Supporting Data

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Orthostatic Hypotension in Parkinson’s Disease: Do Height and Weight Matter?

Every third person with Parkinson’s disease (PD) may suffer from orthostatic hypotension (OH).1 Besides classic OH (cOH), transient orthostatic blood pressure (BP) drops may occur within the first minute upon standing, qualifying for transient OH (tOH).2 It is unclear whether morphometric factors, such as height and body mass index (BMI),3 promote OH in people with PD.

For this reason, we analyzed a previously published cohort of 173 European patients with PD for differences in height and BMI across individuals with laboratory-confirmed cOH, tOH, or no OH.2

After comparing the morphometric and other clinico-demographic characteristics across patients with and without OH, we tested the association between BMI, height, and cOH or tOH, by calculating the area under the receiver operating characteristic (ROC) curve in males and females separately. The Youden index applied to the coordinates of the ROC curves determined the most accurate BMI and height cut-offs distinguishing patients with either cOH or tOH from those without. Whenever significant cut-offs were found, we compared the derived subgroups for differences in clinico-demographic features and autonomic function indices by means of univariate, binary logistic regression analysis and age-adjusted ANOVA for repeated measurements.

The clinicodemographic features of the study population are reported elsewhere.2 In our cohort, cOH occurred in 19% (n = 32) of patients and tOH in 24% (n = 41).

BMI did not differ between patients with either cOH (P = 0.270) or tOH (P = 0.798) compared with those without OH (Fig. 1).

The ROC curve analysis excluded any differences in height among female patients with or without OH, but pinpointed a positive association between cOH and taller stature in male patients (Fig. 1). Male patients with cOH did not otherwise differ for any other clinico-demographic characteristic from those with tOH or no OH. The Youden index identified a height cut-off of ≥172.5 cm for predicting cOH in male patients with PD (Fig. 1). Both univariate and age-adjusted logistic regression analysis confirmed a negative association between cOH and shorter stature in males (odds ratio = 0.14 [95% confidence interval, 0.03–0.66]; P = 0.013), despite higher, yet not significant after Benjamini–Hochberg correction, frequencies of cardiovascular comorbidities and use of antihypertensive medications (Supporting Information Table S1).

At hemodynamic monitoring, shorter patients showed an average systolic BP increase after 3 minutes on standing, while patients ≥172.5 cm tall had a decrease (P = 0.030; Supporting Information Fig. S1). The remaining cardiovascular autonomic function indices did not differ across the height groups (Supporting Information Fig. S1).

Pilot studies in Asian PD populations suggested an association between lower BMI and cOH.4,5 Here we did not observe any difference in BMI across male or female patients with PD with either cOH, tOH or no OH. This inconsistency possibly reflects ethnic and morphometric differences between European and Asian natives.

Elderly, otherwise healthy, shorter subjects show higher BP values compared with taller subjects, potentially reflecting underlying hydrostatic mechanisms.2 The fact that cardiovascular autonomic function indices other than cOH were equally impaired in shorter and taller patients suggests that analogous, non-neurogenic mechanisms may prevent shorter individuals with PD from developing clinically relevant BP declines on standing.

Identifying individual OH risk factors may optimize screening measures for this frequently overlooked condition.

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Data Availability Statement

Due to the retrospective nature of the study, no ethic approval or written informed consent was due. We performed the study in accordance with the Declaration of Helsinki and the current European data protection regulation. The first and last author take responsibility for the integrity of the data and the accuracy of the data analysis. The authors have full access to all of the data, have the right to publish any and all data separate and apart from any sponsor, to obtain independent statistical analyses of the data. We agree to share any data not published within this article upon reasonable request from any qualified investigator.

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FIG. 1. Receiver operating characteristic (ROC) curves and scatterplots of height and body mass index (BMI) in male and female patients with Parkinson’s disease (PD) with laboratory-confirmed classic orthostatic hypotension (cOH) and transient OH (tOH) versus no orthostatic blood pressure dysregulation. The red line indicates the significant associations detected at the ROC curve analysis and related height cutoff values distinguishing male patients with PD with cOH versus no orthostatic BP dysregulation, calculated by applying the Youden index to the coordinates of the area under the ROC curves (AuROC). Nonsignificant ROC curves and cutoff values are reported with gray lines. CI: confidence interval. [Color figure can be viewed at wileyonlinelibrary.com]
with other comorbidities, including intrauterine growth restriction, facial dysmorphism, and congenital defects, are the core features of this syndrome. Movement disorders, mainly dystonia, can also constitute the YY1-related phenotype, although still poorly described, as neurodevelopmental problems have been the focus of previous reports. We present the first case of a patient with isolated generalized dystonia and severe oromandibular involvement associated with YY1 mutation. In addition, deep brain stimulation (DBS) response is detailed.

This 38-year-old female patient is the first child of healthy nonconsanguineous parents, presenting an remarkable family history. Patient’s pregnancy, perinatal period, and psychomotor development were uneventful, except for low birth weight. The first symptom, writer’s cramp, appeared at age 8, although abnormal feet posture motivated orthopedic evaluation at age 3. Dystonia later encompassed other body parts: right upper limb at age 10; right lower limb, laryngeal, and oromandibular dystonia at age 12; and tongue protrusion induced by speech at age 17 (Video S1, Segment 1). There was no evidence of facial dysmorphism, oculomotor dysfunction, and cerebellar or pyramidal signs. In her 20s, oral and written communication was severely impaired due to anarthria and upper-limb dystonia (Video S1, Segment 2). However, she was able to complete secondary school with special education support, currently working as a secretary. During follow-up, diagnostic workup was normal or negative, namely brain MRI; metabolic screening; mitochondrial DNA sequencing; and targeted, sequential, single-gene Sanger sequencing; and performed under suboptimal conditions due to physical limitations, identified minor executive dysfunction. Oral medication for dystonia (triexifenidil, levodopa, and baclofen) did not show clinical benefits. Oromandibular dystonia slightly improved with botulinum toxin. At age 30, she underwent globus pallidus internus-DBS, with significant improvement in the Fahn–Marsden Scale-motor and disabling scores (peak improvement of 40.4% and 38.5%, respectively, at 62 months). Now, 8 years after surgery, the continuous slow disease progression is evident. At age 38, a whole exome sequencing-based gene panel, including 250 genes associated with dystonia, identified a novel, de novo, pathogenic, heterozygous variant in YY1 ((NM_003403.4) c.1099dup; p. (Asp367Glyfs*25)).

To date, 6 patients harboring pathogenic YY1 variants have been reported to exhibit a movement disorder: 2 had tremor, 3 ataxic gait, and 4 dystonia (one generalized dystonia with laryngeal involvement). Nevertheless, contrasting to our patient, they all had psychomotor developmental delay and ID. Interestingly, although most of the clinical features of Grable De Vries syndrome are not present in this case (apart from low birth weight), our patient’s features highly resemble a DYT-THAP1 phenotype, which could derive from, as

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A Case of YY1-Related Isolated Dystonia with Severe Oromandibular Involvement

Yin and yang 1 (YY1) disease-causing variants are responsible for Grabiele-de-Vries syndrome, an autosomal dominant condition, described in 27 patients worldwide.1,3 Psychomotor developmental delay and intellectual disability (ID), along