raises the question of whether MS, as a demyelinating disease with associated retinal vasculitis, could be a risk factor for late-onset ARN in patients who have suffered previous herpetic encephalitis.

References

1. Urayama A, Yamada N, Sasaki T, *et al.* Unilateral acute uveitis with periarteritis and detachment. Jpn J Clin Ophthalmol 1971;25:607–19.
2. Ahmadieh H, Sajjadi H, *et al.* Association of herpetic encephalitis with acute retinal necrosis syndrome. Ann Ophthalmol 1991;23:215–9.
3. Pavesio CE, Conrad DK, McCluskey PJ, *et al.* Delayed acute retinal necrosis after herpetic encephalitis. Br J Ophthalmol 1997;81:415–6.
4. Lewis ML, Gulburtson WW, Post JD, *et al.* Herpes simplex virus type-1: a cause of acute retinal necrosis syndrome. Ophthalmology 1989;96:87–8.
5. Levinson RD, Reidy R, Chiu MT. Acute retinal necrosis after neonatal herpes encephalitis. Br J Ophthalmol 1999;83:123–4.

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Sir

The role of IgM isotype anticardiolipin antibodies in occlusive ocular vascular disease: report of two cases with primary antiphospholipid antibody syndrome

Several studies have clearly shown that the primary antiphospholipid antibody syndrome (PAPS) is associated with cerebral ischaemia and occlusive ocular vascular disease.[1–7] Most of the studies that assayed for anticardiolipin (aCL) antibodies showed that the IgG isotype was clearly more frequent than the other two isotypes and is the only significant one among patients with cerebral ischaemia or ocular vascular thrombosis.[3,5,7–11]

We describe two PAPS patients with vaso-occlusive ocular disease in the presence of high-titre IgM aCL antibodies without a concomitant IgG isotype, and suggest that the IgM isotype is also associated with ocular vascular thrombosis in PAPS.

Case reports

Case 1. A 40-year-old man noted decreased vision in his right eye in July 1998. His visual acuity in the right eye was 20/70 and in the left eye 20/20. The results of a colour vision test (Ishihara) were 7/12 in the right eye and 12/12 in the left eye. The anterior segment and intraocular pressure of both eyes were normal. On ophthalmoscopic examination, the right optic disc was oedematous; the veins looked tortuous and engorged and were surrounded by intraretinal haemorrhages and a few cotton wool spots. The left fundus appeared normal. Fluorescein angiography showed an increased venous transit time with staining of the retinal veins and leakage of fluorescein from dilated capillaries in the right eye and normal findings on the left side (Fig. 1). MR imaging of the brain and routine laboratory tests were all normal except for a low platelet count ($110 \times 10^3/\mu l$). The antinuclear antibody and anti-DNA test results were negative. Further coagulation studies showed an increased level of IgM aCL antibodies of 6.31 MPL (normal values: 0–1.10 MPL). The results of tests for VDRL, Lyme and HIV were negative. The patient had no history of exposure to certain drugs such as phenothiazines.

The patient was diagnosed as having central retinal vein occlusion due to primary antiphospholipid syndrome associated with IgM aCL antibodies. He was treated with warfarin and remained without further episodes during 9 months of follow-up. The latest neuro-ophthalmological examination revealed 20/20 vision in the right eye with a normal fundoscopic appearance (Fig. 1).

Case 2. A 28-year-old woman noted a sudden decrease in vision in the right eye in the first week of January 1999. Fifteen days later a similar symptom occurred in her left eye and she was evaluated in our department. She had no light perception in both eyes. The pupils were dilated and unreactive to light. The fundoscopic examination revealed optic nerve atrophy in the right eye and a swollen disc in the left eye. She had had an unexplained spontaneous abortion at approximately 16 weeks of gestation 2 years previously. MR imaging of the brain and orbits was normal. Routine laboratory tests and spinal fluid examination showed no abnormalities. The

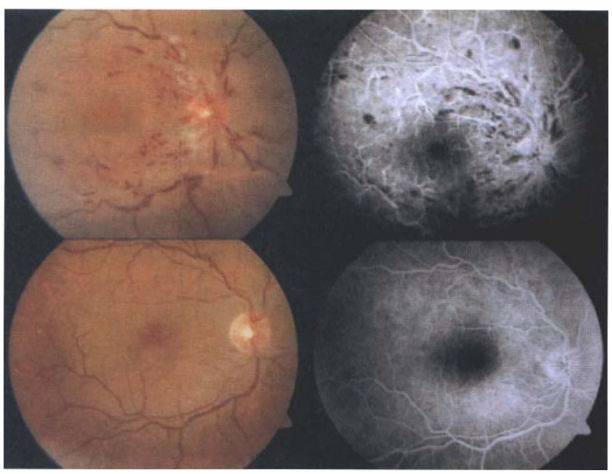

Fig. 1. *Upper left: Fundus photograph shows central retinal vein occlusion with engorged retinal veins, flame-shaped retinal haemorrhages and peripapillary cotton wool spots. Upper right: Fluorescein angiography demonstrates dilatation and staining of retinal veins and leakage from dilated capillary vessels. Lower left: Fundus photograph 9 months later reveals resolution of the retinal haemorrhages and cotton wool spots. Lower right: Fluorescein angiography 9 months later discloses mild leakage at the posterior pole in the late phase. There was no macular oedema.*

anti-DNA, antinuclear antibodies and rheumatoid factor were negative. The results of further coagulation tests were normal except for a significantly elevated level of IgM isotype (9.37 MPL). The tests for VDRL, Lyme and HIV were negative and there was no history of exposure to drugs.

The patient was considered to have bilateral consequent ischaemic optic neuropathy due to primary antiphospholipid antibody syndrome associated with IgM aCL antibodies. She received anticoagulant therapy with warfarin and has had no further episodes to date.

Comment

Previous studies have clearly demonstrated the relationship between PAPS and cerebral ischaemia and ocular disorders such as transient visual loss, diplopia, ischaemic optic neuropathy, retinal artery and retinal venous occlusion.[1–7] Only a few of these studies that assayed for aCL antibodies, especially those related to antiphospholipid antibody syndrome and cerebral ischaemia, separated out the different isotypes and attempted to determine their significance. The Antiphospholipid Antibodies in Stroke Study (APASS) Group prevalence study showed that the IgG isotype was clearly more frequent, and in that study as well, when it was evaluated independently, it was the only one that reached significance.[8] The study by Hess *et al.*[11] also noted that the IgG isotype was the only one significantly higher among patients with retinal or cerebral ischaemia than among controls.

It has been shown that antiphospholipid antibodies can also accompany malignancy, Guillain–Barré syndrome, myelopathy, haematological disorders such as idiopathic thrombocytopenic purpura (ITP), haemolytic anaemia, infections, including syphilis, infection with human immunodeficiency virus type I, Lyme disease, and variety of viral infections.[9,12] In addition, certain drugs, such as phenothiazines, have been associated with aPLs. In these settings, it is postulated that there seems to be a minimal association with thrombosis, thrombocytopenia or recurrent fetal loss, and the antibody characteristics differ from those generally associated with clinical symptoms, typically being of the IgM isotype and low titre.[9]

To define the pathogenic role of IgM aCL antibodies in central retinal vein occlusion and bilateral ischaemic optic neuropathy, both patients were tested for the conditions strictly associated with IgM isotype. There were no evidence of the major clinical or serological features of the reviewed conditions and the elevated levels of IgM aCLs were attributed to vascular thrombosis in our patients.

In contrast to the accepted data, we support the view that high-titre IgM isotype aCL antibodies can accompany PAPS with central retinal vein occlusion and bilateral ischaemic optic neuropathy. Our findings suggest that the IgM isotype may play an important role in the pathogenesis of aCL antibody-associated thrombosis as well as immune-mediated non-vascular neurological injury such as Guillain–Barré syndrome, infections and drug exposure.

In conclusion, the recognition of the importance of IgM isotype aCL antibodies in the aetiology of our patients' vascular events directed our attention to their treatment and they were treated with warfarin appropriately.

References

1. Acheson JF, Gregson RMC, Merry P, Schulenburg WE. Vaso-occlusive retinopathy in the primary antiphospholipid antibody syndrome. Eye 1991;5:48–55.
2. Asherson RA, Khamashta MA, Ordi Ros J, *et al.* The 'primary' antiphospholipid syndrome: major clinical and serological features. Medicine (Baltimore) 1989;68:366–74.
3. Asherson RA, Merry P, Acheson JF, *et al.* Antiphospholipid antibodies: a risk factor for occlusive ocular vascular disease in systemic lupus erythematosus and the 'primary' antiphospholipid syndrome. Ann Rheum Dis 1989;48:358–61.
4. Castañón C, Amigo MC, Bañales JL, *et al.* Ocular vaso-occlusive disease in primary antiphospholipid syndrome. Ophthalmology 1995;102:256–62.
5. Gutrecht JA, Kattwinkel N, Stillman MJ. Retinal migraine, chorea, and retinal artery thrombosis in a patient with primary antiphospholipid antibody syndrome. J Neurol 1991;238:55–6.
6. Reino S, Muñoz Rodriguez FJ, Cervera R, *et al.* Optic neuropathy in the 'primary' antiphospholipid syndrome: report of a case and review of the literature. Clin Rheumatol 1997;16:629–31.
7. Watts MT, Greaves M, Rennie IG, Clearkin LG. Antiphospholipid antibodies in the aetiology of ischaemic optic neuropathy. Eye 1991;5:75–9.
8. The Antiphospholipid Antibodies in Stroke Study (APASS) Group. Clinical and laboratory findings in patients with antiphospholipid antibodies and cerebral ischemia. Stroke 1990;21:1268–73.
9. Dewitt LD. Antiphospholipid antibody syndrome. In: Bogousslavsky J, Caplan L, editors. Stroke syndromes. Cambridge: Cambridge University Press, 1995:412–21.
10. Friehs I, Eber B, Friehs G, *et al.* IgG-anticardiolipin-antibodies are markers for cerebral and peripheral artery disease. Vasa 1992;21:158–62.
11. Hess DC, Krauss J, Adams RJ, *et al.* Anticardiolipin antibodies: a study of frequency in TIA and stroke. Neurology 1991;41:525–8.
12. Coull BM, Goodnight SH. Antiphospholipid antibodies, prethrombotic states, and stroke. Curr Concepts Cerebrovascular Dis Stroke 1990;25:13–8.

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