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Pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis
A report of 50 cases

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Summary

This is the first large series, comprising 50 patients who suffered a total of 164 episodes, of pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis (PMP syndrome). Onset of PMP was between the ages of 14 and 39 years and was most frequent in males (68%). Eight males (24%) and five females (31%) had a personal history of migraine. One-quarter had had a viral-like illness up to 3 weeks prior to the onset of the syndrome. The clinical picture consisted of one to 12 episodes of changing variable neurological deficits accompanied by moderate-to-severe headache and occasionally fever. The headaches were described as predominantly throbbing and bilateral with variable duration (mean, 19 h). The mean duration of the transient neurological deficits was 5 h. Sensory symptoms were most common (78% of episodes), followed by aphasic (66%) and motor (56%) symptoms. Visual symptoms appeared in only 12% of episodes. The most frequent combinations were motor aphasia plus sensory and motor right hemibody symptoms (19% of episodes), motor aphasia plus right sensory symptoms (10%) and isolated right (9%) or left (9%) sensory symptoms. All patients were asymptomatic between episodes and following the symptomatic period (maximum duration 49 days). Visual symptoms appeared in only 12% of episodes. The most frequent combinations were motor aphasia plus sensory and motor right hemibody symptoms (19% of episodes), motor aphasia plus right sensory symptoms (10%) and isolated right (9%) or left (9%) sensory symptoms. All patients were asymptomatic between episodes and following the symptomatic period (maximum duration 49 days).

Lymphocytic pleocytosis ranged from 10 to 760 lymphocytic cells/mm² CSF (mean, 199). In CSF, protein was increased in 96% of patients, IgG was normal in 80% of cases and oligoclonal bands were not found. Adenosine deaminase values were slightly above normal in two out of 16 patients tested. Extensive microbiological determinations, including viral HIV and borrelia serologies, were negative. Brain CT and MRI were always within normal limits, while EEG frequently showed focal slowing. Conventional cranial angiography was performed on 12 patients. In only one were there abnormalities suggestive of localized vascular inflammation, coincident with the focal neurological symptoms. Two patients developed PMP symptoms immediately after angiography. SPECT, performed on only three patients in the symptomatic period, revealed focal areas of decreased uptake consistent with the clinical symptoms. PMP aetiology remains a mystery: chronic arachnoiditis, viral meningoencephalitis or migraine are not plausible aetological explanations. Because a number of patients had had a prodromic viral-like illness, we hypothesize here that such a viral infection could activate the immune system, thereby producing antibodies that would induce an aseptic inflammation of the leptomeningeal vasculature, possibly accounting for this clinical picture.

Keywords: migraine; pseudomigraine with lymphocytic pleocytosis

Abbreviations: ADA = adenosine deaminase; CMV = cytomegalovirus; PMP = pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis

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Introduction

In 1980, Swanson et al. reported in the Annual Meeting of the American Academy of Neurology seven patients who had experienced three to 12 episodes of temporary neurological deficit accompanied or followed by migrainous headache and CSF pleocytosis of unknown origin. All stopped having episodes in <12 weeks. These cases were published the following year (Bartleson et al., 1981). Independently, Martí-Massó et al. in the 1980 Spring Meeting of the Spanish Society of Neurology described three similar patients, who were formally reported together with seven other cases (Martí-Massó et al., 1984). Three similar cases of this pseudomigraine with pleocytosis (PMP) had been published before Bartleson et al.’s paper (Kremenitzer and Golden, 1974; Schraeder and Burns, 1980; Dobkin, 1981) and 23 further cases, in small series, each with up to five patients, were published in English between 1981 and 1987 (Casteels-van Daele et al., 1981; Rolak et al., 1982; Martí-Massó et al., 1983; Brattstrom et al., 1984; Day and Knezevic, 1984; Neufeld et al., 1985; Rossi et al., 1985; Walter and Grogan, 1986; Stamboulis et al., 1987). Although most authors have speculated that this syndrome is more common than is usually recognized, no further cases were published until 1995 when Berg and Williams added seven new patients diagnosed at their hospital in the previous 15 years.

The origin and significance of the CSF lymphocytic pleocytosis are unknown. While some authors consider that CSF pleocytosis is secondary to a migraine attack (Lhermitte et al., 1982; Stamboulis et al., 1987), others attribute this clinical picture to a viral meningitis (Bartleson et al., 1981; Casteels-van Daele et al., 1981) or to Mollaret’s disease (Rolak et al., 1982). Most of these patients, however, were studied before the 1988 appearance of diagnostic criteria for migraine and other headaches (Headache Classification Committee of the International Headache Society, 1988), and were not tested for conditions, such as Lyme disease or AIDS, which could theoretically mimic this syndrome.

In this study, we analyse the demographic, clinical and laboratory data of a large series of 50 patients with PMP.

Patients and methods

The Group for the Study of Headache within the Spanish Society of Neurology asked all the members of the Society (in an official letter of the Society in May 1996) to collaborate in reviewing their cases of PMP syndrome diagnosed in our country. General inclusion criteria were as follows: (i) at least one episode of transient neurological deficit accompanied or followed by moderate-to-severe headache; (ii) CSF pleocytosis with lymphocytic predominance; (iii) negative aetiological studies; (iv) spontaneous resolution of the clinical picture in <4 months. Neurologists with patients meeting these general criteria were asked to fill in an extensive questionnaire prepared by the group coordinator (J.P.) including patients’ demographic data, as well as details of the clinical picture and of the complementary data.

Results

Fifty patients fulfilled the required criteria for PMP syndrome diagnosis. Patients (n = 6) who did not fulfil all inclusion criteria or who had incomplete data were excluded from this series.

Demographic data

Of these 50 patients, 16 were female (32%) and 34 male (68%). Their ages ranged from 14 to 39 years, with a mean (±SD) of 28.1 ± 6.3 years. Thirty (60%) of our 50 patients had a personal history of migraine according to present criteria. Eight (23.5%) were males and five (31.3%) females. Three of these 13 patients suffered from migraine with aura, while the remaining 10 had migraine without aura. No patient referred to a family history compatible with PMP diagnosis. Our patients became ill at different times of the year: winter (30%) > summer (28%) > autumn (24%) > spring (18%). In 10 patients (20%) this syndrome began in August, one patient became symptomatic in October, while in the others the beginning of the clinical picture was quite spaced out throughout the year. Two patients were admitted in August into different hospitals with this syndrome within days of one another. Patients came from most regions; 27 cases (54%) were from the southern half of Spain and 23 (46%) from the northern half. Ten out of 40 patients (25%) for whom this information was available had symptoms of a preceding viral-like illness (general malaise with diarrhoea in four cases and with cough and rhinitis in six cases) varying between a few days and 3 weeks prior to the onset of the syndrome.

Clinical picture

All patients included here experienced a transient syndrome consisting of focal neurological deficits and headache. A total of 164 episodes were documented in these 50 patients. The mean number of episodes per patient (±SD) was 3.2 ± 2.4 (range, 1–12; mode, 2). Single episodes occurred in 11 patients (22%).

Focal neurological deficits

Forty-three patients (86%) had transient neurological deficits restricted either to one hemisphere (40 patients, 80%) or to basilar artery territory (three patients, 6%). Seven (14%) of our patients had episodes affecting different brain regions (then always left and right hemispheres, but never basilar plus carotid territories). Thirty-seven patients (74%) had neurological deficits in their left hemisphere, 10 patients (20%) in their right hemisphere and three (6%) in basilar territory. In five out of the 36 patients having multiple episodes in one hemisphere, the neurological deficit was not the same in different episodes. The duration of focal
neurological deficits ranged from 5 min to 3 days (mean ± SD = 5 ± 13 h). Thirty-five (70%) experienced sensory symptoms in 128 (78%) episodes. The nine patients suffering from left-sided sensory symptoms also had sensory symptoms in their right hemibody in other episodes. Sensory symptoms were usually described as numbness frequently starting in the hand and progressing through the arm, then affecting the face and tongue, whereas the body and legs were rarely involved. Numbness was bilateral in three cases affecting the peribuccal area and at least three extremities. Aphasias were seen in 33 patients (66%) in 99 (60%) episodes. Pure motor aphasia was the most frequent speech disorder [17 patients (34%), 59 (36%) episodes], followed by global aphasia [15 (30%) patients, 36 (22%) episodes] and pure sensory aphasia [three (6%) patients, four (2%) episodes]. Hemispheric weakness, most frequent in the face and distal arm, was recognized in 21 (42%) patients in 94 (56%) episodes. Again, the five patients with transient left hemispheric weakness also had episodes with weakness in their right hemibody. Visual symptoms appeared in nine (18%) patients in 19 (12%) episodes. Two patients (4%) had bilateral blurring of vision, four (8%) homonymous hemianopsia and three (6%) photopsias. Finally, one patient had dysarthria and another an epileptic fit. The distribution of the various symptoms is illustrated in Fig. 1. The frequency of the different combinations of symptoms in each episode is shown in Table 1. The most frequent combinations were motor aphasia plus sensory and motor right hemibody symptoms (31 episodes in five patients), motor aphasia plus right sensory symptoms (16 episodes in four patients), isolated right sensory symptoms (14 episodes in seven patients) and isolated left sensory symptoms (14 episodes in six patients).

Four patients. In 27 (59%) pain was bilateral, in 17 (37%) hemispheric (always contralateral to the focal symptoms), and two (4%) patients had some episodes in which the headache was hemispheric and others with a bilateral headache. Headache duration was variable, ranging from 1 h to 1 week (mean ± SD = 19 ± 30 h; mode = 6 h). During the symptomatic period, 16 patients in this series had episodes of isolated headache not accompanied by transient neurological symptoms. The characteristics of these isolated headaches were identical to those already described for headache accompanied or preceded by focal neurological symptoms. The mean number (±SD) of isolated headache episodes in these 16 patients (30%) was 2.5 ± 2.2 (range, 1–8). Additionally, two patients also had one episode of transient neurological manifestations followed by no headache.

### Table 1 Combinations of transient neurological symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Episodes (n = 164)</th>
<th>Patients (n = 50)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>MAPh + RS + RW</td>
<td>31</td>
<td>18.9</td>
</tr>
<tr>
<td>MAPh + RS</td>
<td>16</td>
<td>9.8</td>
</tr>
<tr>
<td>RS</td>
<td>14</td>
<td>8.5</td>
</tr>
<tr>
<td>LS</td>
<td>14</td>
<td>8.5</td>
</tr>
<tr>
<td>GAPh + RS</td>
<td>12</td>
<td>7.3</td>
</tr>
<tr>
<td>RS + RW</td>
<td>11</td>
<td>6.7</td>
</tr>
<tr>
<td>GAPh + RS + RW</td>
<td>10</td>
<td>6.1</td>
</tr>
<tr>
<td>LS + LW</td>
<td>9</td>
<td>5.5</td>
</tr>
<tr>
<td>GAPh + RS + RW + V</td>
<td>7</td>
<td>4.2</td>
</tr>
<tr>
<td>MAPh + RW</td>
<td>6</td>
<td>3.7</td>
</tr>
<tr>
<td>MAPh + RS + V</td>
<td>5</td>
<td>3.0</td>
</tr>
<tr>
<td>LW + dysarthria</td>
<td>5</td>
<td>3.0</td>
</tr>
<tr>
<td>GAPh + RW</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>GAPh</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>V</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>BilS</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>RW</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>BilS + V</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>SAPh + RS + RW</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>MAPh</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>SAPh</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>SAPh + RW</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>GAPh + RS + V</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

MAPh = motor aphasia; SAPh = sensory aphasia; GAPh = global aphasia; RS = right sensory symptoms; LS = left sensory symptoms; BilS = bilateral sensory symptoms; RW = right weakness; LW = left weakness; V = visual symptoms. *Note that transient neurological symptoms were not always the same for each patient in different episodes (see Results for further information).

**Headache characteristics**

Headache was subjectively referred to as moderate or severe by all patients. Pain quality was not well documented in eight patients. In the remaining 42, headache was described as predominantly throbbing by 34 (81%), as predominantly oppressive by five (12%) and as both oppressive and throbbing by three (7%). Headache localization was not reported by four patients. In 27 (59%) pain was bilateral, in 17 (37%) hemispheric (always contralateral to the focal symptoms), and two (4%) patients had some episodes in which the headache was hemispheric and others with a bilateral headache. Headache duration was variable, ranging from 1 h to 1 week (mean ± SD = 19 ± 30 h; mode = 6 h). During the symptomatic period, 16 patients in this series had episodes of isolated headache not accompanied by transient neurological symptoms. The characteristics of these isolated headaches were identical to those already described for headache accompanied or preceded by focal neurological symptoms. The mean number (±SD) of isolated headache episodes in these 16 patients (30%) was 2.5 ± 2.2 (range, 1–8). Additionally, two patients also had one episode of transient neurological manifestations followed by no headache.

**Accompanying symptoms and signs**

Nausea plus vomiting were reported by 27 patients (54%), isolated nausea was experienced by three further patients (6%). Photophobia and/or sonophobia were mentioned by eight patients (16%), though, on reviewing the clinical charts,
at least 10 patients in this series were not specifically asked about these symptoms in any episode. Fever (37.5–39°C) was recorded in 11 patients (22%), always coinciding with these episodes. No patient had meningeal signs.

**Clinical course and prognosis**
All patients were asymptomatic between episodes. Total duration of the illness ranged from 6 h to 49 days (mean ± SD = 14 ± 10 days). After this period, all patients remain asymptomatic, with a follow-up of between 6 months and 10 years.

**Complementary data**

**CSF parameters**
The results of the first lumbar puncture are summarized in Table 2. Most patients had several abnormal CSF determinations during the symptomatic period as well as a final lumbar puncture with normal results. CSF opening pressure was measured in 18 cases, being elevated (between 180 and 370 mmH₂O) in 10 (56%). CSF glucose, as compared with serum levels, was always normal. All cases showed CSF pleocytosis (mean ± SD = 199 ± 174 cells/mm³; range, 10–760 cells/mm³) with a clear lymphocytic predominance (>65%, >90% in most samples). Protein levels were normal in only two patients (mean ± SD = 94 ± 23 mg/dl; range, 20–250 mg/dl). IgG was measured in 20 patients. Considering the maximum IgG level found in successive lumbar punctures, IgG was within normal limits (<15% of protein levels) in 16 (80%) patients and increased in the remaining four (mean ± SD = 11 ± 8% of the total protein levels for the 20 patients being investigated; range, 4–34%). Oligoclonal bands did not appear in the 18 patients (including those with high IgG levels) on whom this determination was performed. Adenosine deaminase (ADA) levels were measured in 16 cases. In two, slightly increased values (8 and 9 U/l, normal values <6 U/l) were found in the symptomatic period, while in the remaining cases the maximum level was 4.1 U/l (mean ± SD = 3.7 ± 2.2 U/l; range, 0.6–9 U/l).

**Blood determinations**
Routine laboratory determinations, including immunological studies, were within normal limits in most patients. Slight leucocytosis was found in four cases (overall range, 9600–12 000 cells per mm³) and increased levels (always >100 U/l) of transaminases were observed in three patients. Two cases had positive antinuclear antibodies, although at low titres (<1/80). In all cases standard viral serologies [always including herpes simplex, herpes zoster and cytomegalovirus (CMV)] were determined. One case had a 1/256 IgG titre for CMV. IgM was negative. Agglutinations and/or Coombs for brucella, Ziehl, VDRL (venereal disease) and fungi culture were normal or negative, tested in serum and/or CSF in all patients. HIV, borrelia and mycoplasma serologies, performed in 22, 29 and 23 cases respectively, were all negative.

**Other complementary studies**
EEG was performed on 42 patients. Twelve (29%) had a normal EEG. In the remaining 30 (71%), the EEG was clearly abnormal. Unilateral excessive slowing, coinciding with the clinical symptom side, was found in 26 cases (62%) and bilateral slowing was recorded in four (10%). The EEG became normal after the symptomatic period in these patients. CT was available in 46 cases, being within normal limits in all. Cranial MRI was performed on 18 patients. Only two showed any abnormalities, and these were nonspecific small areas of high signal in T₂-weighted images, one in the internal capsule and the other in the pons. [¹⁸F⁻F]-FDG (hexamethylpropyleneamine oxime) SPECT was performed on three patients immediately after one neurological episode. Focal areas of decreased radionuclide uptake, coincident with the neurological symptoms, were observed in these cases. These areas of decreased uptake were seen in one hemisphere in one case and in both hemispheres in the remaining two (most marked in the side of the clinical symptoms in one of these) (Fig. 2). SPECT became normal in these patients when repeated several days after the transient neurological symptoms.

Conventional cranial angiograms were obtained from 12 patients. Eleven had a normal angiogram. In the remaining patient, who had a total of 12 episodes of transient left hemisphere deficit and homolateral headache, the angiogram showed irregularities, suggestive of inflammation of the artery wall, localized in the small vessels dependent on the third and fourth left opercular arteries. This patient had severe focal symptoms, global aphasia and right hemiplegia, beginning just at the end of the angiogram. One further patient had one clinical episode immediately after the carotid angiogram.

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**Table 2 Summary of CSF results**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pressure (mmH₂O) (n = 18)</th>
<th>Glucose (mg/dl) (n = 50)</th>
<th>Cells (x 10⁶/mm³) (n = 50)</th>
<th>Protein (mg/dl) (n = 50)</th>
<th>IgG (%)* (n = 20)</th>
<th>Oligoclonal bands U/l (n = 18)</th>
<th>ADA U/l (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>195 ± 68</td>
<td>199 ± 174</td>
<td>94 ± 3</td>
<td>11 ± 8</td>
<td>Negative</td>
<td>3.7 ± 2.2</td>
<td>0.6–9.0</td>
</tr>
<tr>
<td>Range</td>
<td>180–370</td>
<td>10–760</td>
<td>20–250</td>
<td>4–34</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Percentage of protein.

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**Table 2.** Most patients had several abnormal CSF determinations during the symptomatic period as well as a final lumbar puncture with normal results. CSF opening pressure was measured in 18 cases, being elevated (between 180 and 370 mmH₂O) in 10 (56%). CSF glucose, as compared with serum levels, was always normal. All cases showed CSF pleocytosis (mean ± SD = 199 ± 174 cells/mm³; range, 10–760 cells/mm³) with a clear lymphocytic predominance (>65%, >90% in most samples). Protein levels were normal in only two patients (mean ± SD = 94 ± 23 mg/dl; range, 20–250 mg/dl). IgG was measured in 20 patients. Considering the maximum IgG level found in successive lumbar punctures, IgG was within normal limits (<15% of protein levels) in 16 (80%) patients and increased in the remaining four (mean ± SD = 11 ± 8% of the total protein levels for the 20 patients being investigated; range, 4–34%). Oligoclonal bands did not appear in the 18 patients (including those with high IgG levels) on whom this determination was performed. Adenosine deaminase (ADA) levels were measured in 16 cases. In two, slightly increased values (8 and 9 U/l, normal values <6 U/l) were found in the symptomatic period, while in the remaining cases the maximum level was 4.1 U/l (mean ± SD = 3.7 ± 2.2 U/l; range, 0.6–9 U/l).
Pseudomigraine with pleocytosis has been shown to be greater for females during the third and fourth decades of life. A further clinical difference between PMP and migraine is exemplified by the pattern of focal temporary neurological symptoms and by some of the headache characteristics. The mean duration of temporary deficits in PMP patients (5 h) is clearly longer than the duration of aura in typical migraine with aura (<1 h). Thus the migraine syndrome best resembling PMP is migraine with prolonged aura (Headache Classification Committee of the International Headache Society, 1988; Olesen, 1993). However, this diagnosis is usually given to patients with long-lasting, but otherwise typical, aura symptoms. Migraine with prolonged aura mostly occurs in a few attacks in patients who otherwise have a typical aura duration and patients who virtually always have hemisensory and/or hemiparetic symptoms, such as hemiplegic migraine. Hemiplegic migraine is clearly different from PMP. Hemiplegic migraine starts before the age of 20 years and is often associated with a family history of hemiplegic migraine or migraine. In hemiplegic migraine episodes appear intermittently over years (Whitty, 1953; Bradshaw and Parsons, 1965; Glista et al., 1975; Jensen et al., 1981; Olesen, 1993). The majority of PMP patients do not develop chronic migraine with aura headaches. PMP is also easily separated from the autosomal dominant syndrome of recurrent migraine coma with focal cerebral oedema, CSF pleocytosis and progressive cerebellar ataxia (Fitzsimons and Wolfenden, 1985). In this inherited syndrome, headache with coma is recurrent over years and progressive ataxia ensues. Also, CSF pleocytosis is usually predominantly polymorphonuclear in these patients, and brain swelling is noticeable on CT or MRI (Goldstein et al., 1990). However, the CT/MRI brain swelling in migraine coma is transient, and may not be seen when serious symptoms are present. In the present series, 70% of patients exhibited sensory symptoms, 66% some type of aphasia, moderate-to-severe bilateral and/or hemicranial headache accompanied by changing temporary neurological deficits, usually cheiro-oral numbness plus speech disorder, and occasionally fever; (ii) total resolution of the recurrent episodes within 2 months; (iii) absence of symptoms and signs between episodes; (iv) CSF lymphocytic pleocytosis with negative aetiological results; (v) normal neuroradiological studies, except for transient, focal, decreased radionuclide uptake in brain SPECT; and (vi) non-permanent, focal non-epileptiform EEG changes.

The age of our patients, between 14 and 39 years, is comparable to that of the previously reported cases (Berg and Williams, 1995) and coincides with the maximum incidence of migraine (Stang et al., 1992). Furthermore, the prevalence of migraine in our PMP patients is somewhat higher, mainly for males, than that expected for migraine in these decades of life (Linet and Steward, 1984; Silberstein and Lipton, 1993; Lainez et al., 1994; Lipton et al., 1994). Compared with migraine, PMP is more frequent in men (3 males : 1 female). Both migraine incidence (2.8 females : 1 male) (Stang et al., 1992) and lifetime prevalence (4 females : 1 male) (Rasmussen and Olesen, 1992) have been shown to be greater for females during the third and fourth decades of life. A further clinical difference between PMP and migraine is exemplified by the pattern of focal temporary neurological symptoms and by some of the headache characteristics. The mean duration of temporary deficits in PMP patients (5 h) is clearly longer than the duration of aura in typical migraine with aura (<1 h). Thus the migraine syndrome best resembling PMP is migraine with prolonged aura (Headache Classification Committee of the International Headache Society, 1988; Olesen, 1993). However, this diagnosis is usually given to patients with long-lasting, but otherwise typical, aura symptoms. Migraine with prolonged aura mostly occurs in a few attacks in patients who otherwise have a typical aura duration and patients who virtually always have hemisensory and/or hemiparetic symptoms, such as hemiplegic migraine. Hemiplegic migraine is clearly different from PMP. Hemiplegic migraine starts before the age of 20 years and is often associated with a family history of hemiplegic migraine or migraine. In hemiplegic migraine episodes appear intermittently over years (Whitty, 1953; Bradshaw and Parsons, 1965; Glista et al., 1975; Jensen et al., 1981; Olesen, 1993). The majority of PMP patients do not develop chronic migraine with aura headaches. PMP is also easily separated from the autosomal dominant syndrome of recurrent migraine coma with focal cerebral oedema, CSF pleocytosis and progressive cerebellar ataxia (Fitzsimons and Wolfenden, 1985). In this inherited syndrome, headache with coma is recurrent over years and progressive ataxia ensues. Also, CSF pleocytosis is usually predominantly polymorphonuclear in these patients, and brain swelling is noticeable on CT or MRI (Goldstein et al., 1990). However, the CT/MRI brain swelling in migraine coma is transient, and may not be seen when serious symptoms are present. In the present series, 70% of patients exhibited sensory symptoms, 66% some type of aphasia, 42% motor weakness and only 18% visual symptoms. In the first large detailed nosographic analysis of migraine aura using the International Headache Society criteria (Headache Classification Committee of the International Headache Society, 1988), visual symptoms were the most frequent (99%), followed by sensory (31%), aphasic (18%) and motor (6%) symptoms (Russell and Olesen, 1996). In addition, the characteristic visual symptoms of migraine with aura, that is, a flickering, uncoloured zig-zag line in the centre of the visual field leaving a scotoma (Russell and Olesen, 1996) was not described by any of our PMP patients, only three of whom had ‘positive’ visual symptoms (photopsias). Moreover, while most of our patients had combinations of focal symptoms, mainly aphasia plus sensory and motor symptoms, Russell and Olesen’s (1996) patients with several types of aura symptoms had visual aura in virtually every attack, whereas sensory, motor and aphasic aura were present in only a small number of migraine attacks. Both quality and duration of headache and proportion of nausea and/or vomiting are very similar in PMP and migraine (Rasmussen

Discussion

The present study is the first series of PMP with a sufficiently large number of patients and episodes to secure representative results. PMP should be suspected in patients, mainly if they are male, around the third and fourth decade of life with the following clinical picture: (i) one or more episodes of moderate-to-severe bilateral and/or hemicranial headache accompanied by changing temporary neurological deficits, usually cheiro-oral numbness plus speech disorder, and occasionally fever; (ii) total resolution of the recurrent episodes within 2 months; (iii) absence of symptoms and signs between episodes; (iv) CSF lymphocytic pleocytosis with negative aetiological results; (v) normal neuroradiological studies, except for transient, focal, decreased radionuclide uptake in brain SPECT; and (vi) non-permanent, focal non-epileptiform EEG changes.

The age of our patients, between 14 and 39 years, is comparable to that of the previously reported cases (Berg and Williams, 1995) and coincides with the maximum incidence of migraine (Stang et al., 1992). Furthermore, the prevalence of migraine in our PMP patients is somewhat higher, mainly for males, than that expected for migraine in these decades of life (Linet and Steward, 1984; Silberstein and Lipton, 1993; Lainez et al., 1994; Lipton et al., 1994). Compared with migraine, PMP is more frequent in men (3 males : 1 female). Both migraine incidence (2.8 females : 1 male) (Stang et al., 1992) and lifetime prevalence (4 females : 1 male) (Rasmussen and Olesen, 1992) have been shown to be greater for females during the third and fourth decades of life. A further clinical difference between PMP and migraine is exemplified by the pattern of focal temporary neurological symptoms and by some of the headache characteristics. The mean duration of temporary deficits in PMP patients (5 h) is clearly longer than the duration of aura in typical migraine with aura (<1 h). Thus the migraine syndrome best resembling PMP is migraine with prolonged aura (Headache Classification Committee of the International Headache Society, 1988; Olesen, 1993). However, this diagnosis is usually given to patients with long-lasting, but otherwise typical, aura symptoms. Migraine with prolonged aura mostly occurs in a few attacks in patients who otherwise have a typical aura duration and patients who virtually always have hemisensory and/or hemiparetic symptoms, such as hemiplegic migraine. Hemiplegic migraine is clearly different from PMP. Hemiplegic migraine starts before the age of 20 years and is often associated with a family history of hemiplegic migraine or migraine. In hemiplegic migraine episodes appear intermittently over years (Whitty, 1953; Bradshaw and Parsons, 1965; Glista et al., 1975; Jensen et al., 1981; Olesen, 1993). The majority of PMP patients do not develop chronic migraine with aura headaches. PMP is also easily separated from the autosomal dominant syndrome of recurrent migraine coma with focal cerebral oedema, CSF pleocytosis and progressive cerebellar ataxia (Fitzsimons and Wolfenden, 1985). In this inherited syndrome, headache with coma is recurrent over years and progressive ataxia ensues. Also, CSF pleocytosis is usually predominantly polymorphonuclear in these patients, and brain swelling is noticeable on CT or MRI (Goldstein et al., 1990). However, the CT/MRI brain swelling in migraine coma is transient, and may not be seen when serious symptoms are present. In the present series, 70% of patients exhibited sensory symptoms, 66% some type of aphasia, 42% motor weakness and only 18% visual symptoms. In the first large detailed nosographic analysis of migraine aura using the International Headache Society criteria (Headache Classification Committee of the International Headache Society, 1988), visual symptoms were the most frequent (99%), followed by sensory (31%), aphasic (18%) and motor (6%) symptoms (Russell and Olesen, 1996). In addition, the characteristic visual symptoms of migraine with aura, that is, a flickering, uncoloured zig-zag line in the centre of the visual field leaving a scotoma (Russell and Olesen, 1996) was not described by any of our PMP patients, only three of whom had ‘positive’ visual symptoms (photopsias). Moreover, while most of our patients had combinations of focal symptoms, mainly aphasia plus sensory and motor symptoms, Russell and Olesen’s (1996) patients with several types of aura symptoms had visual aura in virtually every attack, whereas sensory, motor and aphasic aura were present in only a small number of migraine attacks. Both quality and duration of headache and proportion of nausea and/or vomiting are very similar in PMP and migraine (Rasmussen....
and Olesen, 1992). However, headache localization, predominantly bilateral in PMP and predominantly hemicranial in migraine (Rasmussen and Olesen, 1992), and the concomitant presence of fever in 22% of our cases and in 33% of the previously reported PMP patients (Berg and Williams, 1995) are different in PMP and migraine, although fever has been reported in severe migraine, especially hemiplegic attacks (Neligan et al., 1977; Gastaut et al., 1981). An interesting finding of our series, previously unnoticed in PMP, is the presence in almost one-third of cases in the symptomatic period of one or multiple episodes of headache unaccompanied by neurological deficit, as well as the rare occurrence of temporary neurological deficit without subsequent headache.

A constant feature of PMP is the CSF lymphocytic pleocytosis. Although detailed studies of the possible presence of CSF pleocytosis in migraine are not available, CSF pleocytosis of more than 10–15 mononuclear cells (per mm³) probably does not occur in migraine without aura, in migraine with aura, or even in the most severe forms of stuporous migraine or hemiplegic migraine (Van Storch and Merrit, 1935; Bickerstaff, 1961; Lee and Lance, 1977; Fishman 1980; Kovacs et al., 1989; Marchioni et al., 1995). As reported by other investigators (Kremenister and Golden, 1974; Bartleson et al., 1981; Dobkin, 1981; Day and Knezevic, 1984; Berg and Williams, 1995), CSF opening pressure is usually elevated in PMP and >90% of cases show an increased protein level in the first lumbar tap, both of which abnormalities are absent in migraine (Barrie and Jowett, 1967). There are almost no data in the literature regarding CSF IgG or ADA levels, or about the presence of CSF oligoclonal bands in this syndrome. Most of our patients showed normal levels of IgG in successive CSF samples and no patient, not even those with some IgG elevation, had positive CSF oligoclonal bands, thus suggesting that local synthesis of immunoglobulins does not occur in the CSF in PMP (MacLean et al., 1990; Bhigjee and Bill; 1996). The finding of normal or, at most, only slightly elevated ADA values in our PMP cases also helps in the differential diagnosis of this condition from chronic infectious, granulomatous and neoplastic arachnoiditis, where ADA levels are usually increased (Ribera et al., 1987; García-Moncó and Berciano; 1988; Berciano et al., 1994).

Negative cranial CT and MRI studies are a criterion of this syndrome. CT was normal in the 46 patients of this series upon whom it was performed. MRI had already been carried out on five patients in published reports, always with normal or nonspecific abnormalities (Walter and Grogan, 1986; Berg and Williams, 1995). Sixteen out of the 18 patients in this series from whom MRI was obtained also showed normal results and in the remaining two small areas of high signal, not related to the clinical symptoms, were observed. Conventional cranial angiography was also within normal limits in 11 out of the 12 patients on whom it was performed. Interestingly, in the remaining patient images compatible with local inflammation of the arterial wall were detected in the clinically symptomatic area. These findings would suggest a localized sterile ‘vasculitis’ as the cause of focal clinical symptoms and, perhaps, of the predominantly throbbing headache in this syndrome. As has been reported for hemiplegic migraine, in two patients from our series and in two more patients in the literature, cranial angiography was followed immediately by a single clinical episode (Bartleson and Swanson, 1981; Berg and Williams; 1995). These facts, on the one hand, support a role of cranial vessels in the pathophysiology of this syndrome and, on the other, indicate that cranial angiography should be avoided in these patients. EEG is frequently abnormal in PMP showing transient focal, non-epileptiform changes in most patients (Bartleson et al., 1981; Berg and Williams, 1995). To our knowledge, SPECT had never been performed on previously reported patients with this syndrome. The three patients from whom SPECT was obtained here, always on the day following a clinical episode, exhibited reversible focal areas of decreased radionuclide uptake, consistent with the clinical symptoms. Although more experience is necessary with this technique in PMP patients, these findings suggest that SPECT can be of great help in the differential diagnosis of PMP and other conditions, such as focal meningoencephalitis, where an increase in radionuclide uptake is usually seen (Schmidbauer et al., 1991), and migraine with aura, in which the focal decrease in radionuclide uptake, if detected, disappears within 2 h of aura onset, and is usually most marked in posterior brain regions (Davies and Steiner, 1991; Olesen and Friberg, 1991).

PMP syndrome aetiology remains a mystery. There are many conditions which may present with temporary neurological deficits, headache and CSF lymphocytic pleocytosis. Clinical and complementary data in this series rule out conditions such as Lyme disease (Pal et al., 1987; Steere, 1989), neurosyphilis (López de Munain et al., 1990), neurobrucellosis (Pascual et al., 1988; Roldán-Montaud, 1991), mycoplasma infections (Dalton and Newton, 1991), HIV meningitis (Hollander and Stringari, 1987) and granulomatous (Tozman, 1991; Roch-Le Foch et al., 1992) and neoplastic (Grossman and Moynihan, 1991) arachnoiditis which could theoretically account for clinical symptoms such as those observed in this syndrome before the availability of serological testing. An example which was probably the result of HIV infection, is the homosexual man with CMV infection published by Ferrari et al. in 1983. Additionally, patient 5 in the paper of Battstrom et al. (1984) suffered a tick bite 4 months before the beginning of his PMP-like syndrome, thus suggesting a diagnosis of Lyme neuroborreliosis. Mollaret’s disease has been proposed as an aetiology of PMP (Rolak et al., 1982). No present PMP patient fits with this diagnosis. Focal neurological manifestations are very rare in Mollaret’s meningitis, which is characterized by recurrent episodes of meningitis occurring every few weeks to months over a minimum of 1 year (Bruyn et al., 1962; Hermans et al., 1972). Also, neither ‘Mollaret’ cells nor any evidence of herpes virus infection, a demonstrated causative agent of Mollaret’s disease (Steel et al., 1982; Picard et al.,
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1993), were seen in any of our cases. Although it has been proposed by some authors as the cause for PMP, viral meningoencephalitis does not seem to account for most of the cases of this syndrome. Episodic neurological deficits together with headache have been described secondary to CMV infection in a 35-year-old man with no known risk for HIV infection (Richter et al., 1987). The long duration of the clinical picture (6 months) and the absence of positive CMV in our patients rule out this viral infection as the cause for PMP. Despite extensive viral serological evaluation in our PMP patients and in those previously reported PMP patients, only one virus, echovirus 30, could be isolated, and that in only one case (Casteels-van Daele et al., 1981). These data, together with the total absence of meningeval irritation during and between PMP episodes, seem to eliminate conventional viral meningoencephalitis as the aetiology for this syndrome, even though it still appears reasonable to search for neurotrophic viruses in future cases of PMP. As has already been commented on in depth, much of the clinical and complementary data do not support migraine as a plausible aetiological explanation for PMP. If a variety of ‘chronic’ arachnoiditis, viral meningoencephalitis or migraine are not a complete explanation for PMP, what else could be the cause of this syndrome? As is well-known for other monophasic or recurrent neurological disorders, such as Guillian–Barre syndrome, between 25% (in our retrospective experience) and 40% (Berg and Williams, 1995) of PMP cases had symptoms of a viral illness in the preceding 3 weeks. It is possible that a viral infection could trigger the activation of the immune system, which would produce antibodies which could bind to antigens in cranial vessels. This might induce an aseptic inflammation of cranial vasculature, which would account for the ‘vascular’ headache, for the transient neurological symptoms, possibly as a result of temporary cerebral hypoperfusion as shown by our SPECT studies, and for the CSF lymphocytic pleocytosis. Headache is a common side effect of i.v. immunoglobulin infusion (Casteels-van Daele et al., 1990; Watson et al., 1991; Vera-Ramírez et al., 1992). It has recently been shown that the i.v. administration of high-dose immunoglobulins induces aseptic meningitis in ~10% of patients (Sekul et al., 1994), occasionally accompanied by transient focal symptoms (Constantinescu et al., 1993). Interaction of IgG alloantibodies with endothelial antigens in cranial vessels has been proposed as the cause for this complication (Thornton and Ballow, 1993; Sekul et al., 1994). Interestingly, patients with a history of migraine are more likely to develop aseptic meningitis while receiving i.v. immunoglobulin therapy (Thornton and Ballow, 1993; Sekul et al., 1994). This increased susceptibility of patients with migraine to the development of aseptic meningitis implies increased sensitivity of their meningeal vasculature to exogenous IgG (Sekul et al., 1994). Due to the relatively high prevalence of migraine in PMP patients, it is possible that migraine could act as a predisposing factor somewhat facilitating this pathophysiological cascade.

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References


