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Psychiatric Diagnoses and Medications in Wolfram Syndrome

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Abstract

Background: Wolfram Syndrome is a rare genetic disorder usually resulting from pathogenic variation in the *WFS1* gene, which leads to an exaggerated endoplasmic reticulum (ER) stress response. The disorder is typically characterized by diabetes insipidus, diabetes mellitus, optic nerve atrophy, hearing loss, and neurodegenerative features. Existing literature suggests it may also have psychiatric manifestations.

Objective: To examine lifetime psychiatric diagnoses and medication history in Wolfram Syndrome.

Method: Child, adolescent, and young adult Wolfram Syndrome participants (n=39) were assessed by a child & adolescent psychiatrist to determine best estimate DSM-5 lifetime psychiatric diagnoses as well as psychoactive medication history. In addition, the Child & Adolescent Symptom Inventory-5 (CASI-5) Parent Checklist was used to determine likely psychiatric diagnoses based on symptom counts in Wolfram Syndrome patients (n=33), type 1 diabetes (n=15), and healthy comparison (n=18) groups.

Results: Study participants with Wolfram Syndrome had high lifetime rates of anxiety disorders (77%). Also, 31% had an obsessive-compulsive spectrum disorder, 33% had a mood disorder, 31% had a neurodevelopmental or disruptive behavior disorder, and 31% had a sleep-wake disorder. More than half of Wolfram Syndrome participants had taken at least one psychoactive medication, and one third had taken at least one selective serotonin reuptake inhibitor (SSRI). Some individuals reported poor response to sertraline but better response after switching to another SSRI (fluoxetine or citalopram). In general, people with Wolfram Syndrome often reported benefit from psychotherapy and/or commonly used psychoactive medications appropriate for their psychiatric diagnoses.

Conclusions: Wolfram Syndrome may be associated with elevated risk for anxiety and obsessive-compulsive spectrum disorders, which seem generally responsive to usual treatments for these disorders.

Keywords: Wolfram Syndrome, Psychiatry, Anxiety, Obsessive Compulsive Disorder, medication, ER stress

Introduction

Wolfram Syndrome is a rare genetic disorder typically characterized by diabetes insipidus, diabetes mellitus, optic nerve atrophy, hearing loss, and neurodegenerative features (1). The majority of cases are due to autosomal recessive variants in the *WFS1* gene, which codes for the wolframin protein, but there are also cases with autosomal dominant inheritance, or that are caused by a variant in the *CISD2* gene (2). The wolframin protein is present in the endoplasmic reticulum (ER) membrane and protects cells from apoptosis during the ER stress response (3). Animal models studying *Wfs1* gene expression and function suggest brain areas relevant to behavioral stress responses, anxiety, and depression (such as medial prefrontal cortex, temporal lobe, hippocampus, and amygdala) may be affected in Wolfram Syndrome (4-13), and *Wfs1*-

deficient animals show behavioral characteristics analogous to anxiety, depression, and posttraumatic stress phenotypes in humans (8-9, 13-14). Human studies also suggest brain differences, which may be relevant to psychiatric phenotypes. Our own cross-sectional neuroimaging studies have shown small brainstem and cerebellar volumes as well as deficient axon myelination in genetically confirmed Wolfram Syndrome (15, 16). Our longitudinal study has shown a number of differences compared to controls, including abnormal reduction of ventral pons white matter volume and excessive reduction of cerebellar cortex gray matter over time, with evidence of both altered neurodevelopment and neurodegeneration (17). Differences in cerebellar structure and function may be of particular relevance to psychiatric conditions, including liability to general psychopathology (18, 19) and stress-related disorders such as anxiety, depression, and posttraumatic stress disorder (20).

Some studies have suggested individuals with Wolfram Syndrome, and even carrier relatives with only one copy of a dysfunctional *WFS1* allele, may have increased risk for psychiatric problems, such as psychiatric hospitalizations, suicidality, depression, mania, psychosis, irritability, aggression, and/or anxiety (21-26). A chart review of 68 Wolfram Syndrome patients (age 8-43 years) performed in the mid-1980s reported 60% had history of substantial psychiatric problems, such as depression, psychosis (hallucinations, delusions, and/or psychotic behavior), confusion, memory impairment, dementia, temper outbreaks, hostility, and/or impulsive aggression (21). Psychiatric manifestations were considered "very severe" in 17 patients (25%), including 12 who required inpatient psychiatric hospital admission and 11 who attempted suicide. Age at first suicide attempt or psychiatric hospital admission was between 15 and 32 years. Depression was noted in the records of 21 patients, of which nine were treated with antidepressants, and six were also treated with antipsychotic medication. Evidence of psychiatric symptoms was found in only one of the seven patients who were age 14 years or younger (a 9-year-old child had some behavioral difficulties at school). Of note, the chart review was completed at a time when Wolfram Syndrome was diagnosed based on clinical features, so it is unclear how many had pathogenic *WFS1* variants versus some other cause of their symptoms.

Outside of the studies focusing on individuals with Wolfram Syndrome and their families (which are useful in studying rare genetic variants with large effects), additional studies have explored the association of *WFS1* genetic variants or expression levels with psychiatric disorders. Some case reports and genetic association studies suggest an association of *WFS1* variants with mood disorders, aggression, suicidality, impulsivity, and/or autistic traits (27-33); however, several genetic association studies report negative findings (34-38). Clinically significant psychiatric symptoms are not always present in people with Wolfram Syndrome, so if *WFS1* pathogenic variants that cause Wolfram Syndrome also affect risk for psychiatric disorders, there may be different levels of penetrance and/or different effect sizes depending on the specific variant. If only rare *WFS1* variants—such as those known to cause Wolfram Syndrome—increase risk for psychiatric problems, family-based studies should be helpful in examining the association. Large population-based genetic association studies may miss rare variants with large effects, but may detect common variants with small effects on psychiatric symptoms.

Our research group has been following patients with genetically confirmed Wolfram Syndrome in an annual research clinic since 2010. In earlier years of this study, the Achenbach Child Behavior Checklist (CBCL, ages 6-16) or Adult Self Report (ASR, ages 16 and above) was used to assess psychiatric symptoms in 13 individuals with Wolfram Syndrome who were in the age range of 5-25 years (15). Mean percentile scores were 65.6 (SD=32) for internalizing and 33.1 (SD=24) for externalizing symptoms. Five individuals had clinically significant (T score >69) internalizing symptoms, while only one had clinically significant externalizing symptoms. Later, we reported best-estimate psychiatric diagnoses for 19 Wolfram Syndrome participants who attended our 2013 clinic, along with questionnaire-based symptom-count diagnostic estimates for Wolfram Syndrome, type 1 diabetes (T1D), and Healthy Comparison (HC) participants (39). There were no statistically significant differences among the groups with regard to the proportion of individuals with questionnaire-based diagnoses of neurodevelopmental and disruptive behaviors disorders, anxiety disorders, or mood disorders. However, individuals with Wolfram Syndrome showed impairments in sleep quality and smell identification compared to the other groups. The most common best-estimate psychiatric diagnosis assigned to Wolfram Syndrome participants by the study psychiatrist was Unspecified Anxiety Disorder. Four of 19 Wolfram Syndrome participants reported they were currently prescribed psychoactive medication (39).

Since publication of our earlier findings, we have increased our sample size and followed some patients to early adulthood using careful interviews and symptom reports. The current manuscript focuses on lifetime best-estimate psychiatric diagnoses and psychoactive medication use in an expanded group of Wolfram Syndrome research clinic participants

(n=39) who were interviewed at least once by our study psychiatrist between the years of 2013 and 2017. We also include 2014-2017 parent-report psychiatric questionnaire results on Wolfram Syndrome, T1D, and HC participants for informational purposes. Finally, we discuss clinical implications and directions for further study of psychiatric manifestations in Wolfram Syndrome. Because ER stress mechanisms have recently been implicated in a variety of psychiatric disorders (40-45), this work is important not only for understanding Wolfram Syndrome, but for our understanding of mechanisms leading to psychiatric disorders more generally.

Methods

Participants

Wolfram Syndrome participants were enrolled in a longitudinal study at Washington University's Wolfram Syndrome Research Clinic. They were required to have genetically confirmed *WFS1* gene pathogenic variants and were age 30 years or younger at time of enrollment. Wolfram Syndrome participants completed one to seven annual sessions between 2010 and 2017, depending on their availability to participate and when they enrolled in the study. Subsets of the research data have been reported elsewhere (15-17, 39, 46-50). Comparison groups included individuals with type 1 diabetes mellitus (T1D) recruited through a pediatric diabetes clinic and a non-diabetic healthy comparison group (HC). HC participants were recruited through the community or were siblings of T1D participants. For the comparison groups, exclusion criteria at the start of the study included self-reported psychiatric or neurological diagnoses, use of psychoactive medications, contraindication to magnetic resonance imaging (MRI), and birth at <36 weeks gestation with respirator use or other perinatal complications. These exclusions were due to the study's focus on brain MRI differences. This study was approved by the Washington University Human Research Protection Office. Participants or parent/guardians provided written consent, and minors provided assent. The current manuscript focuses on Wolfram Syndrome participants who attended the clinic on at least one occasion between 2013 and 2017 (n=39).

Measures

During each clinic visit, a child & adolescent psychiatrist (AMR) reviewed available questionnaire data and interviewed each Wolfram Syndrome participant, often along with the parents (especially in the case of younger children). Interviews typically lasted 30 to 60 minutes and focused on clarifying the presence/absence of relevant Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria. These interviews were not completed using a published structured or semi-structured interview, but were similar to DSM-based clinical interviews done as part of usual outpatient psychiatric care. Medication history was also collected, with focus on psychoactive medications. Based on information obtained from questionnaire data and interviews, best-estimate lifetime DSM-5 diagnoses were assigned to each patient. Also, based on all available data, the psychiatrist assigned a Lifetime Psychiatric Severity Score on a scale of 0 to 4. This rating scale was developed by the study psychiatrist (AMR) and was scored as follows: **0** = No symptoms reported, or only symptoms that are very typical for age; **1** = Mild symptoms which seem fairly common for age or reasonable considering current stressors, and cause no obvious impairment; **2** = Mild symptoms with some avoidance of activities or mild impairment; may have history of no treatment or rapid improvement of symptoms with treatment; **3** = Moderate symptoms with history of clear impairment (family relationships, social, school, or work functioning affected at some point); may have sought treatment specifically for psychiatric symptoms, or treatment may have been strongly recommended; **4** = Severe symptoms with clear impairment of functioning in multiple areas (i.e., family relationships, social, school, work); more than just brief treatment of psychiatric symptoms has been clearly necessary; there has been a history of psychiatric hospitalization, suicidal thoughts, self-injury behaviors, severe physical aggression, other dangerous behaviors, possible mania with need for an antipsychotic or mood stabilizing medication, and/or clear psychotic symptoms (i.e., delusional thinking or clearly distressing psychotic-quality hallucinations).

The Child & Adolescent Symptom Inventory-5 (CASI-5) Parent Checklist is a largely DSM-5-based parent-report psychiatric questionnaire intended for assessment of children and adolescents in the age range of 5-18 years. It includes items from two older instruments, the Child Symptom Inventory 4 (CSI-4) and the Adolescent Symptom Inventory 4 (ASI-4) and has been updated with additional items relevant to new DSM-5 diagnoses (51-52). Because we wanted to assess the exact same parent-reported symptoms regardless of age, we used the CASI-5 for participants of all ages, including young adults. Most CASI-5 items are rated on a 4-point Likert scale of 0 to 3, corresponding to the frequency of each behavior (never, sometimes, often, or very often). A few items are instead rated as yes versus no. The CASI-5 can be scored in two standard ways. The symptom count cutoff score method allows estimation of likely DSM-5 diagnoses based on symptom counts. With this method, individual DSM-

based items relevant to a particular diagnosis are counted as a symptom only if the behavior is reported to occur above a certain frequency (usually "often"). The symptoms are then counted up to see whether an individual meets the symptom count required for a particular DSM-5 diagnosis. Current analyses include examination of the resulting CASI-5 diagnoses. It is important to note that these CASI-5 diagnoses are not necessarily equivalent to DSM-5 diagnoses since they focus only on the symptom criteria and do not consider additional factors (such as age-of-onset, impairment, and exclusion criteria). CASI-5 items (each scored 0-3) can also be added to produce symptom severity profile raw scores, which can be converted to T-scores based on the distribution of scores in normative samples. We did not use the symptom severity profile scales for the current analysis because the CASI-5 symptom severity profile scales are not identical for all ages, and because calculation of the standard T-scores is not possible for those over the age of 18. Also, for the current manuscript we were more interested in examining the prevalence of categorical diagnoses rather than severity of symptoms.

Analysis

For participants assessed using the CASI-5, we counted a CASI-5 diagnosis if it was present at least once. We grouped diagnoses into general categories (neurodevelopmental and disruptive behavior disorders, anxiety disorders, obsessive compulsive spectrum disorders, mood disorders, eating disorders, schizophrenia, schizoid personality, and posttraumatic stress disorder). We examined prevalence of these general diagnostic categories in addition to individual diagnoses within each. For exploratory purposes, we examined the frequency of these CASI-5 diagnoses in Wolfram Syndrome, type 1 diabetes, and healthy comparison groups, but we do not report any statistical tests comparing the 3 groups since differences in psychiatric symptoms could be due to differences in exclusion criteria.

Considering the medication history of all Wolfram Syndrome participants, medications were given effectiveness ratings using a 3-level scale, with + indicating highest evidence of benefit, 0 indicating unclear or inconsistent response, and - indicating low evidence of benefit and/or problematic side effects.

Results

Table 1 shows demographics and other relevant details about all Wolfram Syndrome participants who had psychiatric interviews. Supplemental table S1 includes the same plus information about the participants who were assessed using the CASI-5 questionnaire (includes a subset of Wolfram Syndrome participants plus T1D and HC participants). Table 2 shows the number and percentage of Wolfram Syndrome participants who had specific lifetime best-estimate psychiatric diagnoses given by the study psychiatrist (percentages are shown for the entire group and separately for child, adolescent, and young adult age groups). Figure 1 shows the distribution of lifetime psychiatric severity scores. Supplemental table S2 summarizes CASI-5 symptom-count-based diagnoses for Wolfram Syndrome, T1D, and HC participants. Supplemental table S3 summarizes psychotropic medications taken by Wolfram Syndrome patients, along with information regarding medication purpose, side effects, and the psychiatrist's overall effectiveness rating for each medication.

Only three (8%) of Wolfram Syndrome participants had no lifetime best-estimate psychiatric diagnosis based on evaluation by the study psychiatrist. One of these participants did report a history of a mild form of hallucination-like perceptual disturbances (briefly seeing a shadow), which was not clinically concerning.

TABLE 1. Characteristics of Wolfram syndrome participants with at least one psychiatric interview in the 2013-2017 timeframe (Total N=39).

1 clinic visit, n (%)	4 (10)
2 clinic visits, n (%)	8 (21)
3 clinic visits, n (%)	8 (21)
4 clinic visits, n (%)	19 (49)
Age at first visit, mean (range)	14 (5-27)
Age at last visit, mean (range)	16 (6-30)
Male sex at birth, n (%)	16 (41)

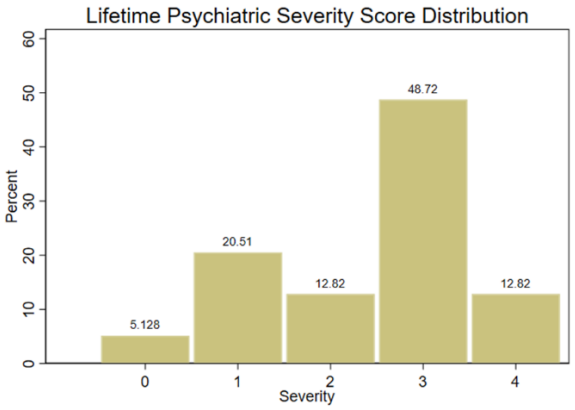

FIGURE 1. *Lifetime Psychiatric Severity Score Distribution. Score Interpretation: 0 = Few or no symptoms; 1 = Mild symptoms, little or no impairment; 2= Mild symptoms, some impairment; 3= Moderate symptoms, clear impairment; 4= Severe symptoms, clear impairment (see methods for more detailed description). Numbers above each bar are the percentage of Wolfram Syndrome participants with the indicated lifetime severity level as of the most recent clinic visit.*

A history of hallucination-like perceptual disturbances was common (seen in 38% of Wolfram Syndrome participants), but in most cases these were somewhat vague auditory or visual misperceptions with full insight that the experiences were not real. Examples include briefly hearing a voice when nobody was there, briefly seeing an object as something else, or briefly seeing figures or shadows in the dark. In most cases, it seemed that these hallucination-like experiences might be explained by vision/hearing loss rather than any psychiatric disorder, but in a few cases they seemed related to anxiety or posttraumatic stress. One child reported detailed history of recurrent vivid visual hallucinations and seemed convinced they were real, which led to an Unspecified Psychotic Disorder diagnosis, but these perceptual disturbances had resolved by the next clinic visit.

The most common best-estimate lifetime psychiatric diagnosis seen in the Wolfram Syndrome group was Unspecified Anxiety Disorder (51%). Other lifetime diagnoses occurring in more than 20% of participants included Hypersomnolence Disorder (26%), Excoriation Disorder (23%), and Attention-Deficit/Hyperactivity Disorder (21% if Unspecified ADHD cases are included, but only 13% met full criteria for a specific DSM-5 ADHD presentation).

Of the 20 participants with Unspecified Anxiety Disorder, five had no other diagnosis, and 15 had at least one additional diagnosis. Unspecified Anxiety Disorder was most common in children age 6-12 (at this age it was often difficult to determine whether criteria for a more specific anxiety diagnosis were met), but it was also common in other age groups. In most cases, those given an Unspecified Anxiety Disorder diagnosis had a mix of specific phobia,

TABLE 2. Best-Estimate Lifetime Psychiatric Diagnoses in Wolfram Syndrome Participants.

Best Estimate Diagnoses	*Children Age 6-12 yrs (N=12)*	*Adolescents Age 13-17 yrs (N=11)*	*Adults 18-30 yrs (N=16)*	*Total 6-30 yrs (N=39)*
Any Neurodevelopmental or Disruptive Behavior Disorder, n (%)	6 (50)	3 (27)	3 (19)	12 (31)
ADHD-full criteria, n (%)	3 (25)	1 (9)	1 (6)	5 (13)
ADHD-unspecified, n (%)	1 (8)	0 (0)	2 (13)	3 (8)
ADHD-any, n (%)	4 (33)	1 (9)	3 (19)	8 (21)
Oppositional-Defiant Disorder, n (%)	4 (33)	2 (18)	1 (6)	7 (18)
Conduct Disorder, n (%)	0 (0)	1 (9)	0 (0)	1 (3)
Autism Spectrum Disorder, n (%)	1 (8)	1 (9)	0 (0)	2 (5)
Tourette Syndrome, n (%)	1 (8)	0 (0)	0 (0)	1 (3)
NDD-Unspecified, n (%)	0 (0)	1 (9)	0 (0)	1 (3)
Any Anxiety Disorder, n (%)	11 (92)	9 (82)	10 (63)	30 (77)
Generalized Anxiety Disorder, n (%)	1 (8)	1 (9)	3 (19)	5 (13)
Social Anxiety Disorder, n (%)	0 (0)	0 (0)	1 (6)	1 (3)
Separation Anxiety Disorder, n (%)	1 (8)	2 (18)	0 (0)	3 (8)
Specific Phobia, n (%)	1 (8)	1 (9)	1 (6)	3 (8)
Unspecified Anxiety Disorder, n (%)	9 (75)	5 (45)	6 (38)	20 (51)
Any Obsessive-Compulsive Spectrum Disorder, n (%)	4 (33)	4 (36)	4 (25)	12 (31)
Obsessive-Compulsive Disorder, n (%)	0 (0)	0 (0)	2 (13)	2 (5)
Excoriation Disorder, n (%)	4 (33)	3 (27)	2 (13)	9 (23)
Unspecified Obsessive-Compulsive Disorder, n (%)	0 (0)	1 (9)	0 (0)	1 (3)
Any Mood Disorder, n (%)	3 (25)	4 (36)	6 (38)	13 (33)
Major Depressive Disorder, n (%)	0 (0)	0 (0)	3 (19)	3 (8)
Persistent Depressive Disorder, n (%)	0 (0)	1 (9)	0 (0)	(3)
Disruptive Mood Dysregulation Disorder, n (%)	1 (8)	1 (9)	0 (0)	(5)
Unspecified Depressive Disorder, n (%)	2 (17)	2 (18)	2 (13)	6 (15)
Unspecified Bipolar Disorder, n (%)	0 (0)	0 (0)	1 (6)	1 (3)
Any Sleep-Wake Disorder, n (%)	2 (17)	3 (27)	7 (44)	12 (31)
Hypersomnolence Disorder, n (%)	1 (8)	3 (27)	6 (38)	10 (26)
Sleep Apnea, reported diagnosis based on past sleep study, n (%)	1 (8)	0 (0)	1 (6)	2 (5)
Restless Legs Syndrome/Periodic Limb Movements of Sleep, based on reported symptoms and past sleep study, n (%)	1 (8)	0 (0)	0 (0)	1 (3)
Unspecified Sleep-Wake Disorder, n (%)	0 (0)	0 (0)	1 (6)	1 (3)
Hallucination-like Experiences, n (%)	6 (50)	3 (27)	6 (38)	15 (38)
Unspecified Psychotic Disorder, n (%)	1 (8)	0 (0)	0 (0)	1 (3)
Unspecified Eating Disorder, n (%)	1 (8)	0 (0)	0 (0)	1 (3)
Any Trauma and Stressor Related Disorder, n (%)	1 (8)	1 (9)	3 (19)	5 (13)

ADHD = Attention-Deficit/Hyperactivity Disorder, NDD = neurodevelopmental disorder. Broad diagnostic categories include the indented diagnoses listed in the rows immediately below.

separation anxiety, and/or generalized anxiety symptoms that were somewhat bothersome (associated with significant distress, avoidance, and/or impairment), but the individual did not seem to meet full criteria for a specific anxiety disorder diagnosis, often due to a subthreshold number of symptoms. Separation Anxiety Disorder was diagnosed most often in adolescents (age 13-17) and Generalized Anxiety Disorder was seen most often in young adults (age 18-30). Overall, 77% percent of Wolfram Syndrome participants had at least one lifetime anxiety disorder.

Although lifetime mood disorders were common (33%), these were generally more episodic and less persistent than anxiety disorders. Thirteen percent of Wolfram Syndrome participants had lifetime history of a trauma- and stressor-related disorder (such as Posttraumatic Stress Disorder or Adjustment Disorder).

Nearly a third of Wolfram Syndrome participants were given a best-estimate lifetime diagnosis of at least one sleep-wake disorder. Ten Wolfram Syndrome participants were given a diagnosis of Hypersomnolence Disorder by the study psychiatrist. Some of these participants might qualify for a more specific sleep-wake disorder if more detailed assessment including polysomnography had been completed and considered in making the diagnosis. A best-estimate diagnosis of Sleep Apnea, Restless Legs Syndrome, or Periodic Limb Movements of Sleep was assigned only if there were symptoms plus reported history of a sleep study confirming the diagnosis. Some individuals reported sleep difficulties due to nocturia (related to diabetes mellitus, diabetes insipidus, and/or bladder problems) or checking glucose levels during the night. If this seemed to be the only reason for sleep disturbance, a sleep-wake disorder diagnosis was not assigned. As part of our 2015 and 2016 clinics, a subset of Wolfram Syndrome participants were evaluated overnight using actigraphy plus a type III ambulatory sleep study device. Five of 17 adults (29%) and all of four children age 12 or younger met criteria for Obstructive Sleep Apnea (50), suggesting Sleep Apnea may contribute to hypersomnolence in multiple participants.

The most common CASI-5 symptom-count-based diagnosis (supplemental table S2) in the Wolfram Syndrome group was Specific Phobia (present in 70%), followed by Obsessions (64%). For these particular diagnoses, CASI-5 requires endorsement of only one item, at a frequency of at least "sometimes", so it is easy to meet the CASI-5 symptom count criterion. Of those who had CASI-5 Specific Phobia, all but two had at least one additional CASI-5 diagnosis. Of those with CASI-5 obsessions, all had at least one additional CASI-5 diagnosis. All Wolfram Syndrome participants with CASI-5 motor tics, vocal tics, or compulsions also had obsessions based on the CASI-5. Of the eight Wolfram Syndrome participants with CASI-5 motor and/or vocal tics, five individuals (63%) also had at least one additional neurodevelopmental or disruptive behavior disorder, most commonly ADHD and/or Oppositional Defiant Disorder (ODD).

To assess whether rates of anxiety and obsessive-compulsive spectrum disorders might be higher than expected in the general population, we considered the results of epidemiological studies. The National Comorbidity Survey Replication–Adolescent Supplement (NCS-A), found a 32% lifetime prevalence of anxiety disorders in adolescents age 13-18 (53), which is lower than the frequency of best estimate lifetime anxiety disorder diagnoses we found in our Wolfram Syndrome participants, whether we look at the entire group (77% lifetime prevalence) or at children, adolescents, or adults separately. In a prospective longitudinal study of an unselected birth cohort in Dunedin, the prevalence of Obsessive-Compulsive Disorder (OCD) was 2% at age 26 years (54), which is substantially lower than the 13% lifetime OCD prevalence in our Wolfram Syndrome young adult group.

For some CASI-5 diagnoses, normative data is available in manuals regarding the CSI-4 or ASI-4, from which the CASI-5 was derived (51-52). These manuals include data on a sample of 551 children (age 5-12 years, 49% male) who were recruited through pediatricians and elementary schools (51), and a sample of 761 adolescents (age 12-18, 49% male) recruited from middle and high schools (52). Students receiving special education were excluded from these samples, which may have reduced the frequency of some diagnoses compared to the frequencies in the general population.

In these normative samples, 7% of children and 5% of adolescents met criteria for some form of ADHD. These frequencies are lower than the 21% frequency of CASI-5 ADHD in our Wolfram Syndrome group.

CASI-5 Specific Phobia is also common in the normative samples (28% of children, 14% of adolescents), but this is well below the 70% of Wolfram Syndrome participants with CASI-5 Specific Phobia. Ten percent of adolescents in the normative sample had CASI-5 Panic Disorder, compared to 45% of our Wolfram Syndrome sample (normative data on this disorder are not available for elementary age children). CASI-5 Posttraumatic Stress Disorder (PTSD) was present in one third of Wolfram Syndrome participants, while in the normative samples it was present in 16% of children and 13% of adolescents. In the normative samples,

20% of children and 9% of adolescents had CASI-5 Obsessions, while 5% of each age group had CASI-5 Compulsions. Our Wolfram Syndrome group had higher rates of these disorders (64% had Obsessions, 24% had Compulsions). It is also useful to consider results of the Dunedin study, in which the prevalence of any obsession or compulsion (assessed by a different method) was 8% at age 11 and 21% at age 26 (54). This is lower than the 64% of our Wolfram Syndrome group who had CASI-5 Obsessions and/or Compulsions.

Twenty seven percent of Wolfram Syndrome participants engaged in skin picking at least "often" based on parent-report CASI-5. Twenty three percent of Wolfram Syndrome participants met DSM-5 criteria for a lifetime best estimate diagnosis of Excoriation (skin picking) Disorder, which is a newly defined diagnosis in DSM-5. In a non-clinical community sample of 354 adults (55), 63% endorsed some type of skin picking behavior, and 5% reported clinical levels of this behavior along with distress/impact. A separate study of 4335 adult college students found 24% had subclinical skin picking and 6% met criteria for Excoriation Disorder (56). The frequency of skin-picking in our Wolfram Syndrome group is higher. Five out of nine Wolfram Syndrome participants with CASI-5 skin picking also had CASI-5 obsessions (with or without compulsions), and two of these also had CASI-5 motor tics. All Wolfram Syndrome participants with CASI-5 tics or compulsions also had obsessions, suggesting that obsessions, compulsions, tics, and skin-picking are closely related symptoms in Wolfram Syndrome. Consistent with this observation, a study of 811 children, adolescents, and adults with Tourette Syndrome (57) found 13% had DSM-5 Excoriation Disorder, and the presence of Excoriation Disorder was associated with OCD, ADHD, and motor tic severity.

The majority of Wolfram Syndrome participants (51%) reported history of taking at least one psychoactive medication (supplemental table S3). Use of medication for anxiety or depression was particularly common. One third of Wolfram Syndrome participants (n=13) took a selective serotonin re-uptake inhibitor (SSRI) at some point in time, and 23% (n=9) were continuing to take an SSRI at their most recent clinic visit. Nine patients had taken sertraline, three had taken fluoxetine, and six had taken citalopram. Five patients had taken both sertraline and another SSRI (the majority of these reported better response and/or less side effects with citalopram or fluoxetine compared to sertraline). In most cases, the sertraline was taken prior to the other SSRI. Most patients who tried sertraline stopped this drug due to ineffectiveness or side effects, but the majority of those who took fluoxetine or citalopram reported benefits and continued the medication. 78% of sertraline trials were stopped due to ineffectiveness and/or adverse effects, but only 22% of the other SSRI trials were stopped.

Discussion

The current study is one of the first to report details of psychiatric diagnoses and treatment history in a moderately sized group of patients with genetically confirmed Wolfram Syndrome. Anxiety and obsessive-compulsive spectrum disorders were particularly common in the Wolfram Syndrome group, and—as expected—psychiatric symptoms were generally responsive to standard therapies. Although we found some evidence of elevated psychiatric risk in Wolfram Syndrome, the most common overall diagnostic category in our Wolfram Syndrome participants was anxiety disorders, which are also common in the general population. It is unclear whether these psychiatric manifestations are secondary to the stress of having a chronic medical illness, a direct effect of having *WFS1* pathogenic variants, or a combination of the two. The frequency of severe psychiatric illness does not seem as high as suggested in some early reports.

It is useful to compare the current findings to Swift, Sadler, and Swift's chart review of 68 Wolfram Syndrome patients (21). In this earlier study, 60% of Wolfram Syndrome patients had "episodes of severe depression, psychosis, or organic brain syndrome, as well as impulsive verbal and physical aggression", and these symptoms were described as "very severe" in 25%. Importantly, Sixteen percent had attempted suicide. As illustrated in Figure 1, we found that 62% of Wolfram Syndrome participants had a moderate or severe lifetime psychiatric severity score (including 13% in the severe range). Although the methods differed, both studies are consistent in estimating about 60% of Wolfram Syndrome patients have substantial psychiatric manifestations. Importantly, the older chart review study relied upon symptom-based Wolfram Syndrome diagnoses since the genetic cause was unknown at the time. Our study instead required a genetically confirmed diagnosis and allowed inclusion of early/milder cases with a lower number of characteristic Wolfram Syndrome features at study entry. These differences may have contributed to lower average severity in our study. The earlier chart review found a higher proportion of patients with severe mental illness, including some individuals with severe mood disorders, psychotic symptoms, psychiatric hospitalizations, and/or suicidality. Although a few individuals in our own study reported they had been diagnosed with Bipolar Disorder, none of them seemed to clearly meet criteria for Bipolar I based on interviews by our study psychiatrist (it was not clear whether any of them

ever had a full manic episode). Although a high proportion reported psychotic-like symptoms, these generally consisted of non-psychotic auditory and/or visual hallucination-like perceptual disturbances with intact insight, which seemed perhaps related to vision and hearing deficits, and in some cases may have been fleeting symptoms related to anxiety or a Trauma- and Stressor-Related Disorder. If these other potential causes were not considered in earlier studies, some misdiagnoses of major mood or psychotic disorders may have been made. Overall, we found little evidence for increased risk of Bipolar Disorder or Schizophrenia in Wolfram Syndrome, though it would be necessary to follow a large group of individuals into later adulthood to confirm this. As far as suicidality, none of the participants were actively suicidal at the time of assessment, but at least two had a history of suicidal thoughts.

Considering frequent reports of skin-picking and other obsessive-compulsive spectrum disorders among our Wolfram Syndrome participants, it is interesting that the antioxidant N-acetyl-cysteine has been shown to reduce skin-picking in adults (58), and has also been shown to reverse abnormalities in embryonic fibroblast cells from a *Cisd2* knockout mouse model of Wolfram Syndrome (59). Also, given the evidence of cerebellar degeneration in Wolfram syndrome (17), it is interesting that structural and functional cerebellar differences have been described in Excoriation Disorder (60).

This study has some limitations. There is a possibility of selection against more severe cases based on ability to travel. When older individuals and their parents are interviewed, the lifetime prevalence of childhood limited disorders may be underestimated because of difficulty recalling symptoms that occurred earlier in life. This may be one reason why younger individuals appear to have higher lifetime prevalence of disorders that are sometimes childhood-limited, such as ADHD and Oppositional Defiant Disorder. Many individuals (especially in the youngest age group) were given a best-estimate diagnosis of unspecified anxiety disorder due to sub-threshold symptoms for a specific anxiety disorder or difficulty obtaining enough information to be certain about a more specific diagnosis. The CASI-5 has not been validated for adults, but should still provide reasonable estimates of whether people of any age meet DSM-5 symptom criteria for several included diagnoses. Although epidemiological studies and published normative data for earlier versions of the CASI-5 instrument suggest increased risk for anxiety and obsessive-compulsive spectrum disorders in Wolfram Syndrome, we do not know to what degree the observed psychiatric symptoms and diagnoses result from direct effects of the genetic disorder versus other factors, such as stress resulting from having a severe, chronic illness, including progressive visual loss.

Clinical Significance

The current study has some clinical implications for the monitoring and treatment of individuals with Wolfram Syndrome. As expected, our Wolfram Syndrome clinic participants reported benefits from standard pharmacologic and psychotherapeutic interventions, so Wolfram Syndrome patients can be reassured that these symptoms are treatable.

Anxiety, depression, and obsessive-compulsive spectrum disorders appear to be particularly common in Wolfram Syndrome. Anxiety and obsessive-compulsive symptoms may be more persistent (though the exact diagnosis may change over the course of development), while depression may occur in episodes. In some cases, social anxiety and certain phobias (crowds, heights) seemed related to sensory deficits in Wolfram Syndrome. It is understandable that hearing and vision problems could make communication with others more difficult and thus increase anxiety in social situations or crowded places. Difficulties with visual perception or balance could contribute to fears of falling from high places. Interestingly, separation anxiety disorder was particularly common in the adolescent age range. In some cases, this seemed related to a youth's dependence on parents to help them manage their medical illness. Some individuals with Wolfram Syndrome had recently become more independent in monitoring their own blood glucose and administering insulin at this age but had concerns about whether anyone would be able to help with any problems if a parent was not with them. Anyone diagnosed with a progressively worsening medical illness might naturally have some anxiety about their future, but the reported types of anxiety/worry were not limited to concerns about health. Of note, some Wolfram Syndrome participants reported an increase in anxiety or other psychiatric symptoms when their sodium level was low, so it may be that acute medical issues common in Wolfram Syndrome can exacerbate psychiatric symptoms.

Although individuals with Wolfram syndrome generally seem to respond as expected to psychopharmacological therapies, there is a possibility they may respond better to some antidepressants than others due to mechanisms influenced by their genetic disorder. Animal studies can generate hypotheses regarding which treatments might be particularly effective in Wolfram syndrome. In a study of *Wfs1*-deficient and wildtype mice (14), ketamine (NMDA antagonist), escitalopram (SSRI), and amitriptyline (SNRI) all showed a stronger antidepressant effect in *Wfs1*-deficient mice than in

wildtype mice, while desipramine (SNRI) had a similar antidepressant effect for each genotype, and bupropion (dopamine and norepinephrine reuptake inhibitor) did not show an antidepressant effect for either genotype. Also, the two SNRIs (amitriptyline and desipramine) contributed to glucose elevation, escitalopram and bupropion had no effect on glucose levels, and ketamine improved glucose metabolism in homozygous *Wfs1*-deficient mice. Based on these results, the authors concluded that SSRIs might be the drug of choice for treatment of depression symptoms in patients with diabetes (14), though studies in humans would be important to confirm this.

Recent studies suggest sigma1 receptor (S1R) activation, which can reduce the ER stress response, may be an important mechanism of some (but not all) antidepressants (66-67). Given the dysregulation of the ER stress response that is present in Wolfram syndrome, it would be useful to know whether drugs with varying action on the sigma-1 receptor produce varying benefits in people with Wolfram syndrome. Of several antidepressants tested, fluvoxamine had the highest affinity for S1R, followed by sertraline, fluoxetine, escitalopram, citalopram, paroxetine, and duloxetine (66). Venlafaxine, milnacipran, and mirtazapine showed very weak affinity for the S1R. Fluvoxamine, fluoxetine, escitalopram, and mirtazapine potentiated neurite outgrowth induced by Nerve Growth Factor (NGF). This effect was blocked by a S1R antagonist (NE-100), and in some cases by sertraline, suggesting sertraline is a S1R antagonist (66). Since sertraline is a S1R antagonist, it may tend to increase the ER stress response rather than reduce it. There is also evidence that sertraline can induce ER stress in hepatic cells (69). In our study, there was a hint that Wolfram Syndrome patients might respond less well to sertraline than to other SSRIs, but this is uncertain. Sertraline was most commonly used and was often the medication tried first, so might be more likely to be discontinued for this reason. Randomized clinical trials are needed to determine whether individuals with Wolfram syndrome show differential response to various antidepressants.

As mentioned previously, we did not see much evidence of true psychotic symptoms or full manic episodes, but some Wolfram Syndrome patients did report auditory and/or visual hallucination-like perceptual disturbances. In such cases, it may be helpful to explain that if the brain is receiving less and less sensory input (due to progressive vision and hearing loss), it may misinterpret these inputs or even create artificial visual and auditory perceptions. If the affected individual is not disturbed by these experiences, has insight that these are produced by the brain, and shows no delusional thought content, then antipsychotic medication is generally not recommended, especially considering the risk for increased appetite, weight gain, and metabolic side effects associated with these drugs. Most individuals with Wolfram syndrome develop insulin dependent diabetes at a young age, but it may still be possible for antipsychotics to worsen glucose control in some individuals. Antipsychotics can be considered if there is clear delusional thinking (fixed, false beliefs) or severe mood instability (manic episodes or severe irritability, agitation, or aggression), or if perceptual disturbances are very distressing or impairing. If hallucinations suddenly worsen or are associated with confusion, memory problems, waxing/waning consciousness, or worsening neurological signs, the possibility of delirium due to a metabolic imbalance or other acute medical condition should be investigated. If hallucinations occur in specific situations or after a stressful or traumatic event, anxiety and post-traumatic reactions should be considered as possible contributing factors. As with all patients presenting with psychotic symptoms, effects of substance use should also be considered, but very few of our study participants reported history consistent with a possible substance use disorder.

In case of hypersomnolence, snoring, restless legs symptoms, excessive movement during sleep, or other sleep difficulties, evaluation by a sleep specialist (including polysomnogram) may be important to determine whether a specific sleep-wake disorder is present. Although several Wolfram Syndrome participants reported hypersomnolence, contributing factors were not always clear. Although we were able to obtain ambulatory sleep study data on a subset of participants during the 2015-2016 clinics (50), few individuals reported having a formal sleep study outside of this. Since sleep-related problems contribute to poor quality of life in Wolfram Syndrome (49), identifying and treating sleep disorders may be very important.

For individuals with Wolfram Syndrome, it is also important to evaluate and treat any acute medical issues that could contribute to psychiatric symptoms, such as unstable glucose or sodium levels, abnormal thyroid function, or vitamin D deficiency.

In conclusion, it appears that individuals with Wolfram Syndrome are at increased risk for psychiatric disorders, especially anxiety and obsessive-compulsive spectrum disorders, which are also fairly common in the general population. Given earlier reports of high risk for severe mental illness and suicide attempts in Wolfram Syndrome, it is important to monitor psychiatric status in these individuals and provide appropriate treatment. The current results are somewhat reassuring, since we did not see as high rates of severe mental illness as

reported in a previous study, and because patients generally reported good response to treatment. Since the ER stress response has been implicated in psychiatric disorders more generally (40-45), further study of psychiatric manifestations in Wolfram Syndrome, including studies of treatment, developmental course, brain imaging, and molecular/cellular mechanisms, may have broad impact on the field of psychiatry.

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Dr. Reiersen is an inventor for a patent application on Methods of Treating COVID-19. All other authors have no conflicts of interest to disclose.

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