Case Report
https://doi.org/10.9758/cpn.2017.15.1.70
Clinical Psychopharmacology and Neuroscience 2017;15(1):70-72
pISSN 1738-1088 / eISSN 2093-4327

Mania in Wolfram's Disease: From Bedside to Bench

Seshadri Sekhar Chatterjee[1], Sayantanava Mitra[2], Salil Kumar Pal[3]

[1]Department of Psychiatry, Medical College, [2]Consultant Psychiatrist, [3]Department of Endocrinology, Calcutta National Medical College, Kolkata, India

Wolfram syndrome is a relatively unexplored entity in clinical psychiatry. Historically, the discovery of a specific *WFS1* gene had generated huge fanfare regarding specific genetic causations of psychiatric disorders. While the initial enthusiasm has faded now, association of Wolfram syndrome with psychiatric illnesses like schizophrenia, psychosis and suicidal behavior still remain important for understanding biological underpinnings of such disorders. We report a case of Wolfram syndrome presenting with multiple manic episodes, discuss possible genetic underpinnings for the affective symptoms and then discuss certain issues regarding management.

KEY WORDS: Wolfram syndrome; Bipolar Disorder; Comorbidity.

INTRODUCTION

Among all the neurodevelopmental disorders associated with psychiatric abnormalities, Wolfram syndrome (WS) is an important but relatively unexplored entity.[1)] The discovery of a specific mutation in *WFS1* gene had ushered in an era of focus on specific genetic causations of psychiatric disorders. Though the initial enthusiasm has faded since then, the fact that mere heterozygous presence of *WFS* gene could increase the possibility of many psychiatric illnesses like schizophrenia, psychosis and suicidal behavior by many folds warrants attention to WS.[2)] There is no specific data regarding mania in Wolfram disease. We here report one case of WS presenting with multiple manic episodes, and try to elucidate psychiatric symptomatology in this patient along with possible genetic underpinnings for the same. We further discuss the issues regarding management.

CASE

Our patient, currently 22 years old male, first experienced rapid weight loss and increasing urinary output at 6-year age and was diagnosed with diabetes mellitus (DM) and subsequently put on insulin. The patient developed dimness in vision with difficulty in colour recognition at the age of 10 years, and thereafter hearing difficulty at 14 years. At 16 years of age, the patient developed an episode of behavioral disturbances characterized by increased physical activity, bossy attitude, along with arrogance, decreased sleep and overtly sexual behavior; all of which subsided with (unnamed) medication. He stopped taking medicines thereafter.

Since then there were multiple hospital admissions for polyuria. At age of 22 years, this patient came to us with reappearance of all the previous mood symptoms in increased severity along with some psychotic symptoms like delusion of grandiosity (that he holds a high post in Indian intelligence and has special connections with President of India). He had an increase in speech productivity, elated mood and increased psychomotor activities. His Young Mania Rating Scale score was 26. He was diagnosed as *Bipolar Affective Disorder*, *current episode manic with psychotic symptoms* as per International Classification of Diseases-10 Diagnostic Criteria for Research.

The patient was of average built, with body mass index of 21.72 kg/m^2. Ophthalmological examination showed decreased visual acuity (right 6/30, left 6/60) bilateral optic atrophy, nondiabetic retinopathy, constricted field of vision and problem in color detection. He had bilateral

Received: September 17, 2015 / **Revised:** December 19, 2015
Accepted: January 5, 2016
Address for correspondence: Sayantanava Mitra, MBBS, MD Psych, DNB Psych
Consultant Psychiarist, 22/D/1 Aswini Dutta Road, Kolkata 700028, India
Tel: +91-8298-187766
E-mail: sayantanava@gmail.com

Table 1. Diagnostic criteria as set by EURO-WABB group developed Wolfram syndrome guideline[3] and findings in our case

Criteria	Our case
Major	
o Diabetes mellitus < 16 yr (87%)	Present
o Optic Atrophy < 16 yr (80%)	Present
Minor criteria	
o Diabetes insipidious (< 42%)	Present
o Diabetis mellitus >16 yr (4%)	Not applicable
o Optic atrophy >16 yr (7%)	Not applicable
o Sensorinural deafness (48%)	Present
o Neurological signs (ataxia, epilepsy, cognitive impairment) (29%)	Present
o Renal tract abnormalities (structural or functional) (33%)	Present
o 1 loss of function mutation in *WFS1/CISD2* and/or family history of Wolfram syndrome	Not done
Others suggestible evidence	
o Hypogonadism in males (6%)	Present
o Absence of type 1 diabetes auto-antibodies	Not done
o Bilateral cataracts (1%)	
o Psychiatric disprder (26%)	Absent
o Gastrointestinal disorders (5%)	Present
	Absent
Minimum required	
2 major	
OR	
1 major plus 2 minor criteria	
OR	
2 pathological WFS1 or CISD2 mutations are identified	

Percentages in parentheses refer to prevalence of feature in EURO-WABB registry.

sensorineural deafness, more on left side. An endocrinological referral confirmed diabetes insipidus (DI) on water deprivation test.

Though the results could not be confirmed with genetic testing due to infrastructural constraints at our set-up, the afore said constellation of symptoms led us to the clinical diagnosis of WS (Table 1).[3]

His blood sugar was 315 mg/dl and dose of insulin was titrated accordingly. Serum sodium level was 127 mmol/L, with mildly increased serum urea and creatinine. Neurological examination revealed gait abnormality with ataxia. No cerebellar signs were noted; thereby indicating a possible abnormality in propriocetpive vestibular function. On psychometric assessment, Weschlar test scored intelligence quotient at 76. There was one suicidal attempt 2 years back—Beck Suicidal Intent score was 25 (moderate).

To manage the manic symptom, aripirazole 10 mg in two divided doses was prescribed and increased to 10 mg twice daily after 7 days. Within 15 days, his mood normalized. At 3 months follow up, though his other symptoms were deteriorating; he was doing well from the psychiatric point of view.

DISCUSSION

WS is a rare (estimated prevalence 1 in 770,000)[3] autosomal recessive neuroendocrinal degenerative disorder caused by mutation in *WFS1* gene which encodes for a endoplasmic reticulam (ER) transmembrane protein wolframin.[1,3] Since the discovery of a specific causative mutation in *WFS1* or wolframin gene, significant progress has been made both with the disease itself and also with several other associated manifestations of its aberration, among which psychiatric disorder feature prominently.[4]

It is estimated that as many as 1% of the general population could carry mutations in the *WFS1* gene[3] and the heterozygosity for the *WFS1* mutations has been reported to be a significant risk factor for psychiatric illnesses.[5,6] Several psychiatric signs and symptoms are reported in homozygous or compound heterozygous patients with wolframin gene. A high probability of carrying a single wolframin mutation and a statistically significant excess of psychiatric hospitalizations, suicidal behavior, completed suicides, and self-reports of mental illness, over spouse controls[6] has been found in first degree relatives of patients with WS. An isolated mutation in the *WFS1* gene have been reported in patients with bipolar disorder (BD), major depression, schizophrenia, and suicide victims even in absence of sine qua non features of WS.[7] There are conflicting reports regarding connection between *WFS1* gene and BD. Though no association of *WFS1* polymorphisms and expression level in postmortem tissue of Japanese BD

patients was found,[8] a recent meta-analysis of genome-wide expression studies on BD revealed *WFS1* expression in prefrontal cortex to be significantly correlated with BD.[9] A report showing DI with mania[10] and locating one locus on linkage analysis to chromosome 4 also empower the above findings.[11]

Impaired ER stress is proposed to be associated with BD. XBP1 protein is a transcription factor of ER stress pathway. In animal model *WFS1* gene is found to be induced in response to ER stress via XBP1 that negatively regulates ER stress, normally.[12] This may have a profound implication regarding genetic causation of BD itself.

As valproate carries a risk of weight gain and insulin resistance, and can also induce ER stress;[13] it is best avoided in patients of WS. Lithium is better than valproate in terms of potential ER stress induction;[14] however, it can aggravate preexisting renal dysfunction in this group. Among the antipsychotics, keeping the metabolic, cardiac and other side effect profiles and local availability in mind, aripiprazole was selected. In our case DM was the earliest to manifest, followed by visual, auditory and gait abnormalities in that order. This is in accordance with the classically reported cases. Interestingly, our patient also showed a decreased serum sodium level on further investigations, despite water deprivation. While this might be indicative of DI; it can also be attributed to concurrent presence of DM and resultant osmotic water accumulation.

Based on this report, we suggest use of aripiprazole in patients of WS presenting with mania. The drug is metabolically safe, as well as effective in managing the psychiatric symptoms. We acknowledge that availability of *WFS1* mutation report could have made the case much stronger, but clinical symptom constellation is too discreet to hint at any other diagnosis.

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