Subclinical Declines in the Verbal Fluency and Motor Regulation of Patients with AVIM (Asymptomatic Ventriculomegaly with Features of Idiopathic NPH on MRI): A Case-controlled Study

Chifumi Iseki, Yoshimi Takahashi, Manabu Wada, Toru Kawanami and Takeo Kato

Abstract

Objective We previously reported that, on brain MRI, iNPH features were observed in approximately 1% of asymptomatic elderly community dwellers. This phenomenon is designated asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM). The aim of the present study was to clarify whether a subclinical decline in the neuropsychological function is present in patients with AVIM.

Methods We examined eight subjects with AVIM, six subjects with possible iNPH and 21 elderly controls. Neuropsychological tests were used, including the mini-mental state examination (MMSE), the Hasegawa dementia scale-revised (HDS-R), the frontal assessment battery (FAB), the trail making test A&B and semantic and letter verbal fluency tests.

Results When comparing the individuals with AVIM with the control subjects, significant differences were found in the scores achieved on the semantic verbal fluency tests and Luria’s motor series (fist-edge-palm), a subtest of the FAB.

Conclusion The present study suggests that individuals with AVIM demonstrate a slight subclinical decline in the cognitive function and motor regulation, which may represent a prodromal stage of iNPH.

Key words: hydrocephalus, MRI, semantic fluency, frontal assessment battery, prodromal iNPH

(Intern Med 52: 1687-1690, 2013)
(DOI: 10.2169/internalmedicine.52.8914)

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) occurs in the elderly without any preceding diseases and is characterized by the clinical triad of gait disturbance, cognitive impairment and urinary incontinence. Because the symptoms of iNPH can be improved with shunt surgery, making an exact diagnosis of the disease is important in the clinical setting. On magnetic resonance imaging (MRI), ventriculomegaly and disproportional narrowing of the subarachnoid space and cortical sulci at the high convexity of the cerebrum have been reported to be characteristic of iNPH (1). These MRI features have proved useful in the diagnosis of iNPH and are now included in the “Guidelines for Management of iNPH” issued by the Japanese Society of NPH (2).

Since 2000, we have conducted a community-based, prospective study of elderly individuals using brain MRI as well as various medical and neurological examinations (3-5). In that study, we found asymptomatic elderly individuals who exhibited the MRI features described above, designated Asymptomatic Ventriculomegaly with features of iNPH on MRI (AVIM) (5). Other community-based studies have also been based on brain MRI screening to identify subjects suspected of having iNPH (6, 7).

In the present study, the individuals with AVIM scored within the normal limits on the screening neuropsychological examinations, such as the mini-mental state examination (MMSE) and the Hasegawa dementia scale-revised (HDS-R). The present study aimed to detect subclinical neuropsychological declines in individuals with AVIM.
Neuropsychological examinations

We selected frequently used neuropsychological tests for patients with iNPH in order to evaluate the comprehensive cognitive function (8, 9). The MMSE and HDS-R were performed as global measurements to estimate the cognitive function. The frontal assessment battery (FAB) was used to estimate the frontal lobe function (10). The trail making test A (TMT-A) was used to measure psychomotor speed, and the trail making test B (TMT-B) was used to measure the executive function (11). In addition, we analyzed the results of verbal fluency tests, including tests of semantic fluency and letter fluency as subparts of the HDS-R and FAB, respectively. Verbal fluency tests were primarily employed to measure the frontal lobe function. In the semantic fluency test, the subjects were requested to produce as many words from the vegetable category as possible within one minute. In the letter fluency test, the subjects were asked to generate as many Japanese words beginning with “Ka” as possible within one minute.

The total scores of the MMSE, HDS-R and FAB, the time (seconds) taken to complete the TMT-A and TMT-B, the number of errors on the TMT-B and the total number of words produced in the semantic and letter verbal fluency tests were compared between the AVIM group and the controls. We also compared these scores between the possible iNPH group and the controls. The statistical differences in the average scores between two groups were analyzed using the Mann-Whitney U-test. Comparisons of the proportions of individuals of each sex and the number of subjects having vascular risk factors (HT, HL or DM/IGT) between two groups were made using the chi-square test. A probability value of <0.05 was considered to be statistically significant. The R version 2.15.2 (12) software program was used for the statistical analysis.

The study was approved by the Medical Ethics Committee of the Yamagata University Faculty of Medicine. Written informed consent was obtained from all subjects.

Results

Seven subjects were assigned to the AVIM group (three men and four women, average age 76±1.9 years). Six subjects (four men and two women, average age: 75±4 years) exhibited one or more symptoms of the triad and were assigned to the possible iNPH group. The control group consisted of 21 participants without any neurological or MRI abnormalities (11 men and 10 women, all 78 years of age).

The mean values ± SD for the neuropsychological tests and the proportions of subjects with vascular risk factors (HT, HL or DM/IGT) are summarized in Table. There were no significant differences between the AVIM group and the controls in the total scores of the MMSE, HDS-R, most FAB subtests and the total FAB score and the TMT-A&B results. However, in the semantic fluency tests and examinations of motor programming, a subtest of the FAB, signifi-
Table. Characteristics of Each Group and Results of Cognitive Examinations

<table>
<thead>
<tr>
<th></th>
<th>Controls N = 21</th>
<th>AVIM N = 7</th>
<th>p value</th>
<th>Possible iNPH N = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>78 ± 0</td>
<td>76 ± 1.9</td>
<td>&lt;0.001</td>
<td>75 ± 4.4</td>
</tr>
<tr>
<td>Sex (men/ women)</td>
<td>11/ 10</td>
<td>3/4</td>
<td>0.66</td>
<td>4/2</td>
</tr>
<tr>
<td>HT (prevalence)</td>
<td>67%</td>
<td>86%</td>
<td>0.33</td>
<td>100%</td>
</tr>
<tr>
<td>HL (prevalence)</td>
<td>33%</td>
<td>43%</td>
<td>0.64</td>
<td>33%</td>
</tr>
<tr>
<td>DM/ IGT (prevalence)</td>
<td>14%</td>
<td>43%</td>
<td>0.11</td>
<td>83%</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.8 ± 2.3</td>
<td>26.3 ± 2.6</td>
<td>0.62</td>
<td>20.3 ± 8.6</td>
</tr>
<tr>
<td>HDS-R</td>
<td>25.8 ± 2.0</td>
<td>26.4 ± 2.1</td>
<td>0.46</td>
<td>15.3 ± 9.4</td>
</tr>
<tr>
<td>Semantic Fluency</td>
<td>12.7 ± 3.3</td>
<td>9.4 ± 1.3</td>
<td>0.024*</td>
<td>7.5 ± 3.4</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>7.2 ± 3.2</td>
<td>5.9 ± 3.1</td>
<td>0.22</td>
<td>3.7 ± 1.9</td>
</tr>
<tr>
<td>FAB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conceptualization</td>
<td>1.8 ± 0.9</td>
<td>2.0 ± 0.8</td>
<td>0.71</td>
<td>1.8 ± 1.2</td>
</tr>
<tr>
<td>Mental Flexibility</td>
<td>1.9 ± 0.8</td>
<td>1.9 ± 0.9</td>
<td>0.88</td>
<td>0.5 ± 0.6</td>
</tr>
<tr>
<td>Motor-programming</td>
<td>2.2 ± 0.8</td>
<td>1.1 ± 0.9</td>
<td>0.01*</td>
<td>1.2 ± 0.8</td>
</tr>
<tr>
<td>Sensitivity to Influence</td>
<td>2.6 ± 0.6</td>
<td>2.4 ± 0.8</td>
<td>0.59</td>
<td>1.2 ± 1.3</td>
</tr>
<tr>
<td>Inhibitory Control</td>
<td>1.4 ± 0.8</td>
<td>1.9 ± 1.1</td>
<td>0.3</td>
<td>0.5 ± 0.5</td>
</tr>
<tr>
<td>Total Score</td>
<td>12.8 ± 2.2</td>
<td>12.3 ± 2.4</td>
<td>0.68</td>
<td>7.0 ± 3.9</td>
</tr>
<tr>
<td>TMT-A (seconds)</td>
<td>74.8 ± 23</td>
<td>77.3 ± 31</td>
<td>0.73</td>
<td>107.1 ± 52</td>
</tr>
<tr>
<td>TMT-B (seconds)</td>
<td>231.7 ± 95</td>
<td>201.0 ± 141</td>
<td>0.29</td>
<td>Note**</td>
</tr>
<tr>
<td>TMT-B (number of errors)</td>
<td>1.1 ± 1.5</td>
<td>1.4 ± 1.5</td>
<td>0.57</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as the mean ± standard deviation except for the indications. p value(s) were gained from comparison between controls and AVIM. Significance, defined as p<0.05, is represented by * for both controls and AVIM. The Mann-Whitney U-tests were employed for analysis of average scores between controls and AVIM. Proportion of sex and prevalence of vascular risk factors (HT, HL or DM/IGT) were analyzed by chi-square test between controls and AVIM.

AVIM: Asymptomatic Ventriculomegaly with features of iNPH on MRI, HT: Hypertension, HL: Hyperlipidemia, DM/IGT: Diabetes Mellitus or Impaired Glucose Tolerance, MMSE: Mini Mental State Examination, HDS-R: Hasegawa Dementia Scale Revised, FAB: Frontal Assessment Battery, TMT: Trail Making Test, **: Three of six subjects could not accomplish the test.

cant differences were observed between the two groups. On the semantic fluency test, the total number of vegetable names given was 9.4±1.3 in the AVIM group and 12.7±3.3 in the control group. The motor programming scores, a sub-test of the FAB, were 2.2±0.8 in the AVIM group and 2.2±0.9 in the control group. In addition to the semantic fluency and motor programming scores, the letter fluency scores gradually decreased in this order: the control group, the AVIM group and the possible iNPH group (Table).

In many tests, the neuropsychological results were obviously reduced in the possible iNPH group compared with that observed in the control group.

Discussion

In the assessments of verbal fluency and motor programming, the cognitive and motor regulation in the AVIM group exhibited some decline compared with that observed in the control group. The total scores in the AVIM group were as the same as those observed in the control group on the FAB and TMT-A and B, which are clinically used to assess the frontal lobe function in iNPH patients. The possible iNPH group demonstrated obvious cognitive impairments that were easy to detect using screening tests. In contrast, the AVIM group exhibited slight but certain declines in the cognitive function and motor regulation that we detected by analyzing each test.

One of the limitations of the present study was the small sample size of the AVIM group, which resulted in weak statistical power. Another limitation was the difference in age between the AVIM group and the controls: the individuals in the AVIM group were younger than the controls, which affected the results of the cognitive tests. However, in spite of their age benefit, the subjects in the AVIM group, demonstrated inferior results in semantic fluency and motor programming, emphasizing that the AVIM group had subclinical declines in the cognitive and motor regulation functions.

Stuss et al. reported that verbal fluency is impaired in patients with focal brain lesions, including left dorsolateral frontal lesions, striatal lesions and right or left superior medial frontal lobe lesions (13). Patients with Alzheimer’s or Parkinson’s disease demonstrate more difficulties in semantic fluency than in letter fluency (14). The physiological mechanisms underlying semantic and letter fluency remain largely unknown; however, the neuropsychological basis of these neurodegenerative diseases may be different. iNPH
and its subclinical stage, AVIM, appear to involve the same tendencies.

We also showed that the motor programming task known as Luria’s motor series, called the “fist-edge-palm” (15), can be used to detect a declining function in patients with AVIM. This task requires the subject to organize several focal brain areas, including the sensorimotor, premotor, supplementary motor and even left parietal areas (16). The task is unique in that it forces iNPH patients to reveal hidden upper extensor clumsiness. In the present study, it was noted that the AVIM subjects were not skillful in this task, although they did not exhibit any gait disturbance.

Takaya et al. (17) conducted a hospital-based study and found that decreases in the cerebral blood flow were observed not only in iNPH patients, but also in AVIM patients. However, in that study, there were no differences between the patients with AVIM and the controls in the total scores obtained on various neuropsychological tests, including the MMSE, FAB, TMT-A, Wechsler memory scale revised attention/concentration and Rivermead behavioral memory test. Our results imply that subclinical symptoms in patients with AVIM are detectable using subtests of screening tests, particularly, tests of verbal fluency and Luria’s motor series. Iddon et al. (18) reported that iNPH patients without overt dementia (with gait disturbance or urinary incontinence) exhibit impairment of verbal fluency, set shifting and space recognition. The patient population and results of that study are similar to the AVIM population and results observed in the present study.

In our previous study, some of the AVIM subjects eventually converted to being symptomatic. In other words, AVIM may be a preclinical stage of iNPH (5). We concluded based on the results of the present study that AVIM is a subclinical state in terms of both the cognitive function and the motor regulation function. Tests of verbal fluency and Luria’s motor series may be candidates for detecting the early signs of dysfunction of prodromal iNPH. Further follow-up studies are needed to determine how and which AVIM individuals will convert to being symptomatic.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Prof. Kyoko Suzuki of the Department of Clinical Neuroscience, Yamagata University Graduate School of Medicine for her advice on the cognitive tests. This study was supported in part by the Research Committee of Normal Pressure Hydrocephalus, Studies in the Epidemiology, Pathogenesis and Therapy from the Ministry of Health, Labour and Welfare of Japan and in part by a Grant-in-Aid from the Global COE (center of excellence) Program (F03) of the Japan Society for the Promotion of Science.

References


