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diopathic normal-pressure hydrocephalus is characterized by the classic Adams triad of cognitive dysfunction, urinary incontinence, and gait disturbance, the latter being the most prominent and predominant symptom in the majority of patients. Improvement in walking performance following a large-volume lumbar puncture (CSF tap test) is the key selection criterion for ventricular shunt surgery and for predicting responsiveness to the shunt therapy. Despite the clinical importance of this symptom, the pathophysiological mechanisms of NPH gait disturbance remain unclear, and objective methods for its assessment are lacking. Our previous study demonstrated that difficulty walking in patients with iNPH is not related to conduction impairment along the corticospinal motor pathways as assessed by TMS. A modulation of corticospinal excitability. The aim of this study was 2-fold: 1) to determine whether iNPH affects corticospinal excitability; and 2) to evaluate changes in corticospinal excitability following ventricular shunt placement in relation to clinical outcome.

Methods. Twenty-three patients with iNPH were examined using single- and paired-pulse transcranial magnetic stimulation of the leg motor area before and 1 month after ventricular shunt surgery. The parameters of corticospinal excitability assessed were the resting motor threshold (rMT), motor evoked potential/M-wave area ratio, central motor conduction time, intracortical facilitation, and short intracortical inhibition (SICI). The results were compared with those obtained in 8 age-matched, healthy volunteers, 19 younger healthy volunteers, and 9 age-matched patients with peripheral neuropathy.

Results. Significant reduction of the SICI associated with a decrease of the rMT was observed in patients with iNPH at baseline evaluation. Ventricular shunt placement resulted in significant enhancement of the SICI and increase of the rMT in patients who markedly improved, but not in those who failed to improve.

Conclusions. This study demonstrates that iNPH affects corticospinal excitability, causing disinhibition of the motor cortex. Recovery of corticospinal excitability following ventricular shunt placement is correlated with clinical improvement. These findings support the view that reduced control of motor output, rather than impairment of central motor conduction, is responsible for gait disturbances in patients with iNPH. (DOI: 10.3171/2011.9.JNS11678)

Key Words: • corticospinal excitability • normal-pressure hydrocephalus • transcranial magnetic stimulation • disinhibition

Abbreviations used in this paper: AHB = abductor hallucis brevis; CMCT = central motor conduction time; EMG = electromyography; ICF = intracortical facilitation; iNPH = idiopathic normal-pressure hydrocephalus; iNPHGS = iNPH grading scale; MEP = motor evoked potential; PL = peripheral latency; rMT = resting motor threshold; SICI = short intracortical inhibition; TGS = total gait scale; TMS = transcranial magnetic stimulation.
The use of TMS in conjunction with recording of MEPs has long been known as a highly sensitive method to detect central motor conduction impairment within the corticospinal pathways.\textsuperscript{5,6} In the past 2 decades, different paradigms of single- and paired-pulse TMS have been proposed for assessment of global corticospinal excitability and separate excitatory and inhibitory responses.\textsuperscript{3,4,11} The aim of this study was 2-fold: 1) to determine whether NPH affects excitatory and inhibitory intracortical circuits in the motor cortex; and 2) to evaluate changes in corticospinal excitability following ventricular shunt placement, and their relationships to the clinical outcome.

Methods

Patient Population

Patients with a clinical and neuroimaging diagnosis of NPH who were admitted to the Department of Neurosurgery and referred to ventricular shunt placement surgery were recruited consecutively for the study. Patients were included in the study if they met criteria for probable iNPH.\textsuperscript{24} Their age was older than 50 years, and they were capable of cooperating sufficiently for neurophysiological testing. The diagnosis of iNPH was based on the presence of the following symptoms and signs: 1) gradually developing gait disturbance; 2) cognitive deterioration, urinary incontinence, or both; 3) progression of symptoms over time; 4) a CT/MR imaging study showing ventricular enlargement (Evans index > 0.3), with trans-ependymal diffusion and no significant cortical atrophy; 5) normal CSF pressure at lumbar puncture; and 6) improvement of clinical symptoms after lumbar tap test or its of the normal range (mean ± 2.5 SDs) were obtained.

Evaluation of Corticospinal Excitability

Evaluation of corticospinal excitability and clinical assessment were performed before treatment and at follow-up 1 month after the shunt operation. The upper limits of the normal range (mean ± 2.5 SDs) were obtained in 8 age-matched (4 women and 4 men; mean age 74.8 ± 4.1 years, range 71–84 years) and 19 younger healthy controls (8 women and 11 men; mean age 32.9 ± 9 years, range 20–52 years). Given the high incidence of peripheral nerve disorders in elderly individuals, 9 other age-matched patients (3 women and 6 men; mean age 71.6 ± 12.5 years, range 58–87 years) with EMG-documented diabetic neuropathy (6 patients) and idiopathic polynuropathy (3 patients) were examined for a comparison.

Participants in the study were questioned (or asked to perform step-up and ball kick tasks) regarding their functional lower-limb dominance. All but 2 participants had right lower-limb dominance.

The study protocol was approved by the local ethics committee. All participants gave written informed consent.

Clinical Assessment

The triad of NPH symptoms was evaluated using an iNPHGS consisting of three 5-point subscales.\textsuperscript{13} The score of each subscale (cognitive impairment, gait disturbance, and urinary disturbance) ranges from 0 to 4, with higher scores indicating worse symptoms. The percentage reduction in iNPHGS scores compared with baseline was used to measure the outcome of shunt surgery. Minimal clinical improvement was arbitrarily defined as at least 15% reduction in the total score, which roughly corresponds to improvement in at least 1 of the 6 scale points. This implies that patients who improved in only 1 of the 3 subscales could be judged to have improved. In addition, gait abnormalities were quantified by a TGS test that evaluates the presence of 10 features of gait and measures the number of steps and seconds required for a 10-m walk.\textsuperscript{23} Marked improvement in walking performance was defined a priori as a reduction of ≥ 50% in the TGS score. Based on CT and MR imaging studies, ventricular enlargement was assessed using an Evans index defined as the maximum width of the frontal horns divided by the maximum inner width of the skull.

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eliciting in the relaxed AHB at least 5 MEPs with amplitude > 50 μV in a series of 10 consecutive single-pulse TMS trials. The CMCT was defined as the difference between the shortest MEP latency and the PL assessed by the F-wave method, as follows: PL = (M + F – 1)/2, where “M” is the latency of the M-wave obtained after supra-maximal peripheral electrical stimulation of the posterior tibial nerve at the ankle, and “F” is the shortest latency of 10 F-waves. The MEP size was measured as the area under the rectified curve of MEPs recorded at a TMS intensity of 20% above the rMT (120% rMT). The averaged MEP/M-wave area ratio of 8 consecutive single-pulse TMS trials was then calculated.

To address whether INPH is associated with changes in intrinsic cortical excitability, the SICI and ICF were evaluated by means of a paired-pulse TMS. The SICI and ICF were assessed in the fully relaxed AHB, by using a conventional paired conditioning test pulse paradigm.14,29 The conditioning (subthreshold) stimulus was applied at an intensity of 80% of the participant’s rMT. The intensity of the test (suprathreshold) stimulus was adjusted so as to produce in the relaxed AHB, when given alone, an EMG response of 0.6–0.8 mV peak-to-peak amplitude. The interstimulus intervals were 2 msec for evaluation of the SICI and 10 msec for evaluation of the ICF. For each interstimulus interval, 10 trials were performed. These were mixed randomly with 16 trials of the test stimulus alone. The size of the mean conditioned MEP at a given interstimulus interval was expressed as a percentage of the size of the mean unconditioned MEP elicited by single-pulse TMS.

Patients were instructed to keep their lower extremities as relaxed as possible. Audiovisual EMG feedback was given to ensure complete relaxation of the AHB muscle. Trials in which EMG activity occurred were discarded from the analysis. In all single-pulse and paired-pulse TMS studies, the interval between trials was at least 8 seconds.

Statistical Procedures

Between-group and dominance-related differences of parameters of corticospinal excitability were assessed by repeated-measures ANOVA, with “Group” (iNPH, age-matched control, young control, neuropathy) as the between-subject factor and “Side” (dominant, nondominant) as the intersubject term. When each side was evaluated separately, between-group comparisons were made using 1-way ANOVA. For assessment of the effects of ventricular shunt placement on neurophysiological measures and clinical scores, another set of repeated-measures ANOVA was performed, with “Outcome” (marked improvement [≥ 50%], mild improvement or no response [< 50%]) as the between-subject factor and “Time” (baseline, follow-up) as the intersubject term. To test the hypothesis that iNPH results in abnormal interhemispheric asymmetries, the absolute interside differences were calculated and analyzed separately by 1-way ANOVA. Conditional on significant F values, the post hoc Bonferroni corrected t-tests were applied for multiple comparisons. The Pearson correlation coefficients were calculated for relations between independent measures at baseline and their percentage changes following the shunt placement procedure. The results were considered significant at p < 0.05.

Results

Control Group

The reproducible MEPs following single-pulse and paired-pulse TMS of the leg motor area could be elicited in all members of the age-matched and young control group as well as the elderly neuropathy group. In 7 healthy participants (3 young and 4 elderly individuals), the rMT was > 84% of the maximal stimulator output, so that the maximal (100%) stimulus intensity was required to produce test MEPs (0.6–0.8 mV), and this intensity was slightly less than 120% rMT. There was no significant difference between elderly and young control groups or between both control and neuropathy groups in any parameter of corticospinal excitability, except for the PL, which was significantly prolonged in patients with neuropathy, due to peripheral conduction slowing (Table 1).

Baseline Evaluation of the iNPH Group

Repeated-measures ANOVA revealed no significant main effect or interactions for the factor “Side,” indicating no dominance-related asymmetry in corticospinal excitability of the leg motor area in patient and control groups. Table 1 summarizes results of the TMS study separately for each side. Significant bilateral reduction and even abolishment of the SICI associated with a significant decrease of the rMT was observed in patients with iNPH, compared with age-matched and younger control volunteers and patients with neuropathy. In addition, 1-way ANOVA demonstrated a significantly higher interhemispheric asymmetry of the SICI in the iNPH group compared with the control and neuropathy groups (Table 2).

In 5 patients (21.7%) in the iNPH group, a bilateral prolongation of the PL was revealed, suggesting a peripheral motor conduction impairment of unknown primary cause. No significant difference in any parameter of corticospinal excitability was found in these 5 patients, compared with patients who had iNPH and whose PL was within the normal range (18 patients).

At baseline, there was no significant correlation between clinical ratings (iNPHGS, TGS), the Evans index, and measures of corticospinal excitability.

Effects of Ventricular Shunt Placement

One month after ventricular shunt placement, at least minimal clinical improvement (reduction of ≥ 15% in iNPHGS score) was observed in 21 patients (91.3%). The mean percentage reduction in global NPH (iNPHGS score) and TGS score was 29.2% ± 23.5% and 34.9% ± 21.1%, respectively. There was no significant difference in the degree of clinical improvement between patients with iNPH in whom prolonged PL was found and those in whom there was no peripheral motor conduction slowing (5 and 18 patients, respectively). Two patients who did not show any improvement in cognitive and motor functions presented with significant periventricular edema and ischemic white matter degeneration, the latter being...
irreversible, as revealed in the postoperative MR imaging evaluation.

Marked improvement in gait (reduction of ≥ 50% in TGS score) was observed in 10 patients (43.5%), in whom significant enhancement of the SICI (Fig. 1A) and in TGS score was observed in 10 patients (43.5%), in whom irreversible, as revealed in the postoperative MR imaging evaluation.

As shown in Fig. 2, the increase in the SICI was weakly but significantly correlated with improvement in walking performance, as assessed using the TGS test ($r = 0.34, p < 0.01$; Pearson correlation), and was associated with a significant decrease of the absolute interside difference ($p < 0.05$). There was no significant relationship between changes in corticospinal excitability and the Evans index scores, or between baseline measures of corticospinal excitability and postoperative improvement in clinical ratings.

**Discussion**

The present study demonstrates that iNPH is associated with impairment of corticospinal excitability. The main finding was a significant reduction of the SICI, indicating a dysfunction of γ-aminobutyric acid-A inhibitory circuits, a phenomenon that could play a key role in mediating the effects of frontal lobe dysfunction on motor performance. The disinhibition of the motor cortex is a common observation in many neurological conditions, and thus could not be considered specific for iNPH. However, the correlation with clinical improvement highlights its potential utility as a biomarker.

**TABLE 1: Parameters of corticospinal excitability of the dominant and nondominant leg motor area in control and patient groups**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>iNPH Group</th>
<th>Age-Matched Control Group</th>
<th>Young Control Group</th>
<th>Age-Matched Neuropathy Group</th>
<th>$F_{1,55}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>23</td>
<td>8</td>
<td>19</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>rMT (%)</td>
<td>60.9 ± 11.6†</td>
<td>86.1 ± 9.8</td>
<td>78.7 ± 8.7</td>
<td>75.3 ± 8.5</td>
<td>17.7; $p &lt; 0.00001$</td>
</tr>
<tr>
<td>MEP/M-wave area ratio (%)</td>
<td>7.7 ± 7.8</td>
<td>8.3 ± 8.3</td>
<td>2.3 ± 0.5</td>
<td>3.9 ± 1.6</td>
<td>1.8; NS</td>
</tr>
<tr>
<td>CMCT (msec)</td>
<td>14.8 ± 2.4</td>
<td>13.5 ± 1.7</td>
<td>13.5 ± 1.1</td>
<td>14.6 ± 1.6</td>
<td>2.2; NS</td>
</tr>
<tr>
<td>PL (msec)</td>
<td>29.8 ± 2.7</td>
<td>28.4 ± 2.4</td>
<td>26.7 ± 2.5</td>
<td>33.1 ± 0.9†</td>
<td>15.5; $p &lt; 0.00001$</td>
</tr>
<tr>
<td>SICI (%)</td>
<td>83.8 ± 38.2†</td>
<td>35.8 ± 14.6</td>
<td>26.1 ± 12.5</td>
<td>32.8 ± 13.6</td>
<td>20.0; $p &lt; 0.00001$</td>
</tr>
<tr>
<td>ICF (%)</td>
<td>184.2 ± 72.1</td>
<td>217.7 ± 136.9</td>
<td>210.2 ± 154.5</td>
<td>186.2 ± 52.8</td>
<td>0.3; NS</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SD. Abbreviation: NS = not significant.
† Significant difference compared to control groups: $p < 0.05$, 1-way ANOVA, post hoc unpaired t-test.

**TABLE 2: Absolute interside differences of parameters of corticospinal excitability in control and patient groups**

<table>
<thead>
<tr>
<th>AISD Parameters</th>
<th>iNPH Group</th>
<th>Age-Matched Control Group</th>
<th>Young Control Group</th>
<th>Age-Matched Neuropathy Group</th>
<th>$F_{1,55}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>23</td>
<td>8</td>
<td>19</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>rMT</td>
<td>4.7 ± 5.4</td>
<td>4.0 ± 3.8</td>
<td>2.8 ± 1.3</td>
<td>2.9 ± 1.9</td>
<td>0.8; NS</td>
</tr>
<tr>
<td>MEP/M-wave area ratio (%)</td>
<td>4.4 ± 5.7</td>
<td>2.8 ± 2.4</td>
<td>1.9 ± 2.1</td>
<td>1.7 ± 2.8</td>
<td>2.2; NS</td>
</tr>
<tr>
<td>CMCT</td>
<td>1.6 ± 0.9</td>
<td>1.3 ± 0.9</td>
<td>1.3 ± 1.1</td>
<td>1.4 ± 1.5</td>
<td>1.5; NS</td>
</tr>
<tr>
<td>SICI</td>
<td>27.8 ± 13.9†</td>
<td>11.1 ± 7.0</td>
<td>10.1 ± 11.2</td>
<td>6.5 ± 4.0</td>
<td>11.0; $p &lt; 0.0001$</td>
</tr>
<tr>
<td>ICF</td>
<td>44.0 ± 46.4</td>
<td>36.8 ± 28.9</td>
<td>47.8 ± 55.8</td>
<td>49.5 ± 96.4</td>
<td>0.1; NS</td>
</tr>
</tbody>
</table>

* Values are expressed as the mean ± SD. Abbreviation: AISD = absolute interside difference.
† Significant difference compared to control groups: $p < 0.05$, 1-way ANOVA, post hoc unpaired t-test.
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The low rMT appears to be related to hyperexcitability of the excitatory circuits of the motor cortex, probably due to weak inhibitory control from the premotor and subcortical regions.

The reduction of the intracortical inhibition in patients with iNPH was bilateral, but more prominent on one side regardless of the lower-limb dominance, thus resulting in a significantly higher interside difference compared with control volunteers. This between-side asymmetry was reversible in patients who improved significantly after ventricular shunt placement and, therefore, it could be attributed to an iNPH-associated impairment. It might be speculated that such an asymmetrical motor cortex disinhibition is related to balance disturbance in iNPH patients. However, this suggestion cannot be confirmed or ruled out on the basis of our data. A further study with a larger number of patients is needed to assess correlations between specific gait abnormalities and asymmetrical changes in the SICI. Besides, a possible effect of asymptomatic unilateral small ischemic lesions or subclinical myelopathy impairments cannot be totally excluded.

Aging and age-associated peripheral nervous system disorders could be additional factors contributing to changes of corticospinal excitability. Significant reduction of intracortical inhibition was found in patients with diabetic neuropathic pain. On the other hand, no impairment of motor cortex excitability was revealed in diabetic patients without pain. Healthy elderly volunteers exhibit even stronger intracortical inhibition compared with young adults. In our study, the parameters of corticospinal excitability remained unaffected in a group of age-matched healthy volunteers and patients with peripheral neuropathy, in comparison with younger controls. Furthermore, there was no difference in any parameter of corticospinal excitability between patients with iNPH who had concomitant peripheral nervous system involvement and patients with “pure” iNPH. Therefore, aging and age-associated peripheral nerve dysfunction could

![Fig. 1. Bar graphs showing significant enhancement of the SICI (A) and increase of the rMT (B) 1 month after ventricular shunt placement in patients who markedly improved in walking performance (10 patients; reduction of ≥ 50% in TGS score) compared with those who showed < 50% reduction in TGS score (13 patients). *p < 0.01, post hoc paired t-test, in comparison with baseline.](image)

![Fig. 2. Scatterplot showing a positive correlation between SICI enhancement (expressed as percentage increase compared with baseline) in the dominant side and gait improvement (expressed as percentage reduction in TGS score compared with baseline) in response to ventricular shunt placement in 23 patients with iNPH (r = 0.34, p < 0.01).](image)
not be responsible for impairment of corticospinal excitability observed in the patients with iNPH in our series.

Ventricular shunt placement resulted in enhancement of the SICI, decrease of its absolute interside difference, and increase of the rMT in patients who showed marked improvement in gait 1 month after surgery. This indicates a close relationship between postoperative changes in corticospinal excitability and positive treatment response. However, it is still unclear whether an increase of the SICI and rMT plays a role in the mechanisms underlying the therapeutic effect of ventricular shunt placement, or whether it reflects plasticity changes in the brain following improvement of motor performance and recovery of motor skills.

In this study we found no relationship between baseline TMS measures and degree of clinical improvement. Therefore, the preoperative evaluation of corticospinal excitability, as applied in our study, seems not to add to diagnostic accuracy in predicting postsurgical outcome. Furthermore, similarities in the neurophysiological patterns of iNPH and neurodegenerative diseases, both of which exhibit features of cortical hyperexcitability, limit the diagnostic value of TMS in differentiating between these conditions. Nevertheless, the reversible nature of changes in corticospinal excitability, and probably selective and asymmetrical involvement of the leg motor area in iNPH, raise the possibility of disclosure of this entity’s distinctive neurophysiological profile. Further comparative TMS studies with recording from both lower and upper limbs, which will include patients with hydrocephalus caused by other reasons (including obstructive and ex vacuo hydrocephalus) and those with ventriculomegaly not accompanied by gait disturbance, are required to address the question of whether the disinhibition of the motor cortex, which occurs within the lower-limb representation and is responsive to treatment, could serve as a neurophysiological marker of iNPH. In this respect, it will be important to elucidate whether the recovery of corticospinal excitability could be detected early after ventricular shunt placement or even after large-volume lumbar puncture.

Conclusions

This study showed that iNPH affects corticospinal excitability, causing disinhibition of the motor cortex. Clinical improvement following ventricular shunt placement is associated with enhancement of the intracortical inhibition and increase of the motor threshold. These results support the view that impaired control of the motor output due to altered connectivity in the motor network, rather than impairment of the corticospinal conduction, is related to gait disturbances in iNPH. The suggestion that evaluation of corticospinal excitability might be useful for the assessment of treatment response should be viewed as preliminary, and calls for further larger studies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Chistyakov, Zaarooz. Acquisition of data: Chistyakov, Hafner, Kaplan. Analysis and interpretation of data: Chistyakov, Hafner, Sinai, Kaplan. Drafting the article: Chistyakov, Hafner. Critically revising the article: all authors. Reviewed the final version of the manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chistyakov. Statistical analysis: Chistyakov, Sinai. Administrative/technical/material support: Hafner, Zaarooz. Study supervision: Chistyakov, Zaarooz.

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Manuscript submitted April 19, 2011. Accepted September 14, 2011.

Portions of this work were presented in abstract and poster form at the 29th International Congress of Clinical Neurophysiology, International Federation of Clinical Neurophysiology, which was held in Kobe, Japan, in 2010.

Please include this information when citing this paper: published online October 14, 2011; DOI: 10.3171/2011.9.JNS11678.

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