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Apathy and higher level of gait control in normal pressure hydrocephalus

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ABSTRACT

Apathy represents the most common behavioral disturbance in patients with suspicion of idiopathic normal pressure hydrocephalus (iNPH) and has a major impact on quality of life. However, its impact on gait –the hallmark motor disturbance of iNPH - has never been studied yet. This study aims to evaluate the impact of apathy on higher level of gait control in patients with suspicion of iNPH. Stride time variability (STV), a marker of higher level of gait control, was quantified during usual walking (single task) and during walking while performing simultaneously cognitive tasks (dual task) of counting and verbal fluency. Among 46 patients with suspicion of iNPH (77.6 ± 6.7 years; 34.8% women), 30 (65.2%) presented apathy (defined by a score ≥ 14 on the Starkstein apathy scale). Backward counting induced more important worsening of STV (i.e. increasing STV) in apathetic compared to non-apathetic patients (14.8 ± 25.1% versus 9.0 ± 20.4%; $p = 0.005$), while both groups presented similar executive functioning. These findings suggest that apathy contributes to gait disorders in iNPH. Apathy is easy to monitor and should be considered as a target symptom of treatment.

1. Introduction

Apathy can be defined as a state of decreased motivation that manifests as a decrease in goal-directed behaviors, and can be characterized by reduced interests or emotions that cannot be attributed to diminished level of consciousness, cognitive impairment, or emotional distress (Pagonabarraga et al., 2015). Apathy is increasingly recognized in non-reversible neurological conditions, such as Parkinson's disease (Hassan et al., 2014; Perez-Lloret et al., 2014), vascular dementia (Moretti et al., 2015), or Alzheimer's disease (Olazaran et al., 2013), but also in reversible neurological condition, such as idiopathic normal pressure hydrocephalus (Kanemoto et al., 2016; Kito et al., 2009). Idiopathic normal pressure hydrocephalus (iNPH) represents the most common cause of reversible dementia affecting around 6% of adults older than 80 (Jaraj et al., 2014). INPH associates a well-known clinical triad of gait, cognitive and urinary disturbances with ventriculomegaly on brain imaging (Gallia et al., 2006); its symptoms are improved by shunt surgery. Apathy represents the most common behavioral disturbance in patients with suspicion of iNPH (Kanemoto et al., 2016; Kito et al., 2009) and has been associated with greater ventriculomegaly in patients with iNPH (Peterson et al., 2016). Besides apathy, the cognitive deficits in iNPH are characterized by a classic frontal-executive dysfunction contributing to higher level of gait control (HLGC) – the hallmark motor disability of iNPH (Gallia et al., 2006). Apathy has been associated with more severe motor disability in patients with Parkinson's disease (Pedersen et al., 2009, 2010), however the relationship between apathy and HLGC has been never studied.

Although the pathophysiology of gait disorders is poorly understood in iNPH, the co-occurrence of executive impairment contributes to the disturbed HLGC, as suggested by the increased tendency of worsening of gait while performing a dual task (Allali et al., 2013; Armand et al., 2011). Quantification of gait parameters during single and dual task conditions has demonstrated that patients with iNPH present similar gait characteristics than iNPH mimics before shunt intervention or cerebrospinal fluid (CSF) tapping (Allali et al., 2013; Armand et al., 2011). These unspecific gait characteristics presented by iNPH are associated with increased stride time variability (STV) that is considered a suitable marker of HLGC (Allali et al., 2013; Armand et al., 2011). STV, which reflects impairment in gait rhythmicity (Hausdorff, 2005), is increased even in the earliest stage of neurological conditions with disturbed HLGC, as shown by patients with mild cognitive impairment (Beauchet et al., 2014). Regarding its relationship with cognition, increased STV has been associated with poor episodic memory and executive performances (Beauchet et al., 2015), but the association between STV and apathy has been never investigated yet.

Abbreviations: (CSF), cerebrospinal fluid; (GHS), global health status score; (HLGC), higher level of gait control; (iNPH), idiopathic normal pressure hydrocephalus; (SAS), Starkstein apathy scale; (STV), stride time variability.

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In order to disentangle this relationship between apathy and gait in the unique model of patients with suspicion of iNPH, we conducted a prospective study in these patients to compare STV (as a measure of HLGC) during single and dual task conditions between patients with and without apathy. Since quantified gait parameters have been extensively studied in iNPH using single and dual tasking (Agostini et al., 2015; Bugalho et al., 2013; Stolze et al., 2000, 2001), and more specifically increased STV were found in iNPH (Allali et al., 2013; Armand et al., 2011), we postulate that STV might be a good candidate marker to better tackle this relationship between apathy and HLGC; and we hypothesized that patients with apathy would show increased STV (i.e. worse HLGC). Establishing a relationship between apathy and the complex motor dysfunction of HLGC in patients with suspicion iNPH would contribute to better understanding of the pathophysiological mechanism of HLGC.

2. Materials and methods

2.1. Participants

All consecutive patients assessed in the Department of Neurology of the Geneva University Hospitals between October 2012 and April 2016 for gait disorders, cognitive dysfunction and ventriculomegaly that led to a suspicion of iNPH were included in this study. The study procedures were previously detailed (Allali et al., 2013). Briefly, inclusion criteria for this study were patients with a suspicion of iNPH with (i) a neurological examination, (ii) a comprehensive neuropsychological assessment with an evaluation of apathy and (iii) a spatio-temporal gait analysis. Exclusion criteria were presence of an acute medical illness in the past three months and a diagnosis of secondary NPH. A total of 46 patients with suspicion of iNPH were included in this study (77.6 ± 6.7 years; 34.8% women). A diagnosis was assigned after reviewing all available clinical data, as well as brain imaging and blood/CSF laboratory results at consensus case conferences involving behavioral neurologists and neuropsychologists blinded for the presence of apathy; the spatiotemporal gait parameters; and the subscores at iNPH grading scale (Kubo et al., 2008). We used the validated iNPH grading scale (Kubo et al., 2008) for describing gait disorders, cognitive impairment and urinary incontinence. This study protocol was approved by the ethical committee of Geneva University Hospitals.

2.2. Apathy and neuropsychological assessment

Apathy was systematically assessed using the Starkstein apathy scale (SAS) (Starkstein et al., 1992). The instruction was given by the same neuropsychologist (ML). The SAS has demonstrated good psychometric properties in patients with Parkinson's disease (Pedersen et al., 2012; Starkstein et al., 1992). Apathy was defined as a SAS score ≥ 14, as recommended (Starkstein et al., 1992). A standardized neuropsychological assessment focused on cognitive deficits encountered by patients with suspicion of iNPH was conducted with each participant before tapping (Laidet et al., 2015). The pre-CSF tapping assessment included an evaluation of executive functions (Color Trails test (D'Elia et al., 1996), Stroop test (Perret, 1974), phonemic and categorical verbal fluencies (Cardebat et al., 1990)), attention (Wechsler Adult Intelligence Scale — III symbol digit test and digit span (Wechsler, 1997a); Wechsler Memory Scale — III spatial span (Wechsler, 1997b)) and memory (the French version of the Free and Cued Selective Reminding Test (Van der Linden et al., 2004)). Global cognitive functioning was assessed with the Mini-Mental State Examination (Folstein et al., 1975).

2.3. Dual task and spatiotemporal gait evaluation

All patients performed a quantitative spatio-temporal gait evaluation at comfortable walking speed performed in ecological condition, while patients wearing their own shoes, as previously described (Allali et al., 2013). In addition to usual walking (i.e. single task walking), we included four individual cognitive dual-tasks (forward counting; backward counting; phonemic verbal fluency; and categorical verbal fluency) that are related with the disturbed cognitive domains observed in iNPH patients: attention, working memory, and executive function (Gallia et al., 2006). The participants performed the five individual conditions in randomized order: usual walking and walking while performing four different dual tasks: forward counting from 1; backward counting from 50; phonemic verbal fluency (enumerating words starting by letter p); and categorical verbal fluency (generating animal names). No prioritization was given for the walking or the cognitive task; the instruction of the dual tasks was: to walk and to perform the cognitive task at the best of their capacity. Stride time variability was computed based on the measurement of the heel marker trajectories on distance of 6 m with an optoelectronic system including 12 cameras. STV was calculated following the formula: standard deviation of stride time/mean value of stride time.

2.4. White matter lesions

White matter lesions were rated by the same neurologist (GA) blinded for apathy status with a valid semi-quantitative scale with moderate to good interrater reliability, the age-related white matters changes (Wahlund et al., 2001), on every neuroimaging scanner at the time of the clinical assessment. Total score (range: 0–30) and subscores (range: 0–6) were computed on the five regions combining the left and right hemispheres: frontal, temporal, parieto-occipital, basal ganglia and infratentorial.

2.5. Covariates

Comorbidities were documented by the global health status score (GHS; range 0–10), based on the presence of diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, Parkinson's disease, chronic obstructive pulmonary disease, angina, and myocardial infarction (Holtzer et al., 2006). A vascular risk factor score (range 0–5) was computed on the presence of diabetes, hypertension, hypercholesterolemia, body mass index >30 or smoking; a cardiovascular risk factor score (range 0–4) on the presence of myocardial infarction, angina, arrhythmia or chronic heart failure; a cerebrovascular score (range 0–2) on the presence of stroke or transient ischemic attacks (Mahoney et al., 2014).

2.6. Statistics

Descriptive statistics of the patients with suspicion of iNPH were calculated. Data were represented graphically; model assumptions were tested with skewness and kurtosis. For the gait parameters, as the distribution of parameters was not normal, we compared STV of patients with suspicion of iNPH with and without apathy with a Mann-Whitney *U* test; tests of the five walking conditions were conducted using Bonferroni adjusted alpha levels of 0.01 (0.05/5). For the others variables (i.e. clinical characteristics and cognitive performances), we used parametric or non-parametric statistics depending on the respective distribution. All analyses were conducted using SPSS version 22 (SPSS Inc., Chicago, Ill., USA).

3. Results

Characteristics of the patients with suspicion of iNPH with and without apathy are compared in Table 1 and neuropsychological performances in Table 2. The mean age of the entire group was 77.6 ± 6.7 years without any difference between patients with and without apathy. The gender distribution was also similar between both groups. The mean MMSE was 23.7 ± 3.9 (range: 13.0–29.0), without any differences between patients with and without apathy. The prevalence of apathy