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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 ($p < 0.001$, $r_s = 0.59$) among typically developing individuals. In the WFS group, mini-BESTest scores were related to overall motor dysfunction, but not age.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest and all funding sources have been disclosed above.

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.

Keywords

Wolfram syndrome; balance; neurodevelopment; pediatric rehabilitation; clinical scale

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 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.

METHODS

Participants

Thirteen individuals diagnosed with Wolfram Syndrome (8 female, mean age 15.5 yrs $\pm$ 6.3 yrs, min 6.4 yrs, max 25.8 yrs) and 29 neurologically healthy young individuals (16 female, mean age 13.4 yrs $\pm$ 6.1 yrs, min 5.6 yrs, max 28.46 yrs) 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, Missouri. 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.

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.

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 allow for a more focused examination of balance that could be administered in 10–15 minutes. The 14 questions of the mini-BESTest are equally divided between the four subcomponent areas. The anticipatory transitions subcomponent uses tasks that require anticipatory, active movement of the individual's center of mass prior to transition from one posture to another [25]. The postural responses subcomponent focuses on postural changes in response to perturbations [25]. Sensory orientation testing examines changes in balance due to altered visual or somatosensory information or processing. Finally, the dynamic gait subcomponent examines balance during gait tasks of varying complexity [25].

For the purposes of this paper we also report the performance times on three timed tasks that are rated as items on the mini-BESTest. The first timed task is the *Timed Get Up and Go* (TUG) which requires the participant to transition from a seated position to a standing position, walk three meters, turn, walk back to the chair and return to the seated position. Timing begins when the “go” cue is given and ends when the participant is seated again. The second timed task is the *Cognitive Get Up & Go With Dual Task (DT-TUG)*. This task adds a mathematical operation to the TUG. Traditionally participants are asked to perform a subtraction task, however, due to the ages and educational levels of the individuals, participants were instead asked to state random numbers while performing the task. This modification was deemed necessary as the youngest participants were not able to complete a subtraction task without a writing implement and paper, however all individuals were able to state numbers aloud without pause. Furthermore, the use of random number generation as the dual task for this item has precedent as this was an option for the DT-TUG item in the original full BESTest [25]. Prior to the initiation cue, participants were asked to begin stating numbers. The “go” signal was given after the participant had stated at least three non-sequential numbers. The third timed task is walking along a 6.1m path and stepping over an obstacle (SOO). The obstacle was 22.9cm tall and was placed in the middle of the path.

Data Analysis

Z-statistic scores were calculated for the Gross Motor subsection scores of the PANESS using previously published normative data [22]. Reverse z-scores were then calculated by multiplying all values by negative one. This conversion was done to allow for increased clarity as positive reverse z-scores indicate the individual scored higher than the normative group and negative z-scores indicate the individuals scored lower than the normative group.

Independent sample, Mann-Whitney U Tests were used to compare groups as the data were not normally distributed. Within group analysis was completed using a simple linear regression analysis. **Additionally, a related samples Wilcoxon Signed Rank test was used to test for differences between the TUG and DT-TUG times within each group.** P-values and Spearman rho values are reported for all comparisons. OriginPro v8.0 (OriginLab Corporation, Northampton, MA) and IBM© SPSS© Statistics Version 19 (IBM

Corporation, Armonk, New York) were used for statistical processing. An a priori level of $p < 0.05$ was set for determining statistical significance. All measures are reported as mean $\pm$ standard deviation, unless otherwise noted.

RESULTS

Clinical Assessment

Demographic data for both groups are shown in Table 1. WFS and age-matched controls did not differ by age ($z = 1.08$, $p = 0.28$), height ($z = -0.59$, $p = 0.56$), weight ($z = 0.37$, $p = 0.71$), or year in school ($z = 1.06$, $p = 0.29$). A significant difference was present between groups for the raw score on the Gross Motor subsection score of the PANESS, with the WFS group showing a significantly greater level of motor impairment ($z = 3.72$, $p = 0.001$).

Balance Assessment

Total mini-BESTest scores were higher (less impaired) for the typically developing group ($z = -3.84$, $p = 0.001$). When individual scores were analyzed in the context of their respective balance subcomponent, the typically developing group scored significantly better in the anticipatory transitions ($z = -4.48$, $p = 0.001$), postural responses ($z = -2.85$, $p = 0.004$) and sensory orientation ($z = -2.70$, $p = 0.007$) sections. The dynamic gait subcomponent did not differ statistically between groups ($z = -1.24$, $p = 0.22$) (Figure 1). The WFS group required more time to complete the TUG ($z = 3.25$, $p = 0.001$) and the SOO ($z = 4.1$, $p = 0.001$) but not the *DT-TUG* ($z = 0.88$, $p = 0.38$) (Figure 2).

Within Group

A main effect of gender on mini-BEST score was not present for either group (typically developing group, $p = 0.354$; WFS, $p = 0.490$). Mini-BESTest scores were positively correlated with age in the typically developing group ($r = 0.595$, $p = 0.001$), but did not significantly correlate to age in the WFS group ($r = -0.162$, $p = 0.307$) (Figure 3a). In contrast, mini-BESTest scores were positively correlated to PANESS Gaits and Stations subsection reverse Z scores in the WFS group ($r = 0.845$, $p = 0.001$), while no significant correlation was present between mini-BESTest and PANESS Gaits and Stations subsection reverse z scores for the typically developing group ($r = -0.016$, $p = 0.468$) (Figure 3b). That is, individuals with WFS who performed better on the mini-BESTest (better balance) also had better PANESS Gaits and Stations subsection reverse z-scores (less overall motor involvement).

A related samples Wilcoxon Signed Rank test was used to test for differences between the TUG and DT-TUG times within each group. A significant difference between tasks was found for both the typically developing group ($p = 0.001$) as well as for the WFS group ($p = 0.019$).

DISCUSSION

The primary aim of this study was to determine if balance is impaired in early WFS as compared to typically developing age-matched controls. Our findings indicate not only an overall difference in balance between individuals with WFS and typically developing age-matched individuals, but more specifically deficits in the anticipatory transitions, postural responses and sensory orientation subcomponents. Dynamic gait was not significantly impacted in the WFS group.

In this investigation, the mini-BESTest was used to assess balance as it can be administered in the clinic, requires less than fifteen minutes, does not necessitate expensive equipment

[21] and, as demonstrated here, can be used to assess children. In typically developing individuals, studies attempting to characterize “normal” developmental trends in balance have assessed postural sway on a force platform [23, 24]. While informative, these studies are laborious, expensive and require analysis beyond that which is easily done in a clinical setting.

In addition to the comparison of total and subcomponent scores from the mini-BESTest, the WFS group took more time to complete both the TUG and SOO, but not the DT-TUG. Our data do not allow for a clear explanation of why dynamic gait and DT-TUG are not affected at the level of the other components, however, one could speculate that learned compensatory strategies would confound these measures more than the others due to the complexity of dynamic gait and the DT-TUG. As individuals with WFS exhibit atypical balance at a very early stage of development (e.g. 6 years of age) but also continue to walk unassisted, compensatory strategies may be incorporated to maintain balance during gait. These compensatory strategies may confound less sensitive measures of complex balance tasks and may have contributed to the generalized description of “ataxia” provided in previous reports. It should be noted that the DT-TUG task could not be performed as described in the original description of the mini-BESTest [21]. Specifically the dual task was altered from a subtraction task to a random number naming task as per the original full BESTest [25]. This modification was made to allow for all participants to complete the same task. While a dual task paradigm has been shown to produce measureable decrements in young (5–6 yrs) and older (7–16 yrs) typically developing individuals, the typically developing group did not differ in age to the WFS group and thus it is unlikely the nature of the task influenced our findings.

As expected, balance in typically developing young individuals correlated with age, indicating a developmentally driven change in mini-BESTest scores. This correlation was not present in the WFS group; rather, mini-BESTest scores for the WFS group were related to overall motor involvement. To our knowledge, this study is the first to quantify this or any neurological deficit related to WFS. This finding supports the idea that balance deficits are present early in the disease process and relate to overall motor involvement of the individual with WFS, independent of age. This suggests that a younger individual with more severe WFS may have more significant balance deficits than an older individual with less advanced WFS, thus the level of impairment and possible intervention strategies cannot be generalized by age but rather require careful assessment of each affected individual.

Recently, increased attention has been given to neurologic complications and neuroanatomical abnormalities associated with WFS. In a retrospective clinical study of medical records and physician reports of 59 individuals with WFS, Chaussenot and colleagues [7] found that 31(53%) of the individuals reported neurological complications at a median age of 15 years. These symptoms included a wide range of clinically described manifestations such as cerebellar ataxia (14 of 31 individuals), peripheral neuropathy (12 of 31 individuals) and cognitive impairment (10 of 31 individuals). This is in contrast to a previous report that found reported onset of neurological symptoms in the late third or fourth decade of life [2]. However, neither study directly evaluated the patients, or used quantified, objective measures. In addition, many reports have cited the lack of relationship between neuroanatomical findings of brain abnormalities in the WFS population and clinical symptom presentation [7, 12, 27]. Here we report measureable differences in balance between typically developing individuals and individuals with WFS across a wide age range (6 to 25 years of age). The early presence of a measureable neurological deficit in our study may indicate that: 1) measures of balance impairment may provide a more sensitive metric of neurologic involvement than have been previously explored and 2) balance deficits may precede the onset of ataxia.

Future studies focused on quantifying the neurological complications of WFS, particularly in young individuals, are needed. As this investigation is the first to measure balance deficits in this population, future work focused on gait tasks and dynamic balance would be a logical progression. Quantification of gait and motor deficits would allow for clinical interventions to be developed and tested in this population. Additionally, longitudinal data are needed on progression of the neurological symptoms associated with WFS.

Currently, no cure has been found for WFS and no standard of care for treatment has been established. Unfortunately, specific treatment strategies are beyond the scope of this investigation as we are only now becoming aware of the early presentation of balance deficits. A multidisciplinary management approach is necessary given the vast number and variable severity of symptoms. Physical therapy may provide a useful venue to address impaired balance and may be able to use tests such as the mini-BESTest to hone a treatment strategy useful to the WFS population. Given the progressive nature of WFS, and the level of deficit present, the goal of any treatment plan may be to maintain the current level of balance function over a longer portion of the individual's lifespan. Future studies will be needed to examine the usefulness of such strategies.

A limitation of the current study is that individuals with WFS present with various individual symptoms that should be considered when investigating balance impairments. Of particular interest are the effects of any form of diabetes which may include peripheral neuropathy, visual impairments, or cochlear implants on an age-matched population. As proprioceptive, tactile, visual and vestibular sensation and perception are related to balance, these components warrant further investigation and could be explored in future work. Additionally, these data are focused on individuals early in the progression of WFS and do not address individuals at later chronological ages or individuals further along in the disease progression. Caution should be used in generalizing these findings to individuals beyond the age ranges and disease severity levels presented herein.

CONCLUSIONS

These findings suggest that individuals with WFS present with balance deficits compared to age-matched controls, when assessed with a quantitative, objective clinical tool (mini-BESTest). These impairments were evident earlier in the disease progression than previously recognized through clinical retrospective studies. Thus, clinicians with younger WFS patients should examine balance and design patient-centered treatment paradigms to address the needs of these individuals to maximize quality of life and overall motor function.

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APPENDIX I

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HIGHLIGHTS

1. Identifies, previously unreported, early neurological complications in Wolfram syndrome.
2. Individuals with WFS present with impaired balance.
3. Supports the MiniBESTest as a clinical measure of balance impairment.

Figure 1.

Frequency of mini-BESTest (A) and mini-BESTest Subcomponent scores (B–E) for typically developing (left) and WFS (right). (A) mini-BESTest total score; (B) anticipatory transitions (AT) subcomponent scores; (C) postural responses (PR) subcomponent scores; (D) sensory orientation (SO) subcomponent scores and (E) dynamic gait (DG) subcomponent, maximum 10. Individual with WFS scored significantly lower in the overall mini-BESTest and all subcomponents except dynamic gait.

Figure 2.

Timed balance tasks for the typically developing (grey) and WFS (white) groups. Times for the *step over an obstacle* (SOO) and *Timed Get Up and Go* (TUG) and subsections differed between groups ($\# = p < 0.001$). *Cognitive Get Up & Go With Dual Task* (DT-TUG) times did not differ between groups ($p = 0.38$). Within group, comparisons of TUG to DT-TUG showed within group differences at all levels ($\#\# = p < 0.05$).

Figure 3.

Mini-BEST total scores compared to (a) age and (b) PANESS Gaits and Stations reverse z-scores. A) A significant positive correlation between mini-BEST and age was present for typically developing individuals (triangles) but not individuals with WFS (squares). B) A significant positive correlation between mini-BEST and PANESS reverse z-scores was present for the WFS group, but not the typically developing individuals.

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 ¹	Clinical Features (yrs)
female	6.4	1	1.13	19.70	0.22	WFS(5), DM(4), DI(*), 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(*), 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

¹ PANESS Gait and Station reverse z scores represent the age normalized level of involvement for gait and motor function.

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.

* Not formally diagnosed but on DDAVP (desmopressin tablet) for enuresis