Vascular Headache: A Presenting Symptom of Multiple Sclerosis

Mark S. Freedman and Trevor A. Gray

ABSTRACT: Vascular headache of migraine-type may be a presenting symptom of multiple sclerosis (MS), a condition usually not considered in the differential diagnosis of a severe headache accompanied by neurological signs. We reviewed records of 1,113 patients with MS seen from 1967-1987 and found 44 cases whose initial attack or subsequent exacerbations were heralded by a migraine-type headache. Twenty-seven patients had no prior history of migraine, and of these, 12 presented simultaneously with their first headache and MS attack. Twenty-three patients had symptoms of a posterior fossa mass lesion. The significance of these results and possible pathogenesis is discussed.

RÉSUMÉ: Céphalée vasculaire comme manifestation initiale de la sclérose en plaques La céphalée vasculaire de type migraineux peut être le premier symptôme de la sclérose en plaques (SEP), une affection qui n'est généralement pas envisagée dans le diagnostic différentiel d'une céphalée sévère accompagnée de signes neurologiques.

Nous avons revisé les dossiers de 1,113 patients atteints de SEP ayant consulté entre 1967-1987 et nous avons retrouvé 44 cas dont la première poussée ou des périodes d'exacerbation subséquentes ont été précédées de céphalée de type migraineux. Vingt-sept patients n'avaient aucune histoire de migraine auparavent et parmi ceux-ci, 12 ont présenté simultanément leur première migraine et leur première poussée de SEP. Vingt-trois patients avaient des symptômes de lésion expansive de la fosse postérieure. Nous discutons de la portée de ces résultats et de leur pathogénèse.

Can. J. Neurol. Sci. 1989; 16: 63-66

Headache has been reported in multiple sclerosis (MS) and even considered as a presenting symptom of the disease. There has been however, a considerable lack of any attempt to either define the type of headache, or relate the symptom to the underlying disease process.

We have observed that a number of patients presenting with acute attacks of MS complained of severe migraine-type headaches preceding their neurological deficits. Headache was often their major reason for seeking medical attention.

We received the records of 1,113 patients with MS seen at St. Michael's Hospital, Toronto over the past 20 years (1967-1987) and found 44 cases whose initial attack or subsequent exacerbations were heralded by typical migrainous head pain.

The presentation of acute headache with neurological deficits has a complicated differential diagnosis.[1] Although an association has been described between migraine and MS,[2] vascular headache as a presenting symptom of the disease has not been hitherto reported. It is possible that mechanisms underlying acute demyelination may also be involved in the triggering of vascular headache.

Materials and Methods

Case Material

Records of patients discharged with a diagnosis of MS between 1967 and 1987, and all current charts in the MS Clinic at St. Michael's Hospital in Toronto formed the database. This was supplemented with information obtained from a questionnaire inquiring into the nature of previous headaches, family history, further details surrounding the documented episode of interest, and recurrences of headache with or without further MS attacks.

Definitions

1. Migraine

Headaches were considered vascular headache of migraine type if they were "recurrent, severe, long-lasting and associated with either anorexia, nausea, vomiting, or visual disturbances".[3] Throbbing character, unilaterality and positive family history were considered supportive but not mandatory features.

From the University of Toronto, Department of Neurology, St. Michael's Hospital, Toronto

Received October 6, 1987. Accepted in final form September 12, 1988

Preliminary results of this paper were presented at the XXIInd Canadian Congress of Neurological Sciences, Vancouver, B.C., in June 1987

Reprint requests to: Dr. T. Gray, University of Toronto, Department of Neurology, St. Michael's Hospital, M.S. Clinic, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8

Patients with head pain which was either lancinating or neuralgic in nature, or associated with a pure optic neuritis were excluded.

2. *Multiple Sclerosis*

The diagnosis of MS was based on the revised new diagnostic criteria proposed for research protocols.[4] Out of the 44 cases described, all were deemed clinically definite except 3 who were considered possible MS.

Results

We found 44 cases of MS who presented either at the onset or exacerbation of their disease with a vascular headache. There were 30 females and 14 males, demonstrating the female preponderance reported for both migraine[5] and MS.[6] Eighteen patients presented at the time of their first MS attack with vascular headache (43% of M and 40% of F) while the rest had headaches with exacerbations (Table 1).

Of 17 patients with a history of migraine, 6 (all F) had headache at the time of their first attack of MS. Twelve out of 18 patients presenting with their first MS attack simultaneously experienced their first vascular headache. It is not surprising that some of these latter patients had their initial neurological deficits ascribed to possible migrainous vasospasm.

Considering the 27 patients with no prior history of vascular headache, at least 11 had subsequent recurrences: 6 with and without MS exacerbations; 3 unrelated to further MS attacks; and 2 patients who only had subsequent vascular headaches with each MS relapse.

A positive family history of migraine was obtained in only 10 patients, or 23%, comparable to another study of migraine in MS.[2]

An acute pounding headache with profound vertigo, ataxia, weakness and diplopia might suggest a sudden expansion of a posterior fossa mass lesion. It is interesting that 23 of our 44 cases presented in this fashion, with 1 developing quadriplegia and requiring artificial ventilation for a prolonged period before recovery.

Discussion

This study has revealed that a vascular headache may herald the appearance of signs and symptoms ascribed to demyelination in at least 4% of patients with MS. Forty-one percent of these experienced their headache with the clinical onset of their disease. The presentation was typically of a young person complaining of headache and progressive neurological deficits, some urgently referred on to our institution with diagnosis such as subarachnoid hemorrhage, tumour, stroke, and/or complicated migraine. Many underwent angiography and lumbar puncture, but often the CSF was not sent for oligoclonial banding studies as MS was not suspected. Our results confirm that MS can present in an acute fashion with neurological symptoms and signs and severe vascular headache, and should certainly be considered in the differential diagnosis of complicated migraine.

Headache as a presenting symptom of MS has been reported previously but without any attempt at defining either its type or its relationship to the underlying disease. A correspondence study of MS patients determined that 32.5% of patients suffered "headache".[7] The frequency of headache at the onset of disease in army patients was 10-26%. These were patients who also had visual or brainstem symptomatology.[9] Watkins and Espir[2] were impressed by a higher incidence of migraine (27%) in 100 consecutive MS patients than in a random selection of age-matched controls (12%). They defined "migraine" as a recurring headache that may or not have been unilateral, throbbing or accompanied by other symptoms. Their MS patients also had twice the incidence of a positive family history for migraine in comparison to controls (20% vs. 10%). This figure is similar to our value of 23%. Although no one is quite sure of the true incidence of a positive family history in migraine sufferers,[9] a higher incidence in MS patients might indicate a certain genetic predisposition to the development of vascular headaches.

Although neurological deficits can occur as a result of migrainous phenomena rather than demyelination, we felt this to be unlikely since in many of our patients the headache appeared hours or even days before the onset of neurologic symptoms. In complicated migraine it is more typical for neurological complaints to actually precede the development of headache by 10 to 30 minutes.[10] Also this relatively uncommon form of headache occurs mainly in known migraineurs. Two-thirds of our patients had no established history of migraine.

The clinical features of severe, persistent headache, nausea and vomiting with focal neurological deficits might raise the suspicion of an expanding intracranial mass lesion. Acute pseudotumourous MS has been described previously.[11] However in these cases the headache was of gradual onset and was accompanied by seizures and neurological signs indicating supratentorial involvement. It is interesting that about half our patients presented with a clinical picture suggesting an expanding posterior fossa mass. Some of their symptoms and signs such as vertigo, nystagmus, internuclear ophthalmoplegia and cranial nerve deficits indicated intrinsic involvement of the brainstem. Vascular theories of migraine pathogenesis invoke early

Table 1: Characteristics of Patients Presenting with Migraine and an Acute Attack of MS

Sex	Number	Average Age	Migraine With Onset of MS	Migraine With Relapse of MS	Previous History of Migraine	Family History of Migraine	Presentation As Acute Post Fossa Lesion
Male	14	31[+]	6	8	3	2	5
Female	30	31[++]	12	18	14	8	18
Total	44	31[+++]	18	26	17	10	23

[+]Male Range: 18-40
[++]Female Range: 19-54
[+++]Average Age Male and Female

involvement of the posterior circulation, possibly via the locus coeruleus and various cranial nerve efferents.[12] Patchy demyelination of the brainstem could either trigger these putative migraine centres or perhaps interfere with inhibitory modulating interconnecting impulses. Moskowitz has speculated that such connections exist to allow the CNS to modulate peripheral mechanisms of migraine through trigeminovascular innervation.[13]

This report suggests that an attack of MS may provoke a vascular migraine-type headache in patients who are not established migraineurs. Although the pathogenesis is unknown for both migraine and MS and many biochemical and neurophysiological alterations have been reported in both disorders, only in MS have consistent pathological changes been demonstrated. One of these is the cuffing of small blood vessels by inflammatory cells, which on occasion resembles an acute vasculitis.[14] Release of vasoactive substances by perivascular inflammatory cells might be an underlying trigger of the migraine attack. Chemical modulators such as vasoactive amines, peptides such as bradykinin, and ATP have all been implicated in migraine pathogenesis.[15] Some of these substances may be released acutely from aggregating platelets.[16] It is of interest that increased platelet stickiness has also been demonstrated in MS.[17]

Migraine has been noted with vasculitis, particularly in association with SLE.[18] Brandt and Lessel[19] reported on a series of 11 patients who had no history of migraines prior to the onset of SLE. They seemed to develop headaches only in association with flares of lupus, only to abate as disease activity waned. In 4, migrainous symptoms were actually the initial presenting complaint.[19] Both MS and SLE are thought to be autoimmune diseases, and are clinically characterized by exacerbations and remissions. Although vascular and neural hypotheses have predominated in considering the pathogenesis of migraine,[20-23] there has been little suggestion that it results from an altered immune response.

When Damasio and Beck[24] noted that migrainous episodes occurred in their ITP or SLE patients during states of thrombocytopenia, they hypothesized that an immunoglobulin active against platelets might also cause the release of serotonin leading to migraine production.[24] They may well have been describing an anti-phospholipid antobody which is present in some 5-10% of SLE sera,[25] and has been noted to react with platelet membranes leading to damage with increased adhesiveness, or hyperaggregatability secondary to inhibition of prostacyclin production by endothelial cells.[26] Levine et al described 2 patients without identifiable SLE who had severe migraines, thrombocytopenia, and a circulating anti-phospholipid antibody; at least one patient's headache improved on steroids.[27] These cases suggest a link between anti-phospholipid antibody activity and migraine production. During an attack of MS with myelin degradation potentially immunogenic breakdown products may be released. Myelin phospholipids have been variably reported to be increased in both CSF[28] and serum[29] of MS patients. It is conceivable that antibodies to myelin phospholipid are generated which cross-react with shared epitopes on platelet or endothelial cell membranes. Further studies aimed both at the detection of these antibodies, as well as the role of platelets in migraine pathogenesis are required.

The results of the present study in MS patients and those of others with various autoimmune conditions imply that a connection exists between active immunological disease states and the generation of vascular head pain.

Acknowledgements

We are indebted to the services of Mrs. Elizabeth Albernaz for her expert typing and generous time spent handling the patient questionnaires.

References

1. Anonymous. Headache in multiple sclerosis. British Medical Journal [Editorial] 1969; 2: 713-714.
2. Watkins SM, Espir M. Migraine and multiple sclerosis. J Neurol Neurosurg Psychiatry 1969; 2: 35-37.
3. Rose FC. Headache: definitions and classification. *In*: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of Clinical Neurology, vol. 48, rev. series 4: Headache. New York: Elsevier 1986; 1-12.
4. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13: 227-231.
5. Ziegler DK. Epidemiology of migraine. *In*: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology, vol. 48, rev. series 4: Headache. New York: Elsevier 1986; 13-22.
6. Kurtzke JF. Epidemiology of multiple sclerosis. *In*: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of Clinical Neurology, vol. 47, rev. series 3: Demyelinating Disease. New York: Elsevier 1985; 259-287.
7. Mathews WB. Clinical aspects (symptoms and signs). *In*: Mathews WB, ed. McAlpine's Multiple Sclerosis. New York: Churchill Livingstone 1985; 96-118.
8. Kurtzke JF. Clinical manifestations of multiple sclerosis. *In*: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology, vol. 9: Multiple Sclerosis and Other Demyelinating Diseases. New York: Elsevier 1970; 161-216.
9. Davies PTG, Rose FC. Migraine genetics. TINS 1986; 9: 541-542.
10. Edmeads J. Complicated migraine and headache in cerebrovascular disease. Neurologic Clinics: Headache 1983; 1: 385-397.
11. Sagar HJ, Warlow CP, Sheldon PWE, et al. Multiple sclerosis with clinical and radiological features of cerebral tumour. J Neurol Neurosurg Psychiatry 1982; 45: 802-808.
12. Edmeads J. Migraine: new views on an old theory. Can J Neurol Sci 1984; 11: 363-364.
13. Moskowitz MA. The neurobiology of vascular head pain. Ann Neurol 1984; 16: 157-168.
14. Adams CWM, Poston RN, Buk SJ, et al. Inflammatory vasculitis in multiple sclerosis. J Neurol Sci 1985; 69: 269-283.
15. Anthony M. The biochemistry of migraine. *In*: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of Clinical Neurology, vol. 48, rev. series 4: Headache. New York: Elsevier 1986; 85-105.
16. Gawel MJ, Burkitt M, Rose FC. The platelet release reaction during migraine attacks. Headache 1979; 19: 323-327.
17. Wright HP, Thompson RHS, Zilkha KJ. Platelet adhesiveness in multiple sclerosis. Lancet ii 1965; 1109-1110.
18. Edmeads J. Headache in cerebrovascular disease. *In*: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of Clinical Neurology, vol. 48, rev. series 4: Headache. New York: Elsevier 1986; 273-290.
19. Brandt KD, Lessell S. Migrainous phenomena in systemic lupus erythematosus. Arthritis Rheum 1978; 12: 7-16.
20. Olsen TS, Friberg L, Lassen NA. Ischemia may be the primary cause of neurologic deficits in classic migraine. Arch Neurol 1987; 44: 156-161.
21. Olesen J. The ischemic hypothesis of migraine. Arch Neurol 1987; 44: 321-322.
22. Blau JN. Migraine pathogenesis: the neural hypothesis reexamined. J Neurol Neurosurg Psychiatry 1984; 47: 437-442.
23. Welch KMA. Migraine: a biobehavioural disorder. Arch Neurol 1987; 44: 323-327.

24. Damasio H, Beck D. Migraine, thrombocytopenia and serotonin metabolism. Lancet i:1978; 240-243.
25. Levine SR, Welch KMA. Cerebrovascular ischaemia associated with lupus anticoagulant. Stroke 1987; 18: 257-263.
26. Correras LO, Vermylen JG. 'Lupus' anticoagulant and thrombosis: possible role of inhibition of prostacyclin formation. Thromb Haemost 1982; 48: 38-40.
27. Levine SR, Joseph R, D'Andrea B, et al. Migraine and the lupus anticoagulant. Neurology 37 (Suppl 1) 1987; 264.
28. Tourtellotte WW, Haerer AF. Lipids in cerebrospinal fluid XXI. In multiple sclerosis and retrobulbar neuritis. Arch Neurol 1969; 20: 605-615.
29. Zilkha KJ. Chemistry of blood in multiple sclerosis. *In*: Vinken PJ, Bruyn GW, eds. Handbook of Clinical Neurology, vol. 9: Multiple Sclerosis and Other Demyelinating Disease. New York: Elsevier 1970; 320-323.