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Balance impairment in individuals with Wolfram syndrome

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ABSTRACT

Aim: Wolfram syndrome (WFS), a rare neurodegenerative disorder, is characterized by early onset insulin-dependent diabetes mellitus, optic atrophy, deafness, diabetes insipidus, and neurological abnormalities. Although previously unreported, we hypothesized that neurological complications may be detectable in relatively early stages of the disease. As the cerebellum and brainstem seem particularly vulnerable in WFS, we focused on balance functions critically dependent on these regions. The primary goal of this investigation was to compare balance in young individuals with WFS, in relatively early stages of the disease, to an age-matched cohort using a clinically applicable test.
Method: Balance was assessed via the mini-BESTest in 13 children, adolescents and young adults with WFS and 30 typically developing age-matched individuals.
Results: A significant difference was observed between groups in balance as well as in three of four subcomponents of the mini-BESTest and in two timed tasks related to balance. Mini-BESTest scores were correlated with age among typically developing individuals. In the WFS group, mini-BESTest scores were related to overall motor dysfunction, but not age.
Interpretation: Impairments in balance in WFS may occur earlier in the disease process than previously recognized and appear to be related to overall neurological progression rather than chronological age. Recognizing balance impairments and understanding which balance systems contribute to balance deficits in those with WFS may allow for development of effective patient-centered treatment paradigms.

1. Introduction

Wolfram syndrome (WFS) is an early onset, autosomal recessive, neurodegenerative disorder with a reported prevalence between 1 in 100,000 [1] and 1 in 770,000 [2]. Typically, the first diagnosed symptom of WFS is diabetes mellitus (median age at diagnosis = 6 years) followed by optic atrophy (median age of diagnosis between 9 and 13 years) [3–7]. The combination of these two manifestations was originally described in four siblings by Wolfram and Wagener in 1938 [8] and is still considered to be the primary feature set of WFS. Since the original report, renal tract abnormalities, deafness, diabetes insipidus, gonadal disorders, and a range of psychological and neurological complications have also been frequently reported (for review see [9] and [10]). Affected individuals have a median life expectancy of 30 years, with early mortality credited to neurological disorders, urological abnormalities and infection [4].

There is currently no cure for WFS. Differential diagnosis and treatment are difficult due to the variable presentation of symptoms [9]. Genetic testing for the *WFS1* gene is available once WFS is suspected, but no current therapeutic genetic intervention is available. Therefore, identifying the symptoms that can be addressed via patient-centered treatment paradigms is vital for

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maintaining the highest possible quality of life for individuals with WFS.

Due to the underlying neurologic condition, maintaining functional motor performance or delaying motor decline should be a primary focus of clinical intervention for individuals with WFS. To date, neurological complications related to motor function have been incompletely studied in the WFS population. Ataxia is the most commonly reported motor manifestation [2,7,11], but has not been quantitatively evaluated. Additionally, evidence from MRI studies suggests the presence of severe atrophy in the cerebellum and brainstem of some individuals with WFS [7,12,13]. As the cerebellum [14–16] and brainstem [17] play important roles in balance, we suggest it would be essential to assess balance in individuals with WFS.

The purpose of this study was to determine if balance is impaired in young individuals with WFS as compared to typically developing, age-matched controls. We hypothesized that quantifiable deficits in balance may be present in the WFS population as compared to typically developing, age-matched individuals and that these deficits may be present much earlier in life than previously reported [2,7]. Furthermore, we sought to measure balance in a manner that is both time-sensitive and clinically relevant, but still provides insight into the nature of the deficit.

A clear determination and quantification of an easily tested metric could offer insight into disease progression, offer additional diagnostic support, and help to focus rehabilitative methods for those individuals currently affected by this disease.

2. Methods

2.1. Participants

Thirteen individuals diagnosed with Wolfram syndrome (8 female, mean age 15.5 ± 6.3 years, min 6.4 years, max 25.8 years) and 29 neurologically healthy young individuals (16 female, mean age 13.4 ± 6.1 years, min 5.6 years, max 28.46 years) completed all phases of the experiment. One typically developing individual (age 5.6 years) attempted to participate but was removed from data analysis as he was not able to complete all tasks independently. Participants were recruited via the Washington University WFS Registry (http://wolframsyndrome.dom.wustl.edu/medical-research/Wolfram-Syndrome-Home.aspx). This investigation was one part of a larger longitudinal study on individuals with WFS. Data were collected as part of an annual 3-day 'Wolfram Syndrome Research Clinic' conducted at the Washington University School of Medicine in St. Louis, MO. All individuals with WFS met the inclusion criteria of diabetes mellitus and optic atrophy before 18 years of age and/or genetic confirmation of *WFS1* mutation. Individuals were excluded if they were naïve to the diagnosis of WFS or if complications of the disease made travel or participation difficult for the individual or their family. Demographic data for individuals with WFS is provided in Table 1. Legal guardians provided informed written consent for all participants under age 18. All participants provided either informed written consent or assent prior to participation in accord with the procedures approved by the Human Research Protection Office of the Washington University School of Medicine.

2.2. Clinical assessment

Height, weight, and year in school data were collected from all participants on the day of testing. The 'Gaits and Stations' subsection of the Physical and Neurological Examination for Subtle Signs (PANESS) [18] was used to assess gait and motor function in all typically developing individuals and 12 of the 13 individuals with WFS (one subject was unable to participate in the second day of testing due to diabetic complications). The PANESS is a validated age-normalized assessment tool which grossly measures coordination, gait, balance, timed movements, lateral preference, motor overflow, dysrhythmia, and motor persistence [18–20]. The gaits and stations subsection of the PANESS consists of eleven tasks: walking on (1) heels, (2) toes and (3) the sides of the feet; (4) forward tandem gait; (5) backward tandem gait; (6) tandem standing; (7) narrow stance with eyes closed, and arms and fingers outstretched; (8) finger to nose test; (9) extending the tongue with the eyes closed; (10) single leg standing and (11) single leg hopping. Each task was observed and scored by a trained rater. For each task the rater scored both accuracy/ability to complete each task as well as observed for neurological soft signs such as motor overflow, awkward posturing, tics, dysrhythmia, choreiform movement or impersistence. Tasks were coded using PANESS coding instructions which provide age appropriate scoring criteria. For example, errors during backward tandem walking are coded as 0 for individuals less than 10 years of age regardless of the number of errors made; however, if the individual is 10 or older the task is coded as 1 if the individual makes 1–2 errors and as 2 if the individuals makes 3 or more errors. All scores were then compared to a sample of typically developing individuals [22] to establish a *z*-score for each individual on the Gaits and Stations subsection. Currently, no assessment tool has been established to rate overall disease severity in Wolfram syndrome, thus the PANESS served as a surrogate measure of overall motor involvement and severity. No typically developing participants were excluded from the study based on PANESS score.

2.3. Balance assessment

The mini-Balance Evaluation Systems Test (mini-BESTest) was used to assess postural stability for all individuals. The mini-BESTest is a 14-item clinical assessment battery which examines four components of balance: anticipatory transitions, postural responses, sensory orientation and dynamic gait [21]. Administration of the test requires subjectively rating task performance on a three-level scale (0 = severe, 1 = moderate, 2 = normal). An individual task is scored as 0 if the individual is unable to complete the task as instructed or requires assistance. The mini-BESTest was administered by a physical therapist and has a maximum score of 32, with lower scores indicating increased impairment of balance.

The mini-BESTest provides an overall score of balance as well as subcomponent scores of anticipatory transitions, postural responses, sensory orientation, and dynamic gait, thus providing a measure of not only gross balance deficit, but also of the specific nature of the balance impairment. Franchignoni et al. [21] selected the four subcomponent measures of the mini-BESTest from the six balance components which comprised the original Balance Evaluation Systems Test (BESTest) [25] to

Table 1
Clinical and demographic data for individuals with Wolfram syndrome. (A negative *z*-score indicates greater impairment and more overall motor involvement.)

Gender	Age	Year in school	Height (m)	Mass (kg)	PANESS Gait and Station reverse *z*[a]	Clinical features (years)
Female	6.4	1	1.13	19.70	0.22	WFS(5), DM(4), DI([b]), OA(5), HL(no)
Male	8.3	3	1.24	24.90	−0.27	WFS(3), DM(3), DI(7), OA(N/A), HL(no)
Male	9.3	4	1.26	24.10	−1.33	WFS(7), DM(7), DI([b]), OA(6), HL(no)
Female	11.9	7	1.64	43.70	0.38	WFS(9), DM(6), DI(7), OA(9), HL(no)
Female	12.6	7	1.38	40.50	−1.61	WFS(8), DM(6), DI(11), OA(7), HL(yes)
Female	12.6	6	1.45	39.30	0.00	WFS(8), DM(7), DI(11), OA(8), HL(no)
Female	14.7	9	1.54	45.20	−9.47	WFS(13), DM(3.9), DI(N/A), OA(13), HL(yes)
Male	15.4	10	1.59	46.60	0.58	WFS(11), DM(10), DI(14), OA(11), HL(no)
Female	17.1	12	1.58	87.90	−5.47	WFS(16), DM(5), DI(N/A), OA(16), HL(no)
Male	18.9	13	1.72	60.80	−1.08	WFS(7), DM(5), DI(7), OA(7), HL(yes)
Male	23.9	17	1.79	87.10	−3.58	WFS(17), DM(7), DI(17), OA(7), HL(yes)
Female	24.7	14	1.53	73.80	−14.80	WFS(12), DM(2), DI(12), OA(5), HL(yes)
Female	25.8	17	1.64	58.10	−2.13	WFS(15), DM(13), DI(19), OA(13), HL(no)
WFS Mean (SD)	15.5 (6.3)	9.2 (5.2)	1.5 (0.20)	50.1 (22.5)	−2.97 (4.54)	
Typically developing Mean (SD)	13.4 (6.1)	7.8 (6.0)	1.5 (0.19)	46.4 (18.1)	0.59 (0.68)	*N* = 29 16 females, 13 males

WFS, age of Wolfram syndrome diagnosis; DM, onset of diabetes mellitus; OA, onset of optic atrophy; DI, onset of diabetes insipidus; HL, presence of hearing loss.
[a] PANESS Gait and Station reverse *z*-scores represent the age normalized level of involvement for gait and motor function.
[b] Not formally diagnosed but on DDAVP (desmopressin tablet) for enuresis.