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Brain comorbidities in normal pressure hydrocephalus

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Abstract

Background and purpose—This cross-sectional study aims to compare gait changes after the cerebrospinal fluid (CSF) tap test between normal pressure hydrocephalus patients with and without brain comorbidities (NPH+ and NPH– respectively) and then to identify significant contributors to a poor CSF tap test amongst individuals with NPH+.

Methods—Gait changes (during the single task and the dual task of backward counting) were quantified before and 24 h after the CSF tap test with an optoelectronic system in 52 NPH patients (77.4 ± 6.0 years; 34.6% women). Changes after the CSF tap test in stride time variability (STV, %) were our main outcome. CSF Alzheimer's disease biomarkers, cerebrovascular white matter changes assessed with brain imaging and neurodegenerative diseases with parkinsonian syndrome represented the three individual brain comorbidities.

Results—Brain comorbidities were frequently identified, NPH+ patients representing 40 patients of our sample (76.9%). NPH– patients improved their STV better in the single task (delta of STV = –58.6% ± 54.3% vs. –14.1% ± 62.0%; $P = 0.031$) and in the dual task (delta of STV = –32.2% ± 33.7% vs. 6.3% ± 58.4%; $P = 0.028$) after the CSF tap test than NPH+ patients. Amongst NPH+ individuals, only comorbid Alzheimer's disease was associated with STV increase (i.e. deterioration of gait) in the dual task [β 38.4; 95% confidence interval (5.64; 71.24); $P = 0.023$] after the CSF tap test, whilst it was borderline in the single task [β 35.0; 95% confidence interval (–1.97; 71.90); $P = 0.063$].

Conclusions—Brain comorbidities affect gait improvement after the CSF tap test in NPH patients; this influence is driven by Alzheimer's disease-related pathology.

Keywords

biomarkers; comorbidity; dementia; gait disorders; normal pressure hydrocephalus

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Disclosure of conflicts of interest

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Introduction

Normal pressure hydrocephalus (NPH) – the leading cause of reversible dementia in older adults – is often associated with brain comorbidities [1]. Isolated or combined Alzheimer's disease (AD), cerebrovascular white matter disease (cWMD) and other neurodegenerative diseases associated with parkinsonism (synucleinopathies and tauopathies) represent the large majority of these brain comorbidities [2]. The brain comorbidities contribute to a certain extent to the triad of NPH diagnosis and more importantly interfere with shunt response and long-term prognosis [3–6]. Previous studies have identified that isolated brain comorbidity, such as AD, is associated with poor response to the cerebrospinal fluid (CSF) tap test [7]. However, the role of these brain comorbidities on symptoms and response to the CSF tap test is still poorly studied.

Gait changes represent the hallmark of NPH and are considered as the most responsive symptoms to the CSF tap test [1]. Quantified gait analysis is a validated tool to measure gait improvement after the CSF tap test and to identify NPH from other neurological conditions [8,9]. Amongst gait parameters, stride time variability (STV) – which reflects gait stability – has been identified as a reliable marker of gait control in normal aging and other neurological conditions [10]. STV, a measure (in percentage) of the variability (standard deviation/mean) of the stride time, has been associated with important clinical outcomes, such as falls or disability, in older adults with and without neurological conditions [10]. Moreover, STV under dual task (walking whilst performing a cognitive task simultaneously) is considered as a marker of cognitive control of gait [11]. Dual-task-related gait changes after CSF tap test capture both gait and cognitive modifications in patients with NPH and help to identify NPH from mimics [8,12]. However, comparing changes in STV in single and dual task conditions after the CSF tap test between NPH patients with and without brain comorbidities (NPH+ and NPH– respectively) has not been studied yet.

Therefore, it is proposed first to compare STV in single and dual tasking before and after the CSF tap test between NPH+ and NPH– patients. Then, since comorbidities interfere with shunt response [3–6] and CSF AD biomarkers are associated with a poor CSF tap test [7], it is hypothesized that NPH+ patients and more specifically those with CSF AD biomarkers will respond poorly to the CSF tap test. Identifying the influence of brain comorbidities in NPH on gait control will improve our understanding of NPH and perfectly fits with the recent recommendations of the International Society for Hydrocephalus and Cerebrospinal Fluid Disorders [2].

Methods

Participants

All consecutive patients diagnosed with NPH in the Department of Neurology of the Geneva University Hospitals between March 2008 and July 2016 were included in this study using a standard protocol described elsewhere [13]. Inclusion criteria were all idiopathic NPH patients with (i) a full neurological examination, (ii) AD CSF biomarkers, (iii) brain magnetic resonance imaging (MRI) in order to quantify cerebral white matter lesions and (iv) a spatiotemporal gait analysis performed before and 24 h after CSF tap test (spinal tap of

40 ml), as gait changes may be assessed at any time within the first 24 h [14]. Exclusion criteria were the presence of an acute medical illness in the past 3 months, a diagnosis of secondary NPH, a territorial stroke, and any changes in treatment between pre and post CSF tap test. The diagnosis of NPH 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 spatiotemporal gait parameters, according to the NPH consensus guideline criteria [15]. A total of 52 patients were included in the study (77.4 ± 6.0 years; 34.6% women). The Geneva University Hospitals Committee on Human Research approved the research protocol, and informed consent was obtained from all participants.

Brain comorbidities

Based on a previous report on comorbidity in NPH from the International Society for Hydrocephalus and Cerebrospinal Fluid Disorders [2], AD pathology, cWMD and neurodegenerative diseases with parkinsonism represent the large majority of brain comorbidities encountered in NPH. AD pathology was based on CSF biomarkers according to the cut-off defined in our laboratory and was considered positive with total tau (t-tau) >360 ng/l; phosphorylated-tau (phospho-tau) >60 ng/l and/or $A\beta_{1-42} <450$ ng/l, as CSF biomarkers are highly correlated with neuropathological findings of AD at brain biopsies of NPH patients [16]. cWMD was considered positive with an age-related white matter changes (ARWMC) total score >6 [17], as reported previously in NPH patients [18]. 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 (rated on 46 T2 and fluid-attenuated inversion recovery (FLAIR) MRI scans and six computed tomography scans). Neurodegenerative parkinsonism was defined by the presence of bradykinesia and at least one of the signs muscular rigidity, rest tremor or postural instability, based on the UK Parkinson's Disease Society brain bank clinical diagnostic criteria, as previously reported [18].

Cerebrospinal fluid sample collection and analysis of CSF biomarkers

The CSF sample collection was performed by an experimental neurologist at the same time of day (between 10 and 12 am). CSF proteins ($A\beta_{1-42}$, t-tau and phospho-tau) were analyzed in 10 ml of CSF, following the international recommendations of the Alzheimer's Biomarkers Standardization Initiative [19]. CSF samples were centrifuged at 4°C for 10 min at $2000g$ within 4 h after lumbar puncture to remove cells, aliquoted into 0.5-ml polypropylene tubes (Sarstedt PP tubes) and stored at -80°C until analysis. $A\beta_{1-42}$, t-tau and phospho-tau were measured in duplicate using a double-sandwich enzyme-linked immunosorbent assay method (INNOTEST®, Fujirebio, Gent, Belgium) according to the manufacturer's instructions.

Gait evaluation

Spatiotemporal gait parameters were assessed at comfortable walking speed, with patients wearing their own shoes. Gait was recorded on a distance of 10 m with an optoelectronic system including 12 cameras; 6 m were recorded by the optoelectronic system, following the guidelines for assessment of spatiotemporal gait parameters [20]. Each participant walks in a

single walking task and a dual task (walking whilst backward counting one by one from 50) in a randomized order before and 24 h after the CSF tap test. STV was calculated as a percentage with the formula (standard deviation of stride time/mean value of stride time) $\times$ 100. Gait changes after the CSF tap test were reported by the delta of STV (in percentage) with the following formula: $(STV_{\text{post CSF tap test}} - STV_{\text{pre CSF tap test}}) / [(STV_{\text{post CSF tap test}} + STV_{\text{pre CSF tap test}}) / 2] \times 100$. A negative delta of STV indicates a gait improvement.

Covariates

Medical comorbidities were rated by the global health status score (range 0–9), based on the presence of diabetes, chronic heart failure, arthritis, hypertension, depression, stroke, chronic obstructive pulmonary disease, angina and myocardial infarction [21]. A vascular risk factor score (range 0–5) was computed on the presence of diabetes, hypertension, hypercholesterolemia, body mass index >30 or smoking, and a cardiovascular risk factor score (range 0–4) on the presence of myocardial infarction, angina, arrhythmia or chronic heart failure [22].

Statistics

Descriptive statistics of the patients were calculated. Data were represented graphically; model assumptions were tested with skewness and kurtosis. NPH patients with and without brain comorbidities were compared based on a two-sample *t* test, Mann–Whitney *U* test or χ^2 as appropriate. Pre and post CSF tap test STV was compared with paired *t* tests (two-tailed) or a Wilcoxon signed-rank test, as appropriate. Multivariable (adjusted on age and gender) linear regression models were used to compute unstandardized β with 95% confidence intervals (CIs) to show an association between the delta of STV (dependent variable) and each individual brain comorbidity amongst positive AD biomarkers, total ARWMC and the presence of parkinsonism (independent variable); in a first model each brain comorbidity was considered individually and in a second model all brain comorbidities were introduced together into the model. All analyses were conducted using SPSS version 22 (SPSS Inc., Chicago, IL, USA).

Results

The characteristics of patients with NPH are compared between those with and without brain comorbidities in Table 1.

The prevalence of brain comorbidities was 76.9%. Positive CSF AD biomarker, cWMD and parkinsonism were found in 56%, 40% and 17% of patients, respectively. For the pre CSF tap test, mean gait speed was 0.69 ± 0.28 m/s for the single walking task and 0.60 ± 0.24 m/s for the dual task ($P < 0.001$). The duration of symptoms differed between the two groups. Otherwise, both groups presented similar clinical characteristics, including the pre CSF tap test spatiotemporal gait parameters.

Regarding STV during single and dual tasking, all NPH patients – both groups together – improved (i.e. decreased) their STV during the single walking task after CSF tap test ($6.24\% \pm 13.31\%$ vs. $5.63\% \pm 15.67\%$, $P = 0.011$), and they presented similar performances for the dual task between the two evaluations ($6.29\% \pm 4.89\%$ vs. $6.68\% \pm 6.48\%$, $P = 0.615$).

When considering NPH+ and NPH- patients separately, NPH- patients improved their STV in both conditions, whilst the NPH+ patients presented similar STV (see Fig. 1). NPH- patients improved their STV more in the single task (delta of STV = $-58.6\% \pm 54.3\%$ vs. $-14.1\% \pm 62.0\%$; $P = 0.031$) and dual task (delta of STV = $-32.2\% \pm 33.7\%$ vs. $6.3\% \pm 58.4\%$; $P = 0.028$) than NPH+ patients. This improvement remained significant after adjusting for age and gender for the single [$\beta 43.9$; 95% CI (2.64; 85.13); $P = 0.038$] and dual tasks [$\beta 40.9$; 95% CI (4.94; 76.82); $P = 0.027$].

When identifying individually every single brain comorbidity, positive CSF AD biomarkers were significantly associated with STV increase (i.e. deterioration of gait) in the dual task [$\beta 36.7$; 95% CI (3.17; 68.16); $P = 0.032$] whilst adjusting for age and gender, and in the single task [$\beta 36.2$; 95% CI (0.06; 72.36); $P = 0.050$]. Both ARWMC and the presence of parkinsonism were not associated with STV change either in the dual or in the single tasks (Table 2, model 1). Similarly, when combining all brain comorbidities together, only positive CSF AD biomarkers were significantly associated with STV increase (i.e. deterioration of gait) in the dual task [$\beta 38.4$; 95% CI (5.64; 71.24); $P = 0.023$] whilst adjusting for age and gender and were borderline in the single task [$\beta 35.0$; 95% CI (-1.97; 71.90); $P = 0.063$]. The presence [$\beta -18.5$; 95% CI (-55.7; 18.6); $P = 0.320$] and severity [$\beta -1.5$; 95% CI (-5.7; 2.7); $P = 0.482$] of ARWMC were not associated with STV change either in the dual or in the single task. The presence of parkinsonism was not associated with STV change either in dual or single task (Table 2, model 2).

Discussion

It was found that quantitative gait parameters before the CSF tap test were similar between NPH+ and NPH- patients. As expected, NPH+ responded more poorly to the CSF tap test than NPH-. AD-related pathology, using CSF AD biomarkers, was associated with poorer response to the CSF tap test during the dual task, unlike cWMD and neurodegenerative disease with parkinsonism.

Both the presence and prevalence of brain comorbidities amongst patients with NPH reported here are similar to those previously reported in autopsy and brain biopsy series of patients with NPH [3,16,23,24], confirming that our methodological approach for assessing brain comorbidity is accurate.

Our findings suggest that quantitative gait parameters after the CSF tap test might discriminate between NPH+ and NPH- patients since NPH- patients significantly improved whilst dual tasking. Since dual-task-related gait changes are associated with executive functioning [25] and have been demonstrated in patients with NPH [8,12], our current findings might indicate that absence of dual task improvement after the CSF tap test is due to an irreversible impairment of the executive-related network and a marker of AD-related pathology [26–28]. A lower improvement after shunt surgery in NPH+ patients supports our results [5]. Similar gait improvement after shunt surgery between patients with and without AD [24] contradicts our findings, but this discrepancy might be explained by a worse gait and cognitive symptoms in NPH patients with AD at baseline reported in the Golomb *et al.* study (Mini Mental State Examination 15.9 ± 8.2 and gait speed 0.49 ± 0.34 m/s vs. Mini

Mental State Examination 22.6 ± 5.6 and gait speed 0.69 ± 0.30 m/s in the current study) [24]. Additional studies and longer follow-up are needed to better understand those heterogeneous findings.

Amongst brain comorbidities, the finding that only AD-related pathology was associated with poor gait improvement after the CSF tap test makes sense since AD is a pronounced cortical condition unlike cWMD and neurodegenerative diseases with parkinsonism. Coexistence of an irreversible cortical neurodegenerative process like AD and a reversible predominantly subcortical one like NPH might explain the poor CSF tap test, as previously reported [7]. Interestingly, a previous report showed that the CSF tap test also improved patients with vascular parkinsonism [29]. In the same line, previous studies demonstrated that some patterns of white matter changes (especially those located in the periventricular regions) were reversible after shunt placement [30,31] or low-dose acetazolamide [32].

Cerebrovascular white matter disease (presence and severity) was not associated with gait changes after the CSF tap test. Using the same white matter scale, Bugalho *et al.* reported a negative correlation between white matter and gait changes in the single walking task after the CSF tap test [33]. Different gait variables (gait speed, stride length, stride duration and number of steps per turn), gait recording time (3, 12, 24, 48 and 72 h after the CSF tap test) and a younger mean age (73.6 years) may explain these discrepancies with our results. Moreover, our inclusion criteria were not based on a specific gait phenotype as in the Bugalho study since brain comorbidities may affect clinical gait abnormalities [6].

Absence of autopsy confirmed diagnosis in our sample constitutes the main limitation of our approach. The relatively small sample size prevents tau and amyloid toxicity being differentiated. The quantification of the nigro-striatal pathway (with a DAT scan or other brain imaging tracers) would allow a better quantification of neurodegenerative diseases with parkinsonism. Nevertheless, autopsy and biopsy-related studies [3,23,24] reporting a similar prevalence of comorbidities validate our approach. Combining brain comorbidities in NPH patients with standardized quantification of gait parameters before and after the CSF tap test represent the main strengths of this study. The study findings need to be confirmed in further studies with a larger sample especially for NPH patients with parkinsonism.

In conclusion, these findings show that brain comorbidities affect gait improvement after the CSF tap test; this influence is driven by AD-related pathology in NPH+ patients. The absence of gait improvement after the CSF tap test may suggest the presence of brain comorbidity, especially AD. Future prospective studies should investigate the respective contribution of individual comorbidities on gait and cognition after shunt surgery in order to better understand NPH prognosis in the long run.

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Figure 1.

(a), (b) Normal pressure hydrocephalus (NPH) patients without comorbidities improve (i.e. decrease) their stride time variability (STV) after CSF tap test in both single and dual task conditions, whereas NPH patients with comorbidities did not report any changes. (a) Single task: STV of NPH patients without comorbidities decreases from $4.55 \pm 2.28\%$ to $2.41 \pm 1.33\%$ after the CSF tap test ($P = 0.006$), whereas the STV of NPH patients with comorbidities was similar before ($6.74 \pm 15.13\%$) and after ($6.65 \pm 17.90\%$) the CSF tap test. (b) Dual task (walking whilst backward counting): STV of NPH patients without

comorbidities decreases from $5.48\% \pm 2.88\%$ to $4.28\% \pm 3.01\%$ after the CSF tap test ($P=0.028$), whereas the STV of NPH patients with comorbidities was similar before ($6.56\% \pm 5.41\%$) and after ($7.48\% \pm 7.13\%$) the CSF tap test.

Table 1Clinical characteristics of idiopathic NPH patients with and without brain comorbidity ($n = 52$)

	NPH with comorbidity (NPH+) ($n = 40$)	NPH without comorbidity (NPH-) ($n = 12$)	P^a
Age (years)	77.8 $\pm$ 5.9	75.9 $\pm$ 6.5	0.336
Gender (% female)	25	38	0.425
Disease duration (months)	29.8 $\pm$ 26.0	44.7 $\pm$ 24.5	0.029
Comorbidities (GHS, 0–9)	1.85 $\pm$ 0.95	1.75 $\pm$ 1.22	0.610
Vascular risk factors ^b (0–5)	1.28 $\pm$ 0.91	1.58 $\pm$ 0.79	0.225
Cardiovascular risk factors ^c (0–4)	0.20 $\pm$ 0.41	0.17 $\pm$ 0.39	0.799
Treatment, n	3.60 $\pm$ 2.18	4.17 $\pm$ 2.59	0.252
Mini-Mental State Examination (/30)	22.6 $\pm$ 5.6	25.9 $\pm$ 2.7	0.154
Gait parameters			
Single task			
Gait speed, m/s	0.69 $\pm$ 0.30	0.73 $\pm$ 0.23	0.681
Stride time, s	1.30 $\pm$ 0.29	1.26 $\pm$ 0.21	0.879
Stride length, m	0.83 $\pm$ 0.32	0.89 $\pm$ 0.22	0.575
Step width, m	0.11 $\pm$ 0.05	0.10 $\pm$ 0.05	0.515
Dual task of backward counting			
Gait speed, m/s	0.60 $\pm$ 0.25	0.61 $\pm$ 0.22	0.908
Stride time, s	1.40 $\pm$ 0.28	1.40 $\pm$ 0.24	0.775
Stride length, m	0.80 $\pm$ 0.29	0.83 $\pm$ 0.25	0.808
Step width, m	0.12 $\pm$ 0.04	0.11 $\pm$ 0.04	0.504
Comorbidity			
CSF AD biomarkers ^d , n (%)	29 (73)	–	<0.001
cWMD ^e , n (%)	21 (53)	–	0.001
Presence of parkinsonism, n (%)	9 (23)	–	0.071
CSF proteins level			
Tau, ng/l	241.9 $\pm$ 178.1	163.3 $\pm$ 64.8	0.196
Phospho-tau, ng/l	46.4 $\pm$ 18.2	32.4 $\pm$ 9.5	0.037
A β -42, ng/l	502.9 $\pm$ 192.2	708.0 $\pm$ 326.4	0.014
White matter lesions ^f			
Total (0–30)	7.65 $\pm$ 4.59	3.00 $\pm$ 2.22	0.002
Frontal (0–6)	3.00 $\pm$ 1.45	1.50 $\pm$ 0.80	0.001
Temporal (0–6)	1.05 $\pm$ 1.48	0.17 $\pm$ 0.58	0.041
Parieto-occipital (0–6)	2.58 $\pm$ 1.82	1.17 $\pm$ 1.34	0.017
Basal ganglia (0–6)	0.78 $\pm$ 0.97	0.17 $\pm$ 0.58	0.037
Infratentorial (0–6)	0.25 $\pm$ 0.59	0.00 $\pm$ 0.00	0.124

NPH, normal pressure hydrocephalus; GHS, global health status; CSF, cerebrospinal fluid; AD, Alzheimer's disease; cWMD, cerebral white matter disease.

^aComparisons are based on the two-sample t test, Mann–Whitney U test or Fisher exact test as appropriate; significant differences ($P < 0.05$) are in bold

^b presence of diabetes, hypertension, hypercholesterolemia, body mass index >30 or smoking

^c presence of myocardial infarction, angina, arrhythmia or chronic heart failure

^d presence of CSF tau >360 or CSF phosphotau >60 or CSF A β -42 <450 ng/l

^e age-related white matter change total scores >6

^f rated with age-related white matter changes.

Table 2

Multivariable (adjusted for age, gender) linear regression showing an association between delta STV: (a) single task (b) dual task (dependent variable) and each comorbidity (independent variable)

	β	95% CI	<i>P</i> value
(a)			
Model 1			
CSF AD biomarkers ^a	36.21	0.06; 72.36	0.050
Cerebrovascular white matter disease ^b	19.43	-21.65; 60.51	0.346
Presence of parkinsonism	6.47	-41.36; 54.29	0.787
Model 2			
CSF AD biomarkers ^a	34.96	-1.97; 71.90	0.063
Cerebrovascular white matter disease ^b	16.18	-24.87; 57.24	0.749
Presence of parkinsonism	0.25	-47.08; 47.58	0.992
(b)			
Model 1			
CSF AD biomarkers ^a	36.67	3.17; 68.16	0.032
Cerebrovascular white matter disease ^b	-16.17	-53.33; 20.99	0.385
Presence of parkinsonism	-24.33	-68.06; 19.41	0.268
Model 2			
CSF AD biomarkers ^a	38.44	5.64; 71.24	0.023
Cerebrovascular white matter disease ^b	-18.54	-55.73; 18.64	0.320
Presence of parkinsonism	-19.01	-62.48; 24.45	0.382

CSF, cerebrospinal fluid; AD, Alzheimer's disease; β , unstandardized β ; CI, confidence interval. Model 1: each brain comorbidity (i.e. CSF AD biomarkers, cerebrovascular white matter disease and presence of parkinsonism) is considered individually in the model. Model 2: all brain comorbidities are introduced together into the model. $P < 0.05$ are in bold.

^a Presence of CSF tau >360 or CSF phospho-tau >60 or CSF A β -42 <450 ng/l;

^b age-related white matter changes total scores >6.