Management of Psychosis in an Adult Cohort of Patients with Prader-Willi Syndrome

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Home for the Summer Program June 7th – July 13th

Stonewall, MB

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Abstract

This case revolves around a 34-year-old patient with a previously diagnosis of Prader-Willi syndrome (PWS). Through the years, this patient has developed a host of comorbidities to PWS, of which one of the most difficult to manage has been his psychosis. Therefore, the clinical question to be addressed in this case report is how to best manage psychosis in patients with PWS.

PubMed was used to conduct the literature search. Two searches were used for this literature review; one search included the key works "Prader-Willi" AND "Psychosis" AND "Management" and the second "Prader-Willi" AND "Psychosis" AND "Pharmacotherapy". These two searches in the PubMed database resulted in 24 different articles. 12 of these were relevant and have informed this discussion.

PWS is a difficult condition to manage as it can come with so many different complications and comorbidities. Psychosis is one of these comorbidities and its management is poorly defined. Although it is suggested that a combination of environmental, behavioural and pharmacological means should be used in the management, it is not clear exactly how or what should be used. Nevertheless, some recommendations were offered, including: to detect behavioural instability as early as possible, educate the caregivers, and to optimize the medications and stabilize their mood. At this point, however, more research is required into specific drug regimens, psychotherapies and other types of management in order to appropriately deal with the problem of psychosis.

Case History

The patient has been known to the practice since 2010 according to the records at Stonewall Medical Group. At that time he was a 26-year-old man and he presented with a known diagnosis of Prader-Willi syndrome (PWS). He is now 34 years old and has a complicated set of comorbid conditions to his underlying PWS. These comorbidities include: type 2 diabetes, morbid obesity, restrictive lung disease, asthma, OSA, hypertension, spondyloarthrosis, hypothyroidism and osteoarthritis. He is currently on oxygen and is under the care of his mother and a support worker.

He has had suspected PWS since he was a child, but it was confirmed in 1994 with FISH studies. However, at this time it was still undetermined if his PWS was due to deletion or maternal uniparental disomy (mUPD). Later tests (done in 2015) had some mixed results. Initially it looked as though his PWS was due to mUPD in the maternal chromosome, but in 2016 the results were re-analyzed and it showed that the PWS was in fact due to an imprinting defect. This version of PWS is non-inheritable as it is sporadic in nature.

During his most recent visit to the office, this June, the patient was, on appearance, morbidly obese, required oxygen constantly, and had blunted affect. The patient was complaining that he had "stepped on a razor blade" and that it was lodged in his heal. The patient's care-worker and mother noted he had been having delusions recently namely, that believes he has a sister (which he does not).

His history of mental health issues and his psychosis dates back as far as 2011. At this time, his symptoms were limited to it generalized psychosis symptoms (restlessness and paranoia). Since these initial symptoms he has tried to commit suicide a number of times, the first of which was in January 2015 when he tried to overdose on ASA and Tylenol. At this time he was prescribed fluoxetine to manage his impulsivity and was also started on olanzapine, quetiapine and risperidone. Between January 2015 and the end of August of the same year, this patient tried to commit suicide a total of five times. In this time he also had

capgras syndrome – which predated the SA - and he had engaged in self-harm behaviours such as stabbing himself in the navel with a knitting needle or scratching his wrists. He was admitted to the hospital after his first suicide attempt, and again at the end of August 2015 when he was having SI. Not much is known about these hospital stays. In Sept 2015 he saw a psychiatrist who recommended that he be started on 2mg TID of risperidone to control his psychosis. He had been taking a lower dose of 0.5mg OD. for 10 years before this. At the time of this last hospital admission, it was noted by the psychiatrist that he had no signs of mania, hypomania, anxiety disorder or mood syndromes. The psychiatrist who saw him noted that he was unfamiliar with PWS. It came to light that no psychiatrists in MB, including the one he saw, is well versed on PWS and thus it was very difficult to get appropriate care the mental health sequela of his syndrome.

In June of 2018, there was an increase in the patient's psychotic behaviour. He was still on the risperidone but now at 1.5mg daily and if the symptoms spiked his mother or care-worker were instructed to give him olanzapine rapid 5mg OD PRN. When he was seen in the clinic most recently, his complaints were about a razor blade, which he believed to be stuck in the heel of his right foot. On exam there was no sign of razor blade entry or any trauma to the heel. It was also decided that, in the event the delusions persisted, he should be given an x-ray to rule it out the possibility of their truly being a razor blade in his heel.

Literature search

Table 1: Search terms and results generated by searching PubMed*

Search Number	Search Term	Results
1	"Prader Willi"	3658
2	"Management"	2458601
3	"Psychosis"	76329
4	"Pharmacotherapy"	
5	"Prader Willi" AND "Psychosis"	69
6	"Prader willi" AND "Management"	258
7	"Prader willi" AND "Psychosis" AND "Management"	10
8	"Prader Willi" AND "Psychosis" AND "Pharmacotherapy"	17

* Filters used were only limiting article types to: case reports; any stage clinical trial, journal article, meta-analysis, RCT, review, practice guidelines

A literature review of the results from searches 7 and 8 in table 1 above was conducted. Out of the two searches there were a combined total of 24 papers. Of these 24, there were 12 relevant articles, 8 that were not relevant, 3 that were not available for download and 1 article not in English. This literature search indicated to me that there is a need for more research on all aspects of psychosis in PWS including its environmental, behavioural and pharmacological management

Discussion

PWS is a neurodevelopmental sporadic genetic disorder with an incidence of 1/15,000 – 1/30,000.[1] PWS develops by several mechanisms, the commonest of

Table 2: manifestations of PWS[2,3]

Infancy	Hypotonia
	Lethargy
	Poor Feeding
	Failure to Thrive
	Weak Cry
	Hip Dysplasia
	Hypogonadism
Childhood-Adolescence	Intellectual Disability
	Progressive Obesity
	Short Stature
	~~Acromicria~~
	Hyperphagia
	Characteristic Facial Appearance
	Temper Tantrums
	Compulsive Traits
	High Pain Threshold
	High Vomiting Threshold
	Skin Picking
	Menarche/Testicular Decent Delay
	Scoliosis
	Epilepsy
	Altered Temperature Regulation
Comorbidities	Osteopenia/Osteoporosis
	Gastric Distention and Rupture
	Cholelithiasis
	Adrenal Insufficiency
	Hypothyroidism
	Hypertension
	Non-Alcoholic Fatty Liver Disease
	GERD
	Dyslipidemia
	Seizures
	Atherosclerosis
	Diabetes
	Hypoventilation Syndrome
	Sleep Apnea
	Cor Pulmonale
	Sterility
Psychiatric Comorbidities	Sleep Disorders
	Bipolar
	Disorders of Elimination
	ADD
	ADHD
	Disruptive Behaviour Disorders
	Anxiety Disorders
	OCD
	Dysthymia/Depression
	Psychosis
	Developmental Learning Disorders
	Autism Spectrum Disorder
	Impulse Control Disorder
	Factitious Disorder

these being paternal deletion of chromosome 15q11q13. The other two major mechanisms are maternal uniparental disomy and imprinting defects. The different genetic subtypes of PWS each come with a few features that are more characteristic to that type, with psychosis being particularly common among the mUPD cohort[5]. A more extensive list of the features of PWS can be found in table 2, but the more characteristic features include hypotonia, failure to thrive, hypogonadism and poor suck in the neonatal period as well as hyperphagia, progressive obesity, short stature, developmental delay and behavioural issues in the childhood-adolescent period.[2,3] If there is sufficient concern that a patient may have PWS (e.g. poor suck and hypotonia when they are neonates) then a DNA methylation analysis should be conducted. There are other ways to tests for PWS, but DNA methylation is the best because it can differentiate PWS from Angleman's syndrome as well as distinguish between paternal deletion, mUPD or imprinting errors.[1,5,6] The management differs from patient to patient and depends upon the specific symptomology, sequela and comorbidities present in each case. Some commonalities between all management are control of daily calories, hormone replacement, behavioural management and special education/employment.[1]

Psychotic illness (with positive psychosis symptoms) in patients who have PWS is fairly common and shows up at a higher prevalence in the PWS cohort than it does in a cohort of people with similarly low IQ conditions.[4] The cohort with the mUPD type of PWS have been found in many studies to be at higher risk than those with the paternal deletion type with the numbers suggesting 60-100% for mUPD and only 20% for the deletion type.[5, 6,] It was suggested that the imprinting type, which is very similar to mUPD, may be included in with that category when analyzing psychosis in PWS.[5] The development of psychosis has been suggested to be multifactorial, involving genetics, biologics and environmental aspects. Recently it has been proposed that the mUPD leads to 5-HT_{2C}R dysfunction and this may be the reason for the high rates of psychosis within this type.[6] The average age of those getting

psychosis in the PWS cohort is typically around 21.9 years and this does not differ between parental deletion and mUPD types.[5]

Management for psychosis has to be approached in many different aspects (environmental, behavioural and pharmacological) and seems as though it needs to be individualized between members of this cohort. Various sources suggest these following interventions and strategies: detect behavioural issues early on; education of caregivers; minimize mood related symptoms and stabilize on medication. [1,6,7,8] Early detection and good education of caregivers to detect psychosis symptoms can lead to earlier treatment and therefore stabilization of the psychosis symptoms. Mood symptoms often precipitate episodes of psychosis so it was proposed that making sure mood was stable would help prevent psychosis.[7] For the stabilization of psychosis, it has been suggested that a combination of antidepressants and antipsychotics be used.[7,9] Once stabilization on medication has been reached it has been shown that recurrence rates are rare.[7] Some medications that have been found to help achieve stabilization are SSRIs, antipsychotics and mood stabilizers.

SSRIs have be touted as beneficial for minimizing compulsivity, temper issues, OCD, mood swings and may decrease the appetite.[4, 10] Although there is no direct effect of SSRIs on psychosis symptoms, reducing mood swing may help to prevent episodes of psychosis and it was found in one article that patients put on SSRIs prior to any psychotic symptoms never had any occurrence of those symptoms.[6] Although SSRIs are suggested as being an effective drug in PWS, they should be used with caution and appropriate follow up. One of the results of the literature search showed a case where fluoxetine induced psychosis in a patient with PWS. SSRIs may affect people with PWS differently or more severely.[11] It should, however, be noted that fluoxetine does have a rare side effect of psychosis, so this case may just be an example of this side effect as opposed to than an example of the way fluoxetine may affect PWS patients differently.[11]

Antipsychotics are also a common drug used in the management of psychosis in PWS, with almost all patients receiving some kind in their care. The most commonly used antipsychotics are risperidone, haloperidol and chlorpromazine – with risperidone being found as the drug of choice among most practitioners.[9] Risperidone may be used more because in one study it was found to have positive effects on weight and appetite in addition to helping with the psychosis symptoms.[9] One of the difficulties with treating this condition is that some drugs in this class, the second generation antipsychotics in particular, are known to have metabolic side effects, such as weight gain, and thus are poor choices for PWS.[10]

Mood stabilizing agents have mixed reviews in the management of PWS psychosis. Soni et. al found that most mood-stabilizing agents, especially ones that act on GABA receptors, were infective in the management and may even exacerbate the problem. However this study had a small sample size, so the findings may or may not be clinically significant.[9] Another study however suggested that mood-stabilizing agents may be helpful because they will moderate the highs and lows that are associated with the psychotic episodes.[6]

A final drug to consider is rimonabant, which is an endocannabanoid CB1 antagonist (obesity treatment). One study touts this agent as being beneficial for the psychosis in PWS. There was an RCT found that suggested that rimonabant was helpful for delusions as well as mood disorders, anxiety disorders and weight loss.[10] However, another study suggested the opposite saying that 50% of their participants had to drop out of the study because of the negative psychiatric effects of ricomabant.[12]

Conclusions

This case as well as the literature review indicates to me that psychosis in Prader-Willi syndrome is a poorly defined and insufficiently understood topic. The current management appears to be multifactorial, with environmental, pharmacological and behavioural modifications required. Some more specific suggestions include detecting behavioural issues early; educating caregivers; minimizing mood related symptoms and stabilizing medications. Although there is somewhat of a consensus that this multifactorial management is required, there seems to be little information as to which interventions work best. Much more research is required to identify the possible effect of CBT as well as more information is needed to see which pharmacologic agents work the best and should be tried in the case of PWS. The psychosis in PWS is difficult to manage, but quite common and therefore should be given appropriate attention.

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