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Brief Report

Bipolar Disorder Type 1 in a 17-Year-Old Girl with Wolfram Syndrome

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Abstract

Objective: Wolfram syndrome (WS, MIM 222300) is a rare autosomal, recessive neurodegenerative disorder associated with mutations in WFS1, a gene that has been associated with bipolar disorder (BD). WS, characterized by the association of juvenile-onset diabetes mellitus (DM) and bilateral progressive optic atrophy (BPOA), encompasses several other clinical features, including cognitive impairments and psychiatric disorders. Detailed data on the psychiatric phenotype are still scarce, and how WS relates to BD is still unknown.
Method: A 17-year-old girl with WS was hospitalized for early-onset BD. A multidisciplinary and developmental assessment was carried out to control mood symptoms and address how BD could be related to WS.
Results: Besides DM and BPOA, the patient had several risk factors for BD/mood disorders as follows: (1) a history of abuse and maltreatment; (2) a history of specific language disorder and borderline intelligence associated with academic failure; and (3) a comorbid hypothyroidism. Treatment encompassed all aspects of the adolescent's conditions, such as the use of mood stabilizers, addressing psychosocial and scholastic problems, and treating hypothyroid dysfunction.
Conclusion: Given the complexity of WS, this case suggests that the possible association between WS and BD should not only be merely limited to a possible statistical association with WFS1 polymorphism but also to developmental, cognitive, and endocrine risk factors for BD.

Background

Wolfram syndrome (WS, MIM 222300) is a rare autosomal recessive neurodegenerative disorder (Fraser and Gunn 1977). The syndrome occurs in 1 in 770,000 children and has a carrier frequency of 1 in 354 people (Barrett et al. 1995; Cano et al. 2007). This progressive condition has a mortality rate before the age 35 of ~65%, due to central respiratory failure associated with brainstem atrophy, renal failure (Kinsley et al. 1995), food aspiration, or suicide (De Heredia et al. 2013). The disease phenotype is associated with mutations in WFS1, a gene mapped on the short arm of chromosome 4 (Inoue et al. 1998; Strom et al. 1998) and located within exon 8 (Torres et al. 2001). The frequency of heterozygous carriers of WFS1 mutations is about 1% of the general population (Swift et al. 1991). WFS1 encodes for a membrane glycoprotein named Wolframin, essentially expressed in the brain and pancreas. Wolframin is thought to play a role in maintaining the functioning of the endoplasmic reticulum (ER), an intracellular organelle involved in the elimination of defective proteins. If cells are unable to dispose off defective proteins, they become ''stressed'' and die (Inoue et al. 1998; Khanim et al. 2001; Osman et al. 2003; Yamada et al. 2006; Fonseca et al. 2010). More recently, the CISD2 gene on chromosome 4q22–q24 has been identified as a second causative gene associated with WS (El-Shanti et al. 2000; Amr et al. 2007).

Clinically, WS is characterized by juvenile-onset diabetes mellitus (DM) and bilateral progressive optic atrophy (Wolfram and Wagener 1938; D'Annunzio et al. 2008; Bonnet Wersinger et al. 2014), both usually occurring by the age of 15 (Rigoli et al. 2011). In addition, organized along a spectrum, the disorder encompasses central diabetes insipidus (DI), deafness, abnormalities of the endocrine glands (e.g., hypothyroidism and hypogonadism), urinary tract abnormalities, and multiple neurological abnormalities (e.g., cerebellar ataxia, brainstem dysfunction, peripheral neuropathy, and epilepsy; Barrett et al. 1995; Hardy et al. 1999; Cryns et al. 2003; Medlej et al. 2004; Cano et al. 2007; Chaussenot et al. 2011; Marshall et al. 2013). Magnetic resonance imaging studies have indicated that neurodegeneration occurs in optic neurons and brain neurons. Cerebral, cerebellar, and brainstem atrophy may also be present (Chaussenot et al. 2011). The pleiotropic effects caused by Wolframin mutations also include cognitive impairment and psychiatric disorders. However, detailed data on the psychiatric

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phenotype are still rare. Several authors reported psychotic symptoms, attempted suicide, violent behavior, and affective disorders (e.g., mixed mood swings), in WS homozygous patients (Swift and Swift 2000; Matsunaga et al. 2014; Ramli et al. 2014).

Heterozygous carriers of Wolframin mutations may also be predisposed to psychiatric illness (Swift et al. 1990; Swift and Swift 2000). The pathophysiological significance of WFS1 in bipolar disorder (BD) has been suggested by psychiatric manifestations in patients or carriers of Wolfram disease and linkage studies of BD with 4p16, the locus of WFS1 (Kato et al. 2003). Consequently, mutations in the gene WFS1 were examined in participants affected by BD. Except for Furlong et al. (1999), most studies did not identify a potential role for WFS1 variants in affective disorders (Kato et al. 2003).

Few studies have explored behavioral and cognitive aspects in patients with WS. Nickl-Jockschat et al. (2008) and Chaussenot et al. (2011) found an association between psychiatric symptoms (e.g., anxiety, disruptive behavior, mood swings) and learning difficulties underlined by impaired cognitive function (e.g., planning features, memory) and psychomotor delay. Interestingly, Bischoff et al. (2015) found similar psychiatric features but, consistent with other reports (Verri et al. 1982; Marshall et al. 2013), no cognitive impairments.

Case Report

M was the second child of unrelated parents. Her mother had a history of major depressive episodes with several suicide attempts. Her father suffered from chronic alcoholism and was described as an abusive man. Her parents separated when M was 6 years old. She lived with her mother in Portugal until age 14 when her mother moved to France, and she remained with her father in Portugal. She went to live with her mother in France at age 17, where she subsequently came to our attention as detailed below.

Early Developmental and Clinical History

M was born at full term, following an uneventful pregnancy, and with no early developmental abnormalities. Her mother was 22 years old and her father 33 years at conception. At 9 months, she walked and used her first words. At 18 months, she was able to form short sentences. M's schooling was difficult to trace. Her mother noticed that M had difficulties in spoken and written language, but there was no further investigation. Visual impairments were detected when she was 8 years old, but correction with prescription lenses was ineffective. DM was discovered during a systematic review at age 14, associated with DI. The coexistence of DM and DI, accompanied by bladder atony leading to enuresis, optic atrophy, and neuropathic pain (i.e., intermittent paresthesia with restless leg syndrome), led to a diagnosis of WS that was confirmed by genetic testing, which revealed a heterozygous mutation in exon 5 (c.505G > A, p.E169K) and a heterozygous mutation in exon 8 (c.2050G > A, p.A684T) of the WSF1 gene. Both mutations have previously been described as causes of the disease (Hardy et al. 1999; Waschbisch et al. 2011).

Between the ages of 14 and 17, M was physically abused by her father. M described herself as having behavioral disorders, such as school absenteeism, drug use, and sexual disinhibition. M was referred to an inpatient unit for a suicide attempt by insulin at age 15.

When we first met her, M was a 17-year-old girl referred to our inpatient unit for two reasons as follows: first, a marked affective liability and endangering behavior and second, uncontrolled diabetes. Furthermore, M was in a vocational school where she showed significant absenteeism. To organize a care project addressing the complexity of her pathology, a thorough and multidisciplinary evaluation was necessary.

Somatic Symptoms Assessment and Genetic Analysis

Clinical examination revealed neuropathic pain with absent lower limb tendon reflex associated with an impairment vibratory sense. She also complains of urinary symptoms such as enuresis.

The patient had juvenile DM for at least 4 years and a central DI. The control of DM was poor; M had no regular practice of glycemic measures and no observance of diet recommendations. In addition, hypothyroidism was discovered during her hospitalization. Magnetic resonance imaging scans identified a slight atrophy of optochiasmatic structures and of the occipital periventricular white matter, but without demonstrable pituitary abnormalities. The bilateral optic atrophy was confirmed, with complete blindness in the left eye and partial loss of visual field in the right eye. Electromyographic examination showed an early distal sensitive axonal neuropathy of the lower limbs. Her audiometric examination revealed no abnormalities.

The study in the family showed that only the mother carried the mutation (c.2050G > A, p.A684T), and M's father was probably the carrier of the second mutation according to the recessive inheritance of the disease, however, no segregation was possible as no sample was available for him.

Psychiatric Assessment

M was cooperative, but hindered by difficulties of expression and a limited vocabulary. Subjectively, M acknowledged suffering from mood swings that she described as hard to bear. Interviews revealed multiple episodes of severe sleep deprivation, nocturnal graphomania, and changes in behavior, including extreme irritability, sexual disinhibition, and alcohol consumption. During these episodes, she did not go to school. Also, her familial relationships were severely impaired; she would verbally abuse her mother and had been physically aggressive toward her younger brother. At other times, she could experience episodes of sadness, abulia, anorexia, and intense tiredness. She reported suicidal thoughts occurring either during temper outbursts, especially after conflicts with her family, or during times of sadness.

This symptomatology was confirmed during her hospitalization. Over periods of a few days, M alternated between excitation phases, characterized by sleep disturbances, sexually disinhibited behavior, marked irritability, and times of intense sadness with weeping and dark thoughts, to which she could not relate any event. Thus, M experienced manic episodes alternating with major depressive episodes, consistent with the DSM-5 diagnostic criteria for BD type 1.

Cognitive Assessment

To define her academic difficulties more precisely, we conducted psychological and language testing, which included investigations of oral and written language in Portuguese, general cognitive abilities, and neurovisual skills (Table 1). For the last two investigations, items were translated into Portuguese. The score of total intelligence quotient (IQ) did not reflect the reality of her intellectual abilities because of the heterogeneity of the intrascalar results. Indeed, M could pass difficult reasoning tests, but failed to develop sentences or find the correct word. In line with her peripheral visual impairment, M showed difficulties for all events that

Table 1. Summary of Interdisciplinary Assessments in a 17-Year-Old Girl with Wolfram Syndrome

General cognition—Wechsler adult intelligence	*Scales index and scores*	*Comments*
Scale 3rd edition WAIS III		
Full-scale IQ	FSIQ = 74	Homogeneous profile in interscalar results, except for Processing Speed Index. Her visual acuity is not sufficient enough to achieve the test code and symbols.
Verbal Comprehension Index	VCI = 84	
Vocabulary	5/19	
Similarities	9/19	
Information	7/19	
Comprehension	6/19	Intrascalar results show a very heterogeneous profile: categorical reasoning tests (similarities) are succeeded, but vocabulary subtests are failed.
Perceptual Organization Index	POI = 82	
Picture completion	7/19	
Block design	6/19	Despite her peripheral visual disturbance, in nonverbal tests, she can achieve average performances
Matrix reasoning	8/19	
Working Memory Index	WMI = 73	Low scores on working memory subtests
Arithmetic	5/19	
Digit span	5/19	
Letter-Number Sequencing	7/19	
Processing Speed Index	PSI = 61	
Digit symbol coding	2/19	
Symbol search	4/19	
Neurovisual assessment		
Visual field confrontation testing	6/6	
Pursuit testing	Smooth	
Oculomotor praxis	4/4	
Visuomotor coordination	5/5	Surprisingly given her history, we found a normal neurovisual assessment. Except that she was not able to complete the Rey–Osterrieth Complex Figure.
Bells cancellation test	34/35 (2 min)	
"A" cancellation	15/15	
"T" cancellation	31/40	Her reading difficulties and her inability to perform the Rey–Osterrieth Complex was understood as a consequence of her insufficient visual acuity
Pillon'15 figures	15/15	
Somatognosia	10/10	
Digital gnosia	5/5	
Reflexive praxis	24/24	
Rey–Osterrieth Complex Figure	Impossible	
Language observation checklist school level	Scores	
Semantics	29/40 (–0.6 SD)	Low scores in morphosyntax
Morphosyntax	38/50 (<–2 SD)	Absence of phonological impairments
Phonology	38/40	
ALO (oral language assessment)		
Understanding of complex structures	30/32	Low scores in morphosyntax reflection
Morphosyntax reflection	36/62	
Psycholinguistic assessments of language processing in aphasia (spelling to dictation)		
Letter length	36/36	
High abstractness and high frequency	10/10	
High abstractness and low frequency	5/10 (–1.2 SD)	
Low abstractness and high frequency	10/10	M exhibits minor difficulties in writing and spelling concerning irregular words, words with low use frequency and for homophones
Low abstractness and low frequency	7/10 (–1 SD)	
Grammatical class nouns	5/5	
Grammatical class adjectives	5/5	
Grammatical class verbs	4/5	
Grammatical class function words	4/5	
Regular words	18/20	
Irregular words	17/20	
Nonwords	13/24 (–1.2 SD)	
Disambiguated homophones	12/16	
Clinical Global Impressions		
Therapeutic effect	Marked	
Side effects	None	
Global Assessment of Functioning Scale	At admission	At 2 months follow-up
	25	75

WAIS (Wechsler 1997); Rey–Osterrieth Complex Figure (Osterrieth 1944); Language Observation Checklist School Level (Sua Kay and Santos 2003): Mean and standard deviation to children between 6 and 10 years old. ALO, Sim-Sim (2003): Mean and standard deviation to children between 9 years and 4 months and 9 years and 9 months. Psycholinguistic Assessments of Language Processing in Aphasia—Section of Reading & Spelling (Kay et al. 1992) Subtest 29, 44, and 45: Mean and standard deviation to university students. Subtests 40, 41, and 46: Mean and standard deviation to 14 years old. Clinical Global Impressions (Guy 1976); Global Assessment of Functioning (Endicott et al. 1976).

ALO, assessment of oral language; IQ, intelligence quotient.

rely on visual material. Her average scores on the neurovisual tasks ruled out the presence of visuospatial or praxic impairments. Finally, M had a moderate working memory impairment (IMT = 73). The WAIS subtasks (vocabulary and comprehension) and the oral language skills examination revealed specific language impairment that affects lexical evocation and morphosyntax. These impairments in lexical evocation were revealed by semantic memory difficulties regarding words used less frequently in the written assessment. M also exhibited minor difficulties in written language.

Outcome

With regard to medication, we introduced levothyroxine sodium for treatment of the hypothyroidism (25 μg/day), desmopressin for her DI (desmopressin acetate nasal spray 20 μg/day), pregabalin for her neuropathic pains (pregabalin 10 mg/day), and insulin therapy for her DM (glargine—long-acting insulin—22 UI/day, adapted doses of lispro—fast-acting insulin during the day). We assessed M's clinical severity at admission and her improvement under treatment using the Clinical Global Impressions (CGI) (Guy 1976) and the Global Assessment Functioning (GAF) (Endicott et al. 1976). Lithium carbonate was introduced at the dose of 400 mg/day (intake at 8 pm) and progressively increased to 1000 mg/day, which maintained stable blood levels (between 0.85 and 0.97 mEq/L, on day of discharge: 0.92 mEq/L).

Clinically, M showed a quick and marked improvement, as assessed by three clinicians (N.B., D.P., J.X.). In particular, sleep quality and attention improved significantly. In addition, she did not display aggressive outbursts, sexually disinhibited behavior, or alcohol consumption. She herself reported feeling fewer mood fluctuations and the disappearance of suicidal thoughts. This progression was confirmed by the evolution of the CGI and GAF scores after 2 months of lithium treatment (cf. Table 1). She demonstrated a better adaptation to the care unit in daily life and in her relationships. With regard to her oral and written language impairments, we recommended learning accommodations along with speech therapy.

Discussion

In accordance with several authors (Verri et al. 1982; Marshall et al. 2013; Bischoff et al. 2015), M had a verbal IQ in the average range. Further detailed examination of the various subtests revealed a heterogeneous verbal IQ, suggestive of a specific language disorder (noticed by her mother in her childhood), which was confirmed by oral and written tasks in Portuguese. It is important to note that the socio-familial context, in which M grew up, could have also played a role in her specific language disorder.

Behavioral difficulties and mood swings were the first psychiatric manifestations of WS. The clinical picture of BD type 1, associated with high impulsivity and episodes of suicidal thoughts, led to the prescription of a mood stabilizer. The therapeutic option between lithium and valproic acid (VPA) was discussed in this case, given the complexity of the somatic background and the great attention to possible side effects. Lithium is the gold standard therapy for BD (Cipriani et al. 2005; Kowatch et al. 2005), especially in the context of endangering behavior and acknowledged suicidal risk. Nevertheless, lithium has side effects, including acute and chronic effects on the kidney (e.g., nephrogenic DI) (Bassilios et al. 2008; Grunfeld and Rossier 2009) and on thyroid metabolism (Hundley et al. 2005; McKnight et al. 2012). VPA does not have renal or thyroid effects, but several secondary metabolic side effects, including the development of insulin resistance and weight gain, have been reported (Martin et al. 2009; Chateauvieux et al. 2010). In M's case, lithium carbonate was chosen, given (1) the severity of the psychiatric manifestations, (2) the satisfactory control of her renal and thyroid disturbances, and (3) the poor control of her DM, associated with other risk factors of metabolic syndrome.

BD can be conceptualized as the fruit of interplay between factors that are present in M's history, genetic vulnerability (mood disorders, depression in family history), and environmental factors (low socioeconomic status and a history of maltreatment) (Brunelle et al. 2009). Otherwise, mood swings and aggressive behavior in WS are said to also be caused by recurrent episodes of severe hypoglycemia, which have been shown to cause brain structure anomalies in children suffering from type 1 DM, including brain atrophy (Ho et al. 2008). Abnormalities in brain imaging for M can therefore be partly explained by DI.

As previously mentioned, Wolframin plays a role in the proper functioning of the ER (Inoue et al. 1998). Moreover, β-cell death and neuronal cell dysfunction in WS are attributed to high levels of ER stress (Rigoli et al. 2011) and are consequences of the loss of function of WFS1. Interestingly, the impaired ER stress response has been proposed as a pathway involved in BD (Kato 2008). Both lithium and valproate facilitate the ER stress response (Chuang 2005), but unlike lithium, valproate specifically increases the expression of WFS1; therefore, it increases the production of the protein, Wolframin (Kakiuchi et al. 2009). In this respect, VPA could then be considered as a valuable treatment for patients with BD, who are also affected by WS, if the mutated protein is still functional. This would mean reduced cell death, thereby inhibiting the progression of the disease. In fact, VPA was recently granted orphan designation (EU/3/14/1428) by the European Commission in treatment of WS.

Conclusion

Finally, in terms of clinical practice, this case report emphasizes the importance of a multidimensional assessment of patients who exhibit this complex phenotype. This may help in creating tailored therapeutic strategies.

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Disclosures

No competing financial interests exist.

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