggested caution in diagnosing psychosis in WS stating that such symptoms might represent “transient exaggerated responses to life stresses, superimposed on baseline intellectual disability and anxiety disorders” (Cherniske et al. 2004). It is also possible that rates of psychosis may be underestimated by clinicians who do not assess for these symptoms during the psychiatric evaluation of a patient with WS due to the perceived rarity and unlikelihood of such symptoms.

We present the clinical histories and therapeutic management strategies of three adults with WS and co-morbid major depressive disorder with psychotic features. These cases are being highlighted so that clinicians become more aware that psychotic depression does occur in individuals with WS. This co-morbidity may not be apparent to many clinicians, as the stereotypic clinical phenotype of individuals with WS is represented by a highly social, affable personality. Furthermore, clinicians with limited experience treating individuals with intellectual disability may be less likely to inquire about psychotic symptoms. Finally, this clinical

presentation has not been described previously in the published literature.

## Case 1

Mr. A. was a 25-year-old male with a diagnosis of WS based on fluorescence in situ hybridization (FISH) genetic testing. Mr. A.’s developmental history was notable for delayed attainment of motor milestones and slow language progression for which he received twice weekly speech therapy at school until the age of 8 years. At that point, he was speaking in complete sentences and could engage in near-typical reciprocal conversation. His medical history was significant for hypertension and mild mitral valve prolapse and insufficiency. Previous surgeries included an adenoidectomy and ear tube placement (twice) for recurrent otitis media. Mr. A. was determined to have mild intellectual disability (full-scale IQ = 68). He graduated from a public high school with the assistance of a 1:1 aide, lived with his parents and younger brother, and worked 5 days a week delivering mail in an office. His cognitive skills were such that he completed activities of daily living (ADLs) independently and could complete tasks at work adequately without supervision.

At the time of initial evaluation, Mr. A. presented with a 3-week history of severe depressive symptoms. These included difficulties falling asleep, mid-nocturnal awakening, frightening and “almost realistic” nightmares, and early morning awakening. His energy level, motivation, and appetite were reduced and he had lost 10 pounds. He described his mood as “a nightmare.” He felt hopeless and helpless with low self-esteem. He endorsed hearing a male voice inside his head that he described as “evil” and “a monster.” The voice told him negative things about his parents and encouraged him to kill himself. He reported thoughts of hanging or stabbing himself or jumping off a bridge but denied any intent or plan to do this. In addition, Mr. A. had visual hallucinations consisting of many “beings” dressed in black cloaks, with red eyes, lined up as far as he could see (Fig. 1). Mental status examination was also notable for depressed affect and anxiety-related, voluntary body movements. There was no history of aggression, suicide attempts, self-harm or psychiatric hospitalizations. There was a family history of mild depression in Mr. A.’s mother as well as depression in a paternal aunt and uncle.

Mr. A. met *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)* criteria for diagnoses of major depressive disorder, single episode, severe, with psychotic features, generalized anxiety disorder, and mild intellectual disability (DSM-5; American Psychiatric Association 2013). Prior to the initial evaluation, he had been prescribed amlodipine 10 mg daily for hypertension and lorazepam 1–2 mg every 2 h, as needed, for anxiety not to exceed 8 mg



**Fig. 1** Mr. A.'s drawing of "a being" in a black cloak with red eyes depicting his visual hallucination. (Color figure online)

a day. Fluoxetine 20 mg per day had been started three weeks earlier but had recently been decreased to 10 mg daily due to irritability. A magnetic resonance imaging brain scan and sleep-deprived electroencephalogram (EEG) were normal. After our evaluation, fluoxetine was stopped and bupropion extended release (XL) was started at an initial dose of 150 mg per day and increased to 450 mg daily over a period of six weeks due to persistent depressive symptoms. To target the psychotic symptoms, risperidone was begun at a dosage of 0.25 mg twice daily and increased to 1 mg twice a day over three weeks. The psychotic symptoms began to improve shortly thereafter and resolved entirely after 5 months. The depressive symptoms, however, were only partially improved at that time. Mr. A. developed akathisia on risperidone so propranolol was initiated at 20 mg three times daily and was helpful. Risperidone was subsequently tapered off and discontinued due to daytime sedation in favor of aripiprazole which was increased to 7.5 mg at night over a period of 4 weeks. The addition of aripiprazole resulted in improved depressive symptoms and the auditory and visual hallucinations remained in remission. Buspirone was later added up to 15 mg three times daily to target anxiety with good effect. Two years after starting treatment, Mr. A.'s depressive and psychotic symptoms were in remission, although anxiety remained somewhat interfering. He began seeing a therapist to help with persistent anxiety. Mr. A. gained 12 lbs over the

course of treatment (body mass index [BMI] increased from 28.3 to 30.14) which he attempted to manage with routine exercise on the treadmill. He did not develop any abnormal, involuntary motor movements. Results of the electrocardiogram (ECG) obtained prior to initiation of pharmacological treatment in our clinic and then annually were normal, with no prolongation of the QTc interval. Laboratory testing for fasting blood glucose and lipids was normal at baseline and every 6 months during treatment. Mr. A. was unable to resume his previous job due to the impact of the psychiatric symptoms on his functioning.

## Case 2

Mr. B. was a 24-year-old male with a diagnosis of WS confirmed via FISH genetic testing at 3.5 years of age. He was born full-term and was evaluated in the Neonatal Intensive Care Unit (NICU) for a few hours after birth due to "blue spells." He was also jaundiced at birth. The developmental history was remarkable for delayed motor milestones; he walked at 3 years of age. Mr. B. developed first words at 1 year of age but was slow to combine words, not developing this skill until 2–3 years of age. His medical history was significant for mild pulmonary and aortic stenosis, left renal artery stenosis, and frequent otitis media for which myringotomy tubes were placed twice. Surgical history also included adenoidectomy/tonsillectomy and bilateral inguinal hernia repair. Mr. B. had a normal EEG. His full-scale IQ of 56 represented a mild degree of intellectual disability. Mr. B. graduated from a public high school in a special needs program where he received speech, occupational and physical therapy. He then attended a social skills program which supported his employment at a grocery store and other activities. He performed ADLs independently and conversed with others in a near-typical reciprocal manner.

At the age of 18 years, Mr. B. had the onset of symptoms consistent with major depressive disorder with psychotic features. He became uncharacteristically withdrawn and isolative and lost interest in preferred activities including watching television and playing video games. He started talking to himself which he had not done before and would whisper in the presence of others. He became angry and paranoid if approached by family and secluded himself in his room with the door closed where he paced and chanted loudly. His mother reported that he acknowledged "talking" to school mates that had bullied him in the past even though they weren't physically present in his room. He attended individual supportive therapy for 2 years with no improvement in symptoms. Six months prior to his initial evaluation, risperidone was started and increased to 1.5 mg at bedtime. His mother reported 90% improvement in social withdrawal, paranoia related to interpersonal interactions, and talking to

himself and others not in his present company; however, his motivation and energy remained low. Mental status examination on initial evaluation was notable for depressed and anxious affect and limited insight into his symptoms. No clear signs of psychosis were identified at that time. Mr. B.'s sleep and appetite were both adequate. He had no history of suicide attempts, aggression, self-harm or psychiatric hospitalizations. The family history included various maternal family members with schizophrenia, bipolar disorder, depression, ADHD, and autoimmune-inflammatory disease.

Initial DSM-5 diagnoses of major depressive disorder, single episode, severe, with psychotic features, generalized anxiety disorder, and mild intellectual disability were made. Bupropion was initiated at 37.5 mg every morning to treat depressive symptoms and increased and switched to bupropion XL 300 mg per morning over a period of six weeks. He continued risperidone 1.5 mg per day. Mr. B.'s depression improved with bupropion XL administration with increased motivation and future orientation and resulting euthymic affect on mental status examination. After a period of 1 year, monthly reductions of risperidone 0.25 mg were begun and were initially successful. Attempts to lower the dosage of risperidone below 0.25 mg per day, however, resulted in the patient becoming more withdrawn, suspicious, and less interactive. The psychotic depression remained in remission on bupropion XL 300 mg per day and risperidone 0.25 mg per day over the next 2 years. Mr. B. developed no adverse effects during treatment with bupropion XL and risperidone. He did not experience an increased appetite or weight gain nor did he develop any abnormal, involuntary motor movements. The ECG obtained at baseline and then annually was normal with no evidence of prolongation of the QTc interval. Laboratory blood work obtained at baseline and then every 6 months revealed no abnormalities in fasting glucose or lipids.

### Case 3

Ms. C. was a 26-year-old female with WS confirmed via FISH genetic testing. She was born full-term and was delayed in both developmental motor and language milestones but eventually progressed to full verbal fluency. Her medical history was notable for long-standing nausea and vomiting attributed to various etiologies, including extrinsic compression of the esophagus from anatomical abnormalities arising from a right sided aortic arch, atypical migraines, and (most recently) central nausea. These symptoms were further exacerbated by gastroesophageal reflux disease as well as symptoms of severe depression and anxiety. Four years before presenting for initial evaluation, Ms. C. had a brainstem stroke related to vertebral artery narrowing with persistent balance difficulties. Other medical problems

included hypertension, constipation, chronic urinary tract infections, and obesity. Neuropsychological testing revealed a full-scale IQ of 67, placing her in the range of mild intellectual disability. She completed high school at 21 years of age in a vocational program through the public-school system. Ms. C. volunteered working with animals. At the time of initial consultation, she had moved out of her parents' home, had been living for approximately 1 year in an "adult foster care" setting, could perform her ADLs adequately, and attended a day program 5 days a week.

The initial evaluation was notable for a history of severe depressed mood since her late teens and intermittent suicidal ideation. Ms. C.'s depression began when her younger sister moved away to attend college, her grandmother and grandfather died, and her nausea and vomiting became progressively debilitating. She described daily worrying about her medical conditions and her father's health, and feelings of depression and loneliness. She had decreased interest in preferred activities, low energy, and difficulty falling asleep. Mental status examination was notable for blunted affect and psychomotor retardation. No symptoms of psychosis were elicited. Ms. C. reported four previous psychiatric hospitalizations in the context of depression with suicidal ideation and one previous suicide attempt. During the most recent hospitalization she endorsed auditory hallucinations and was started on aripiprazole 5 mg daily with uncertain effect. Other psychiatric medications at the time of our initial evaluation included pregabalin 150 mg in the morning and at bedtime, along with 100 mg mid-afternoon for anxiety and venlafaxine extended release (XR) 150 mg per day. Ms. C. was meeting weekly with a psychotherapist which she found helpful. She had no known family history of psychiatric illness.

Initial DSM-5 diagnoses of depressive disorder secondary to a medical condition, generalized anxiety disorder, and mild intellectual disability were made. Pregabalin was reduced and then discontinued and Ms. C. was started on buspirone 10 mg two times a day for anxiety, in addition to ongoing aripiprazole 5 mg per day and venlafaxine XR 150 mg per day. With a change of diet and titration of buspirone to 10 mg three times a day, Ms. C. reported an improvement in her nausea, decreased depression, some reduction in anxiety and improved energy over 2 months. Despite this improvement she continued to experience cognitive dulling thought to represent sedation from aripiprazole. Aripiprazole was reduced to 2.5 mg daily and within 1 week Ms. C. reported worsening depressed mood. She was noted to be tearful and withdrawn. She endorsed hearing a voice telling her to harm herself which she reported to her caregivers. Aripiprazole was increased to 5 mg daily with rapid improvement in depressed mood and resolution of auditory hallucinations. Buspirone was increased to 30 mg twice a day over a period of 6 weeks with a significant

reduction in residual anxiety. On follow up, Ms. C. reported “good” mood with intact sleep, energy, and level of interest. She had started participating in swimming and group activities without being hampered by nausea and her self-esteem was improved. She still reported daytime sedation, possibly due to the aripiprazole, and occasionally poor sleep at night. Ms. C. had an increase in appetite and gained approximately 15 lbs, possibly in association with aripiprazole, during treatment in our clinic. She did not develop any abnormal, involuntary motor movements. Baseline ECG was normal, without evidence of QTc prolongation, as were subsequent, annual ECGs. Fasting blood work at baseline and then every 6 months thereafter found no abnormality in glucose or lipids. Ms. C.’s mood disorder diagnosis was revised to major depressive disorder, recurrent, severe, with psychotic features, in full remission. She has continued to do well for the past 2 years on the same medication regimen.

## Discussion

This report describes the clinical presentation and treatment management of three adults with WS diagnosed with major depressive disorder with psychotic features. To our knowledge this is the first report describing patients with WS who had psychotic symptoms in the context of an episode of major depressive disorder. In all three cases, resolution of the depressive and psychotic symptoms occurred following institution of an atypical antipsychotic medication in combination with an antidepressant (with or without an anxiolytic).

The potential benefits of treatment with an antipsychotic and antidepressant medication must be carefully weighed against the risks among all patients and especially those with WS. Antipsychotic medications are associated with metabolic side effects, including weight gain, dyslipidemia, increased susceptibility to diabetes, and cardiac effects, such as hypertension (Cohn and Sernyak 2006). Weight gain is common in adults with WS, with two-thirds having a BMI greater than 25 (Pober 2010). A meta-analysis of 307 articles was conducted of clinical trials of antipsychotics that reported weight change, with most trials being antipsychotic switch studies. Almost all antipsychotics showed a degree of weight gain after prolonged use, except for amisulpride, aripiprazole, and ziprasidone. In antipsychotic-naïve patients, weight gain was much more pronounced for all antipsychotics (Bak et al. 2014). Rates of impaired glucose tolerance are particularly high in adults with WS, with those that are obese at a somewhat greater risk (Pober et al. 2010). Antipsychotic treatment is associated with increased susceptibility to type 2 diabetes (Cohn and Sernyak 2006). Regarding cardiac complications, hypertension, occasionally beginning in childhood, ultimately develops in approximately 50% of

patients with WS (Pober 2010). Furthermore, the risk of sudden death in WS is significantly higher than in the age-matched general population. It is believed that sudden death in WS may be due to significant supra-aortic stenosis and/or peripheral pulmonary artery stenosis, coronary artery stenosis, and malignant arrhythmias, to which WS patients with left ventricular hypertrophy may be prone (Wessel et al. 2004). Moreover, cardiac repolarization is prolonged in WS, as determined by corrected QT (QTc) prolongation on ECG. In a retrospective review, 13.6% of patients with WS vs. 2.0% of controls had QTc prolongation, a highly significant difference (Collins et al. 2010). A meta-analysis was performed on various randomized controlled trials to determine the effects of atypical antipsychotics on the QTc interval. Aripiprazole was found to be the only one out of seven that demonstrated both a statistically significantly lesser mean change in QTc and a statistically significant lower risk of causing QTc prolongation (Chung and Chua 2011). Regarding the effects of antidepressants, a cross-sectional study using electrocardiographic, prescribing, and clinical data from electronic health records was completed to explore the relation between antidepressant dose and QTc. A dose–response association with QTc prolongation was identified for citalopram, escitalopram, and amitriptyline. An association with QTc shortening was identified for bupropion. Within-subject paired observations supported the QTc prolonging effect of citalopram (Castro et al. 2013).

Considering the risks associated with antipsychotic and antidepressant medication in patients with WS, it is important to monitor patients being treated with these drugs for safety in a systematic manner. For patients treated with an antipsychotic medication, BMI should be determined at baseline, 4, 8, 12 weeks, and then every 3 months ongoing. Fasting blood lipids should be measured at baseline, 12 weeks and then every 5 years. Fasting blood glucose and blood pressure should be measured at baseline, 12 weeks, and then annually (Cohn and Sernyak 2006). For patients with WS beginning treatment with an antipsychotic and/or an antidepressant medication, an ECG should be obtained at baseline to determine the QTc interval, and if it is within the normal range, once the target dosage of the medication has been reached. If the QTc interval is prolonged at baseline, strong consideration should be given to involving a cardiologist in the pharmacotherapy decisions, including the timing of obtaining subsequent ECGs (Collins et al. 2010).

There are several limitations to this report. All treatments were open-label and there was no control group. Standardized assessment of treatment outcome did not occur; rather, change in clinical status was based upon clinical observation. In some cases, patients were receiving psychotropic medications besides an antidepressant and antipsychotic and may have also been in psychotherapy. We cannot rule out the possibility that clinical improvement was partially related to

these other treatments. Additionally, all three cases received a co-morbid anxiety disorder diagnosis. Symptoms attributed to psychosis, such as auditory hallucinations, could conceivably represent anxiety symptoms or other emotional distress in individuals with limited ability to fully describe their internal state. It also must be kept in mind that the patients were seen in a tertiary referral center. Many of the patients seen in this setting present with severe symptoms; accordingly, it is not possible to draw inferences about the prevalence of this psychiatric co-morbidity in WS.

This case series describes symptoms of psychosis during major depressive disorder episodes in three adults with WS and their course of treatment. Assessment for psychosis among depressed patients with WS is warranted and recommended. It is also important that clinicians less familiar with individuals with neurodevelopmental disorders, including individuals with WS, seek expert consultation if they are uncertain about the presence of psychotic symptoms in such patients.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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