Headache as the initial presentation of Wegener's granulomatosis

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In Wegener's granulomatosis (WG), neurological involvement is rare at onset. We present an unusual case where headache was the initial, dominant presentation of WG.

CASE REPORT

A 34 year old white man presented with a three month history of headache. The headaches were migratory, throbbing, and were accentuated with head movement. Physical examination was normal. Computed tomography (CT) of the sinuses was normal. The patient was diagnosed with non-specific vascular headaches, and was prescribed pizotifen, which alleviated his headaches.

One month later, the patient developed a red right eye. Bilateral papilloedema was noted. He was now unable to work because of the headache. Magnetic resonance imaging (MRI) of the brain disclosed a normal ventricular system, but pronounced gadolinium enhancement of the meninges around the entire left hemisphere, most of the parieto-occipital region on the right, as well as the tentorium bilaterally (fig 1). Lumbar puncture disclosed a high cerebrospinal fluid (CSF) opening pressure of 27 cm (13–18 cm). A CSF examination was entirely normal and cultures were negative. The headache was partially relieved by CSF drainage, and acetazolamide was started.

One week later, the patient developed a red left eye and left knee arthritis. Over the course of the next week, his condition progressed rapidly with purpuric lesions appearing on his hands and feet, followed by pericarditis and pulmonary haemorrhage. Biopsy of the purpura disclosed leucocytoclastic vasculitis. Antineutrophil cytoplasmic antibody (cANCA) taken at the time that he complained of the red left eye was positive at a titre of 1/80, with specificity for proteinase-3. A week later, repeat testing showed that cANCA had risen to 1/320. There was also a mild normochromic, normocytic anaemia, and raised inflammatory markers. Urine analysis disclosed microscopic haematuria and mild proteinuria. No casts were identified. A CSF examination was again normal, but the opening pressure had risen to 36 cm. WG was diagnosed.

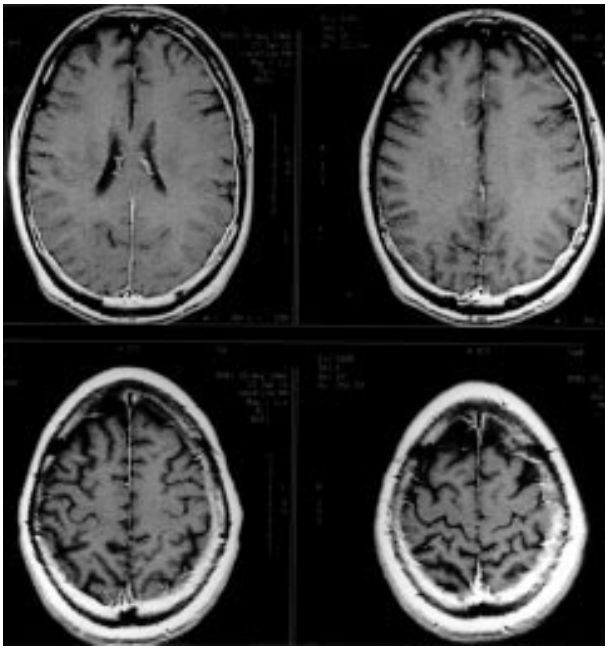

Figure 1 MRI showing diffuse meningeal enhancement.

Treatment was started with a 1 g pulse of intravenous methylprednisone, followed by oral daily doses of 1 mg/kg prednisone and 2 mg/kg cyclophosphamide. A few days after the start of treatment, the headaches had resolved and the CSF opening pressure was normal. Six months later, the patient is symptom-free, the papilloedema has resolved, MRI is normal, and the patient has returned to full-time work.

DISCUSSION

It is rare for WG to present with neurological symptoms. Neurological presentations described include ataxia, ocular nerve palsies, seizures, and deteriorating mental status.[1–4] Shiotani *et al* described a 37 year old man with chronic sinusitis, who presented with fever and headache for 10 days before CT disclosed subdural and paranasal masses with marked thickening of the nasal mucosa.[5] Our patient presented far more insidiously, with significant headache that persisted and worsened with time. The headache had clear vascular features but, beyond this, was non-specific. It was only four months later that musculoskeletal, cutaneous, ophthalmic, and cardiorespiratory features developed. Although neurological involvement may eventually develop in 33.6% of patients with WG,[6] meningeal involvement, as gauged by meningeal enhancement on MRI or by biopsy is particularly uncommon, being recorded in only a handful of case reports.[2–5 7–10] There also seems to be no relation between CSF abnormalities, clinical symptoms, or extent of meningeal involvement on MRI.[7] A CSF examination may show no abnormality[3 4 7] or a pleocytosis.[3 5 8 9] High opening pressures are unusual but have been described.[9 10]

In conclusion, we have presented a case of WG with extensive meningeal involvement. The exceptional feature in this case is the fact that headache was the sole symptom of the disease over several months, before a dramatic activation of the disorder with more typical features of WG.

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Extremely high dose pravastatin may suppress amyloidogenesis in a mouse model

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Pravastatin is a cholesterol lowering agent,[1] recently reported to have anti-inflammatory properties.[2] It was suggested that the prevention and regression of atherosclerosis by pravastatin is partially related to its anti-inflammatory effect,[2] probably mediated by inhibition of proinflammatory cytokines.[3] Pravastatin's anti-inflammatory effect is associated with, and probably reflected by, reduced levels of the acute phase reactants, C reactive protein and serum amyloid A (SAA).[2] The N-terminal fragment of the SAA is amyloid A (AA), which is deposited in a fibrillar form in the tissues of up to 30% of patients with a variety of chronic infectious and chronic inflammatory disorders, leading to reactive amyloidosis.[4]

Because prevention and treatment of AA amyloidosis are currently unsatisfactory and reactive amyloidosis is a potentially lethal complication, it is important to find out whether pravastatin affects amyloidogenesis.

The effect of pravastatin on amyloidogenesis was studied in several groups of male Swiss mice 7–17 weeks old, which were subjected to amyloid induction, using intravenous amyloid enhancing factor (1 μg in 0.5 ml phosphate buffered saline on day 0) and subcutaneous $AgNO_3$ (0.5 ml 2% daily, on days 0, 1, and 2), according to our published protocol.[5] Two groups of study mice (groups I and II) received intraperitoneal pravastatin 0.4 mg/day in 0.5 ml saline, and two other groups (III and IV) received intraperitoneal pravastatin 10 mg/day. The human oral dose analogous to these regimens is 0.5 mg/kg and 12.5 mg/kg respectively (assuming a 20-fold increase in drug catabolism in mice as compared with man). The experiments lasted for 72 hours (groups I and III) or 96 hours (groups II and IV). The 72 hour interval, during which the amount of amyloid deposits is still low, allows the detection of a mild inhibition. All experiments were controlled by mice of the same strain, sex, and age, which received the same amyloid induction regimen, but 0.5 ml saline intraperitoneally instead of pravastatin. The amount of amyloid deposition in the spleen was studied by the crush and smear technique and a five grade score, estimated by polarised microscopy.[6] All experiments were repeated two to three times.

Amyloidosis in mice receiving pravastatin was somewhat less abundant and developed in fewer animals than in controls (table 1). This trend was noted only in animals receiving 10 mg/day and only in the short term experiments, but the statistical significance obtained was inconsistent (table 1). No amyloid inhibition by pravastatin was seen in any of the other experiments, either when a lower pravastatin dose (0.4 mg/day) was used or when mice were subjected to a longer (96 hours) amyloidogenic stimulus.

These findings suggest that pravastatin in a very high dose may have a mild amyloid protecting effect and thus increases the spectrum of drugs with a possible tangible amyloid preventive effect. Further studies are warranted to determine underlying mechanisms and to see whether other statins also have anti-amyloidogenic qualities.

Table 1 High dose pravastatin may suppress amyloidogenesis

Group III* experiment number	Type of experiment	Amyloid positive mice per group	Median (range) of amyloid grade	p Values†
1	Study	5/6	2.5 (0–3)	0.24
	Control	6/6	1.5 (1–3)	
2	Study	4/6	0.75 (0–1.5)	0.03
	Control	6/6	2.0 (0.5–3)	
3	Study	2/5	0.5 (0–3)	0.07
	Control	5/6	2.0 (0–2.5)	
Combined	Study	11/17	1.0 (0–3)	0.05
	Control	17/18	2.0 (0–3)	

*Amyloidosis was induced by amyloid enhancing factor and $AgNO_3$. Study animals received intraperitoneally pravastatin 10 mg/day on days 0, 1, and 2. Control mice received 0.5 ml saline instead. The mice were killed after 72 hours (24 hours after the last pravastatin injection) and the amount of splenic amyloid was estimated by the Crush and Smear technique; †using Fisher's exact probability test.

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