Letter to the Editors JOON

TITLE PAGE

TITLE: SELF-REPORTED POSTURAL SYMPTOMS PREDICT VESTIBULAR DYSFUNCTION AND FALLS IN PATIENTS WITH MULTI-SYSTEM IMPAIRMENT

Running title: Falls in patients with multi-sensory impairment

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INTRODUCTION

Postural control is regulated by a highly complex system of efferent and afferent pathways of the central nervous system. Interactions between the vestibular system, cerebellum, cerebral cortex and reticular formation are integrated with inputs from the exteroceptors, visual receptors and proprioceptors to maintain postural control . In many neurological disease states postural control may be compromised, particularly in those with sensory impairment [1].

Whilst sensory disturbances have been thoroughly investigated individually against postural dysfunction [2, 3], multisensory dysfunction and its effect on postural control is an area of active research. Mitochondrial diseases (MD) are a genetically heterogenous group of conditions, caused by mutations to either mitochondrial or nuclear-encoded DNA [4]. Large phenotypic variations are seen in people with MD, with presentations ranging from single organ involvement to multisystem disorders, which commonly give rise to multi-system impairment including ataxia, neuropathy, myopathy, and vestibular dysfunction [5-8], thus constituting a model of multi-system impairment. Positional sense information (proprioception) from golgi tendon organs and muscle spindles represent a sensory component of balance perception from within muscles, with myopathy also potentially compromising balance reactions. Understanding the relative contributions of these impairments to postural control and falls may have therapeutic implications, given the differences in physical therapy approaches across these impairments [16].

Here, we investigate the relative contributions of sensory impairment to postural control in patients with MD as a human model of multisensory dysfunction and explore how these impairments relate to falls risk.

METHODS

This was a single-centre, retrospective, observational study based on chart review of patients attending an out-patient Mitochondrial Disease clinic at the National Hospital for Neurology and Neurosurgery, between September 2020 and February 2021. The inclusion criteria of this study included adults (over the age of 16) with a confirmed genetic and/or clinicopathological diagnosis of MD. Patients were identified from a large clinical database of patients enrolled in an ongoing prospective study of audiovestibular function.

Demographic and clinical data was systematically collected for each patient from medical records. Details of the genetic and/or clinicopathological cause of MD was recorded. We specifically recorded the presence of ataxia, peripheral neuropathy, and myopathy, in addition to symptoms of dizziness and imbalance. In patients who had undergone objective vestibular investigation, the presence of confirmed vestibular dysfunction (VD) was recorded. Self-reported falls were also recorded.

- *Statistical Analysis*

Descriptive analyses were conducted on patient reported symptoms. Chi-square tests were used to assess the association between sensory impairment and dizziness, imbalance, and falls. A logistic regression model was utilised to identify odds ratios (and 95% confidence intervals) between clinical factors (sensory impairment and symptoms) and falls.

RESULTS

- *Clinical Data*

A total of 98 patients with a genetic and/or clinicopathologically confirmed diagnosis of MD met the inclusion criteria for this study. The subjects comprised 58 females and 40 males, with a mean age ± standard deviation of 46.7±16.6 years.

Neuropathy in 26/98, ataxia in 25/98, and myopathy in 23/98 patients. Of 98 patients in our cohort, 30 patients underwent vestibular investigations of whom 25 were diagnosed with vestibular dysfunction.

- *Sensory Impairment and Falls*

Of the patients who presented with ataxia, 13/25 patients reported that they had experienced falls. Similarly, 13/25 patients who presented with VD reported falls, versus 10/26 patients with neuropathy and 7/23 patients presenting with myopathy.

Using a logistic regression model, we found that imbalance, dizziness and ataxia significantly contribute to falls risk. Specifically, patients who reported imbalance are approximately 4.5-fold likely to fall [Odds Ratio (OR) = 4.57; 95% CI (1.53, 13.64); p=0.008], and patients experiencing dizziness are approximately 9-fold more likely to fall [OR = 8.92, 95% CI (2.28, 34.84); p=0.002]. Similarly, patients with ataxia are approximately 7.5-fold likely to fall [OR = 7.63, 95% CI (2.25, 25.82); p=0.001; Figure 1A]. Other clinical and demographic variables were not seen to influence falls in this cohort.

- *Self-reported Symptoms and Vestibular Dysfunction*

We found a significant association between imbalance and VD (p=0.001). We found significant associations between both dizziness (p<0.001) and falls (p=0.005) and VD. Patients reporting dizziness, imbalance, and falls were more likely to have VD than those reporting one or two of these symptoms [RR=3.530 (95%CI 1.826 to 6.822)].

Dizziness or imbalance were prominent symptoms in those with confirmed vestibular dysfunction on formal testing (22/25 patients, Figure 1B). We found a statistically significant

association between vestibular dysfunction and symptoms of dizziness and balance ($\chi^2 = 14.92$; p=0.002), but not with imbalance ($\chi^2 = 1.52$ with a p=0.68). No correlations for dizziness alone were performed given n=2.

DISCUSSION

We sought to assess the relationship between sensory impairment and both self-reported postural symptoms and falls in patients with MD, as a model of multi-system impairment. Patients with objective evidence of VD were at greater risk of imbalance, dizziness, and falls. We have previously shown that dizziness and imbalance are in turn associated with an increased risk of VD (RR=3.33; 4.67 and 1.56 respectively)[8], and therefore our current data suggest that symptom reporting is a clinically useful measure of VD in patients with MD. Furthermore, objective abnormalities across sensory impairments (PN, ataxia, VD) were significantly associated with self-reported symptoms, suggesting that dizziness, imbalance and self-reported falls may help to identify the need for further formal assessment of balance function. Only 2/25 patients with VD reported isolated dizziness (Figure 1B), whereas 22/25 reported either dizziness or imbalance, suggesting that dizziness sensations are often accompanied by imbalance.

Unsurprisingly, dizziness and imbalance were common symptoms in patients with multisensory impairment. More importantly, the presence of dizziness, imbalance, and ataxia predicted a greater risk of falls. Ataxia is an established cause of falls, and a recognised feature of MD, but dizziness symptoms and vestibular dysfunction may be more prevalent than is currently reported [8]. This study highlights the importance of identifying dizziness symptoms in patients with other established sensory impairments, given the risk of falls, but also the potential to intervene therapeutically [9].

A lack of an association between PN and falls, despite PN being a risk factor for imbalance, is intriguing and may indicate that proprioceptive deficits can be better compensated for than ataxia and vestibulopathy for upright stability. Alternatively, a proportion of patients reporting imbalance may present with subclinical PN, given that whilst only 7/32 patients presented symptoms in line with PN, nerve conduction studies revealed that about 25% of patients had nerve dysfunction [10]. Similarly, Kaufmann et al. [11] investigated PN in 30

patients with MD, 15 of whom reported imbalance and almost all of them (29/30) had abnormal nerve conduction studies indicative of PN suggesting that imbalance and falls in patients with MD often reflect an underlying PN or ataxia. Here we show that the presence of dizziness is an important risk factor for falls.

This is to our knowledge the first study to explore the prevalence of PN, ataxia, and myopathy in patients with MD. PN was the most frequent sensory impairment, with a prevalence of 20%, in keeping with the range reported in the literature [10, 12]. Ataxia was present in 19% of patients, and myopathy in 18%, although not all patients in our cohort had undergone electromyography and myopathic features may be sub-clinical in a large proportion of patients with MD [13]. The results from the present study are indicative of an unselected cohort of MD, extending prevalence data to a more complete MD population [12, 14] that may complement the design of future clinical research. Our study had some noteworthy limitations; first, while we had robust data on a range of sensory factors, other factors such as hearing and vision impairment could have influenced our study findings. Future studies should assess the association between hearing and vision impairment and incidence of falls in MD population. Second, in line with retrospective studies [12], our data may underestimate the prevalence of sensory impairment in MD. However, false negative or positive cases are less likely, given the detailed neurological examination completed with all patients seen by this National Rare Mitochondrial disorders service.

CONCLUSIONS

Dizziness and imbalance are useful self-reported indicators of vestibular dysfunction in patients with multisensory impairment, and highly predictive of falls. Given the potential for targeted interventions for vestibular dysfunction, future studies should develop a simple diagnostic framework for vestibular dysfunction in patients with multisensory impairment.

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Figure 1. Percentage of patients with dizziness, imbalance, or a combination of the two in 25 patients with confirmed vestibular dysfunction on objective clinical testing (A). Odds ratios for falls in patients reporting imbalance, ataxia, and dizziness, using a logistic regression model (B).

DECLARATIONS

Conflicts of Interest/Competing interests

The authors report no disclosures relevant to the manuscript.

Availability of data and material (data transparency)

Data will be shared upon request from any qualified investigator, while maintaining anonymisation of the patients.

Code availability

Not applicable

Authors' contributions

Study concept and design: DK/RP/AM/SH. Data collection: EB/SH/NK/DK. Drafting the manuscript: all authors. Data interpretation: all authors. Critical revision of the manuscript: all authors.

Ethics approval

This study was performed under the ethical guidelines of the governing institution.

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