Risk factors for the syndrome of ventricular enlargement with gait apraxia (idiopathic normal pressure hydrocephalus): a case-control study

M CASMIRO, R D'ALESSANDRO, F M CACCIATURE, R DAIDONE, F CALBUCCI, E LUGARESI

From the Institute of Neurology, University of Bologna, and the Neurosurgical Division, Bellaria Hospital, Bologna, Italy

SUMMARY A case-control study was performed to verify the association between the risk factors for cerebrovascular disease and the syndrome of ventricular enlargement with gait apraxia (VEGAS). This syndrome was defined on the basis of clinical and CT criteria alone; however, it may be representative of patients with idiopathic normal pressure hydrocephalus in whom gait disturbance is the initial symptom. Seventeen patients were matched for age and sex with one hospitalised and two general population controls. Among the risk factors considered we found a significant statistical association between VEGAS and hypertension (odds ratio = 3.14; p = 0.032), ischaemic heart disease (odds ratio = 4.20; p = 0.013), ECG ischaemic changes (odds ratio = 3.67; p = 0.029), low HDL-cholesterol levels (odds ratio = 3.75; p = 0.028) and diabetes (odds ratio = 6.00; p = 0.018). Our findings indicate that risk factors for cerebrovascular disease may play a role in the development of VEGAS.

Normal pressure hydrocephalus (NPH) is characterised by a clinical triad (gait disturbance, impairment of mental function and sphincteric incontinence) associated with neuroimaging findings of non-obstructive ventricular enlargement. Reversal of the symptomatology by a shunt is another important feature.

NPH has been traditionally divided into secondary and idiopathic forms. The former is related to head trauma, meningitis or subarachnoid hemorrhage but the aetiology and pathogenesis of idiopathic normal pressure hydrocephalus (INPH) remain uncertain.

The pathogenesis of INPH has traditionally been attributed to a low-grade asymptomatic meningeal disease causing meningeal thickening over the convexity of the cerebral hemispheres and resulting in reduced CSF reabsorption. A chronic inflammatory meningeal disease has been hypothesised, but not proved. A correlation between INPH and cerebrovascular disease has been proposed, based on anatomopathological and clinical correlations. Cerebrovascular changes have been reported in eight out of ten cases studied pathologically; these changes mainly consisted of atherosclerosis of cerebral vessels, lacunar and cystic infarctions, microinfarctions, concentric hypertrophy, hyalinosis and fibrinoid necrosis of the small intraparenchymal arteries, arteriolar and capillary sclerosis and demyelination areas.

Clinical correlates of INPH have included hypertension, diabetes, heart disease, obesity, and cerebrovascular disease. Graff-Radford and Gersky recently stressed the association between INPH and hypertension. Earnest et al. described in detail two patients with INPH who showed gross pathological findings typical of cerebrovascular disease (but no fibrosis) and numerous old microscopic bilateral infarctions in the basal ganglia (clinically asymptomatic). On the basis of these findings they hypothesised that hypertensive vascular disease with multiple deep cerebral infarctions may be the initial pathological process in some cases of INPH, acting through a reduction of tissue bulk and tensile strength of the periventricular white matter and basal ganglia, together with an increased intraventricular CSF pulse pressure due to hypertension. In order to investigate...
this hypothesis we performed a case-control study aimed at verifying if risk factors for cerebrovascular disease were also risk factors for INPH.

Methods

Cases: Diagnostic criteria

The cases had to satisfy the following diagnostic criteria: (a) A clinical picture of INPH (gait disturbance with or without impairment of mental function and urinary incontinence) and as the first symptom a gait disturbance characterised by shortened steps, slowed rate of stepping and scuffing feet, widened base and frequent falling (so-called "gait apraxia"). Impairment of mental function was assessed on the Blessed dementia scale; (b) A CT scan showing (1) dilatation of the ventricular system without obstruction, (2) obliteration of the cerebral sulci at the convexity, (3) areas of periventricular low density and (4) "rounding" of the frontal horns of the lateral ventricles. We excluded patients whose clinical history suggested a possible aetiology for NPH (head trauma, meningitis and subarachnoid haemorrhage).

Cases: inclusion criteria

To avoid possible bias we included in the study all patients consecutively admitted between December 1986 and February 1988 because of a gait disturbance, provided that the gait disturbance was the primary reason for seeking medical care. We therefore excluded from the study patients affected by gait disturbance but primarily seen for other neurological or non-neurological symptoms (such as TIAs, myocardial infarction).

Controls

Each case was paired to three controls, matched for sex and age (an age range of ± 3 years, with respect to each case, was chosen). One of these controls was represented by every next patient admitted because of a neurological disease not known to be related to the risk factors for cerebrovascular disease. Diagnoses of these hospitalised controls are shown in table 1. Each of these subjects underwent CT. The two other controls were randomly chosen among the general population of Bologna, using the General Registry Office lists. These subjects were contacted by telephone and asked to come forward for a free medical examination. Agreement was about 70%. The protocol required the exclusion from general population controls of those subjects who suffered from gait disturbance, since for ethical reasons we did not perform CT in this population group. However, nobody had to be excluded for this reason.

Risk factors

The following risk factors were evaluated: Hypertension: blood pressure values exceeding 160 and/or 95 mm Hg on at least three different measurements, or treatment with antihypertensive drugs, irrespective of blood pressure values; Ischaemic heart disease: documented previous clinical admissions for myocardial ischaemic disease; Ischaemic ECG changes: at the time of examination both cases and controls had a standard ECG record. Each ECG was evaluated independently by two "blind" expert cardiologists, and only concordant reports of ischaemic myocardial changes were accepted; HDL-cholesterol levels: reduced fasting blood high density lipoprotein (HDL)-cholesterol levels (below lower limits: 35 mg/100 ml for males and 45 mg/100 ml for females); Diabetes: fasting blood glucose levels were determined; values exceeding upper normal limits (110 mg/100 ml) or treatment with hypoglycaemic drugs; Transient ischaemic attacks (TIAs): only documented or highly suggestive episodes of transient ischaemic cerebral attacks were considered; Obesity: body mass estimate as a risk factor was carried out by means of the Body Mass Index (BMI = weight/height2 expressed as kg/m2) and obesity was defined on the basis of a BMI value exceeding 27 kg/m2; Smoking: present or past smoking habits were taken into account, irrespective of daily number of cigarettes smoked or duration of smoking habit; Alcohol: although alcohol is not considered a risk factor for cerebrovascular disease, we took it into account because of some reports in the literature of an association with INPH; daily alcohol consumption was estimated from questioning, and approximate volume values were converted into daily grams consumption using conversion tables of the Italian Istituto Nazionale della Nutrizione, a daily consumption exceeding 50 grams was considered.

Treatment of patients

A test removal of 20–30 ml cerebrospinal fluid was performed, according to Fisher, whenever patients agreed. Furthermore, each patient whose general condition made surgical treatment possible was referred for further investigations (RISA18 and infusion manometric test7); if results from these examinations showed inversion of CSF flow, a ventriculostomy was performed. All patients underwent physiotherapy.

Statistical analysis

Data analysis was carried out calculating odds ratios and p values by means of the Mantel-Haenszel matched chi-square test for multiple controls. Comparison between hospitalised and general population controls was performed by means of Fisher's exact test.

Table 1  Diagnoses of hospitalised controls

<table>
<thead>
<tr>
<th>No</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73 / M</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>2</td>
<td>68 / M</td>
<td>Meningioma of atlas</td>
</tr>
<tr>
<td>3</td>
<td>73 / M</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>4</td>
<td>65 / M</td>
<td>Acute disseminated encephalomyelitis</td>
</tr>
<tr>
<td>5</td>
<td>63 / M</td>
<td>Cervical spondylosis with myopathy</td>
</tr>
<tr>
<td>6</td>
<td>75 / F</td>
<td>Idiopathic sensorimotor polyneuropathy</td>
</tr>
<tr>
<td>7</td>
<td>75 / M</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>8</td>
<td>64 / M</td>
<td>Ocular myasthenia</td>
</tr>
<tr>
<td>9</td>
<td>64 / M</td>
<td>Orthostatic tremor</td>
</tr>
<tr>
<td>10</td>
<td>71 / M</td>
<td>Metastatic spinal cord compression from lung carcinoma</td>
</tr>
<tr>
<td>11</td>
<td>76 / F</td>
<td>Chronic polyradiculoneuritis</td>
</tr>
<tr>
<td>12</td>
<td>67 / F</td>
<td>Ocular myopathy</td>
</tr>
<tr>
<td>13</td>
<td>69 / M</td>
<td>Cerebral metastasis from lung carcinoma</td>
</tr>
<tr>
<td>14</td>
<td>71 / M</td>
<td>Progressive supranuclear palsy</td>
</tr>
<tr>
<td>15</td>
<td>66 / F</td>
<td>Idiopathic multiple mononeuropathy</td>
</tr>
<tr>
<td>16</td>
<td>78 / M</td>
<td>Brachial plexus metastatic infiltration from lung carcinoma</td>
</tr>
<tr>
<td>17</td>
<td>69 / M</td>
<td>Amyotrophic lateral sclerosis</td>
</tr>
</tbody>
</table>

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Results

The study included 17 patients with INPH (13 males and four females; mean age = 69-65 years, range 62-78 years) and 51 controls (mean age 70-25 years, range 63-79). General features of the patients are summarised in Table 2.

As regards mental impairment, the mean value of Blessed score was 4-26, ranging from 0 to 14-5; only six cases had a Blessed score over 4.

Six patients underwent RISA and an infusion manometric test: in each inversion of CSF flow was found and in four patients a ventriculo-atrial shunt was performed. The effect of treatment was assessed both on clinical grounds and by the subjective evaluation of patients and their relatives. Three patients showed marked improvement of gait disturbance at follow-up (six months later); the fourth (case 15) had a poor result. In another nine patients a CSF removal test was performed: in eight improvement of gait disturbance (from slight to marked) was achieved.

The associated CT scan findings were mainly ischaemic lacunes, found in five cases; slight atrophy was present in three cases and a cyst of the septum pellucidum in two. By comparison, among hospitalised controls we found ischaemic lacunes in one case and slight atrophy in five.

Risk factors

There were no statistically significant differences in risk factors among the two control populations (Table 3).

As far as the cases are concerned, odds ratios and p values for the risk factors under examination are shown in Table 4.

As can be seen, a significant association (p < 0.05) was found between INPH and hypertension, ischaemic heart disease, ECG ischaemic changes, reduced HDL-cholesterol levels and diabetes. There was not a significant association with the other factors under examination.

Discussion

This study was mainly concerned with the “special clinical problem” of idiopathic normal pressure hydrocephalus (INPH). Since Hakim and Adams"
Table 4 Results of case-control study

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Outcome among case-control quadruplets (case, control 1, control 2, control 3)*</th>
<th>Odds ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>+ + - - + + + - + - - + - - + - + + + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>3.14</td>
<td>0.032</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>- - + - + + + - - - + - - + - + + - + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>4.20</td>
<td>0.013</td>
</tr>
<tr>
<td>ECG ischaemic changes</td>
<td>2 - - + - + + + - - - + - - + - + + - + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>3.67</td>
<td>0.029</td>
</tr>
<tr>
<td>HDL-cholesterol levels</td>
<td>5 - - + - + + + - - - + - - + - + + - + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>3.50</td>
<td>0.028</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 - - + - + + + - - - + - - + - + + - + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>6.00</td>
<td>0.018</td>
</tr>
<tr>
<td>TIA</td>
<td>2 - - + - + + + - - - + - - + - + + - + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>1.67</td>
<td>0.096</td>
</tr>
<tr>
<td>Obesity</td>
<td>3 - - + - + + + - - - + - - + - + + - + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>1.67</td>
<td>0.343</td>
</tr>
<tr>
<td>Smoking</td>
<td>1 - - + - + + + - - - + - - + - + + - + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>1.08</td>
<td>0.893</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3 - - + - + + + - - - + - - + - + + - + - - + - + + + - + - + - + + + - - + - + + +</td>
<td>1.60</td>
<td>0.354</td>
</tr>
</tbody>
</table>

*Control 1 = hospitalised control; Control 2 and 3 = general population controls. + = Risk factor present; - = risk factor absent.

- + + - + = Matched quadruplets with risk factor present in case and absent in controls.
- + - + + = Matched quadruplets with risk factor present in case and only one control.
- + - + + = Matched quadruplets with risk factor present in case and two controls.
- + - + + = Matched quadruplets with risk factor present both in case and controls.
- - - + - = Matched quadruplets with risk factor absent in case and controls.
- - + - + = Matched quadruplets with risk factor absent in case and present in one control.
- - - + + = Matched quadruplets with risk factor absent in case and present in two controls.
- - - + + = Matched quadruplets with risk factor absent in case and present in three controls.

original description of this syndrome very little has been added to the understanding of its aetiology. Most of the studies on this topic have focused on the physiological and neuroimaging aspects of the syndrome. Others have attempted to define which parameters are likely to predict a good outcome following a shunt procedure.

Nevertheless, results are still unsatisfactory, showing only 40% positive responders to shunt with worse results than in patients with “secondary” NPH. The reason for this difference in outcome is uncertain but may reflect different underlying mechanisms. Furthermore, it must be emphasised that even the clinical features of this syndrome are not precisely defined,
Risk factors for the syndrome of ventricular enlargement with gait apraxia

and are limited to the general statement of a clinical triad ("a slowly progressive gait disorder, impairment of mental function and sphincteric incontinence"). The triad is not always present. Thus, the gait disturbance, may be the only obvious symptom and, although the features are often of the so-called "gait apraxia", it has also been described as "spasticity" or even as a Parkinsonian feature. Fisher stated that "it is obviously easier to say what the gait disturbance is not than what it is". These uncertainties make it difficult to perform clinical studies on INPH because selection criteria can always be questioned to some degree.

In this study patients were included on the basis of clinical and CT criteria alone. The reasons for this were, first, it was not ethical to submit a patient to an invasive diagnostic procedure unless there was the possibility of surgical treatment, and, second, the need to avoid the possible bias arising from considering only patients in good general condition. A definitive diagnosis of INPH requires RISA and an infusion manometric test. Since we limited our diagnostic criteria, we think it correct to call this clinical pattern "Ventricular enlargement with gait apraxia syndrome" (VEGAS), which is what clinicians really see. However, the diagnostic criteria we adopted are highly relevant because an onset with gait disturbance of INPH has been correlated with a good outcome following a shunt procedure.

In our study all patients showed an uniform clinical and CT picture and the six patients who underwent RISA and manometric infusion test showed patterns typical of INPH. On the other hand, these laboratory procedures have been judged as "often unnecessary with respect to the diagnosis of INPH if CSF removal test is positive". On the basis of these considerations we think that VEGAS is representative of a subgroup of patients with INPH and gait disturbance as first symptom.

In order to avoid possible selection bias we included only patients primarily seen because of gait disturbance. Also, we excluded from the study patients seen primarily because of other focal neurological symptoms suggesting cerebrovascular disease and showing a gait disturbance as well.

We found a significant association between the risk factors for atherosclerosis and VEGAS. This finding is in agreement with the hypothesis of Earnest et al. that at least in some cases of INPH "a hypertensive vascular disease with multiple deep cerebral infarctions may be the initial pathological process." Furthermore our data confirm and extend the finding by Graff-Radford and Godersky of an association between INPH and hypertension. We cannot speculate on the pathogenesis of VEGAS but only on the aetiology; we cannot exclude that a meningeal thickening may play a role in the development of VEGAS but our findings showed more support for the hypothesis of Earnest et al.

Further studies are needed of the mechanism by which cerebrovascular disease contributes to the development of this syndrome. If our findings are confirmed, future studies should be developed to verify whether optimal treatment of risk factors may improve the course of the disease. In any case, neurologists examining such patients will be aware of the need to screen them for potentially dangerous cardiovascular diseases.

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