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Antiphospholipid Antibodies in the Aetiology of Ischaemic Optic Neuropathy

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Summary

The involvement of antiphospholipid antibodies in the mediation of acute anterior ischaemic optic neuropathy (AION) was studied, in the light of recent associations between these autoantibodies and other vascular events. A strong association between IgG anticardiolipin antibodies and AION secondary to biopsy proven giant cell arteritis was identified, which did not exist with the 'non-arteritic', biopsy negative form of AION. The possible implications of this finding on the aetiology, diagnosis, and treatment of giant cell arteritis are discussed.

Anterior ischaemic optic neuropathy (AION) results from compromise of the peripapillary choroid and posterior ciliary artery vascular supply to the optic nerve head.[1,2] Extensive study of the condition has identified a number of contributory factors to such ischaemia,[3,4] and in particular, has identified giant cell arteritis as a cause in a proportion of cases, and hence the opportunity to minimise second eye involvement by the use of systemic steroid treatment in AION of 'arteritic' origin.[5]

Other than 'vascular insufficiency, however, no common factor has been identified in the aetiology of AION, which may either offer a diagnostic marker for the disease, or suggest a line of management.

In recent years, a strong association has been noted between the presence of antiphospholipid antibodies and a number of vascular events,[6] such as arterial and venous thrombosis,[7] recurrent fetal loss due to placental vascular insufficiency[8] and thrombocytopenia.[9] Furthermore, identification of such autoantibodies has suggested new modes of treatment of certain vascular disease, by reduction of antiphospholipid antibody activity. Though success has been reported in isolated cases,[10] results of a prospective study of a series of such treatment are not yet available.

In an attempt to identify a common factor in the aetiology of ischaemic optic neuropathy, we investigated the possible involvement of antiphospholipid antibodies in this disease.

Materials and Methods

Nineteen consecutive patients presenting with acute AION were studied. This was defined as a sudden loss of either visual acuity, visual field, or both, in association with the appearance of a swollen optic nerve head in the affected eye(s) and peripapillary retinal haemorrhages, in the absence of any anterior or posterior vitreous activity. Eleven patients were female and eight male. Patients were asked about systemic symptoms of giant cell arteritis, and a past medical history was taken, with particular attention paid to previous vascular events, hypertension, connective tissue disease, such as systemic lupus erythematosus, and spontaneous fetal loss. No patient

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had any history consistent with previous optic neuritis. Exposure to steroid or phenothiazine drugs (which can produce a lupus anticoagulant effect[11]) was sought.

Ophthalmological and general medical examinations were undertaken, the former including assessment of best corrected visual acuity and visual field assessment using Goldman perimetry in patients with acuity of 6/60 or better, and confrontation fields when acuity was less than this. Temporal artery biopsy was performed in all, a minimum of 15 mm of artery being taken, which was examined after paraffin sectioning at 200 μ intervals. The erythrocyte sedimentation rate (ESR) was measured. The patients were classified as suffering from either 'arteritic' (i.e. secondary to giant cell arteritis) AION or 'non-arteritic' AION on the basis of symptoms, clinical examination, ESR and temporal artery histology, according to the criteria of Ellis and Ralston.[12] Patients considered to be suffering giant cell arteritis were immediately started on systemic steroid treatment and admitted to hospital (prior to awaiting temporal artery biopsy histology).

Coagulation tests including the Dilute Russel's Viper Venom Time (DRVVT) with platelet neutralisation procedures (PNP) were undertaken, this being among the most sensitive tests for lupus anticoagulant activity.[13] IgG and IgM antibodies to cardiolipin were measured using an enzyme linked immunosorbent assay.[14] All these assays were performed on blood samples taken at the same time as the ESR on presentation, by staff with no knowledge of the clinical features, and prior to the institution of any treatment.

Because of the skewed distribution of values in a normal population recognised in these assays, the upper limit of normality was defined as mean + 3 Standard Deviations (mean determined in the study of 70 healthy subjects). This value was 8.0 IU/ml for IgG and 5.0 IU/ml for IgM antibody. Anti-dsDNA and anti-Ro antibodies were assayed to exclude the presence of systemic lupus type disease.

Results

Of the 19 patients presenting with acute AION, seven were suffering from giant cell arteritis, as confirmed by positive temporal artery biopsy histology, and 12 from a 'non-arteritic' form of the disease. The clinical features, past medical history, ESR on presentation, and biopsy histology are shown in the Table, together with the results of the ELISA assays for IgG and IgM anticardiolipin antibodies. The presence of significantly elevated levels of IgG anticardiolipin antibody in all patients with giant cell arteritis, but in only one of the patients with 'non-arteritic' disease is highly statistically significant using chi-squared test, with Yates' correction for continuity ($p<0.001$). Such an association was not seen with the IgM antibody.

None of the patients demonstrated either anti-dsDNA antibody or anti-Ro antibody, and none conformed with the clinical criteria required for diagnosis of systemic lupus erythematosus.[15]

Only one patient demonstrated lupus anticoagulant activity (detected by prolongation of the DRVVT which can be reversed by the addition of freeze-thawed platelets).

Discussion

It is interesting to note that three of the patients with giant cell arteritis mediated AION had none of the systemic features of the disease, such as scalp tenderness, jaw claudication and malaise. Although one of them had suffered premonitory amaurotic episodes for three days prior to presentation, the other two had experienced no symptoms at all prior to sudden visual loss. In one of these patients, the ESR on presentation was only 20 mm/hour, and, had temporal artery biopsy not shown active arteritic disease, would have been considered to be suffering 'non-arteritic' AION. This highlights the high index of suspicion of giant cell arteritis required, and may explain the relatively higher proportion of giant cell arteritis mediated disease in this series as compared to others, when temporal artery biopsy was not undertaken in all.[16]

The presence of IgG anticardiolipin antibodies in patients suffering an 'arteritic' AION, and their absence in patients with a 'non-arteritic' form of the disease, raises questions as to their possible involvement in the pathogenesis of giant cell arteritis. The

Table I. *Ocular and systemic features, age, sex, ESR on presentation, temporal artery biopsy histology and anticardiolipin antibody titres*

Patient	Age	Sex	Ocular features (V.A. = best corrected visual acuity in affected eye)	Systemic features	Past medical history	ESR	Temporal artery biopsy histology	Anticardiolipin antibody titres (IU/ml)	
								IgG (mean +3SD* <8.0)	IgM (mean +3SD* <5.0)
1	76	F	V.A. = H.M. Central scotoma	None	None of note	20	Negative	22.5	4.4
2	74	F	V.A. = 6/6 Central + inferior altitudinal scotoma	None	None of note	22	Negative	1.8	1.1
3	72	F	V.A. = 6–36 Generalised field constriction	None	Previous central retinal artery occlusion in fellow eye	32	Positive	29.1	1
4	70	F	V.A. = 6/24 Inferior altitudinal scotoma	Malaise, myalgia, temporal artery tenderness, jaw claudication	None of note	60	Positive	45.1	1
5	79	M	V.A. = 6/24 Inferior nasal quadrant scotoma	Headache, scalp tenderness	None of note	60	Positive	13.5	2.5
6	61	F	V.A. = N.P.L.	None	Hypertension	16	Negative	2.3	1
7	79	F	V.A. = 6/24 Inferior arcuate scotoma	None	None of note	12	Negative	1.0	1
8	83	M	V.A. = H.M. Generalised field constriction	None	None of note	52	Positive	14.1	1
9	76	M	V.A. = 2/60 Central scotoma inferior altitudinal	None	Hypertension Myocardial infarct	13	Negative	1.8	1
10	77	F	Bilateral visual loss V.A. = N.P.L. right and left	None	None of note	20	Positive	9.6	1
11	76	F	V.A. = 6/36 Generalised field constriction	Malaise	Angina	1	Negative	2.8	1
12	64	M	V.A. = 6/60 Central + inferior altitudinal scotoma	None	Previous central retinal vein occlusion in fellow eye	4	Negative	1.9	1
13	79	M	V.A. = 5/60 Inferior-nasal only remaining field	None	Hypertension	37	Negative	3.4	1
14	62	M	V.A. = 6/36 Central scotoma	None	Diabetes mellitus	15	Negative	4.4	1
15	74	M	V.A. = H.M. Small temporal island of field only remaining	None	None of note	47	Negative	4.4	1.1
16	69	F	V.A. = P.L. Generalised field loss	None	Hypertension Deep vein thrombosis	15	Negative	2.4	1
17	76	F	V.A. = 6/60 Central scotoma	Headache	Hypertension	8	Negative	1	1
18	74	F	V.A. = H.M. Generalised field constriction	Malaise, scalp tenderness, jaw claudication	None of note	54	Positive	46.5	6.4
19	77	M	V.A. = H.M. Small temporal island of field only remaining	Malaise, scalp tenderness	Hypertension Myocardial infarct	14	Positive	11.5	58.6

* Normal = <[mean + 3 Standard Deviations] determined in study of 70 healthy normals.

absence of such an association with the IgM antibody is in agreement with previous work on antiphospholipid antibodies mediating other vascular events, when the IgG antibodies have been shown to correlate best with clinical disease.[17] However, the absence of other autoantibodies, such as anti-dsDNA, anti-Ro, and those responsible for the lupus anticoagulant effect identifies the patients with giant cell arteritis mediated AION as a group with a highly specific antibody. In other disease states with antiphospholipid mediated vascular events, a more diffuse range of autoantibodies has been identified.[18]

The mechanism by which antiphospholipid antibodies mediate thrombosis remains undefined, and similarly their precise role in giant cell arteritis is obscure. It may be that the antibodies are part of a humorally mediated immune response, and indeed, the presence of immunoglobulins on the walls of arteries affected by giant cell arteritis has been well documented.[19,20] Alternatively, the antibodies may initiate a microvascular thrombosis in the posterior ciliary arteries and peripapillary choroidal vasculature, as they do in the plancental microvasculature in cases of recurrent fetal loss.[21] The possibility that the antibodies are merely an epiphenomenon also exists, since in certain situations they may be a consequence of tissue damage, for example after myocardial injury. However, their absence in the patients with 'non-arteritic' AION, and presence in three patients with AION secondary to giant cell arteritis, but without systemic involvement, argues against this.

Although the numbers are as yet relatively small, the results of IgG anticardiolipin assay have so far provided a sensitive (100%) and specific (91%) test to distinguish between 'arteritic' and 'non-arteritic' AION, as defined by conventional criteria. The distinction is often not easy to make, and this additional marker of the disease may be of benefit.

The recognition of the importance of antiphospholipid antibodies in the aetiology of certain vascular events has directed attention to their treatment using techniques aimed at their elimination. For example, successful pregnancies have been achieved in patients with a history of recurrent fetal loss in association with antiphospholipid antibodies, using corticosteroid treatment to reduce antibody levels,[22] and plasmapheresis has also found success.[23] Such studies may explain the mechanism of action of steroids in treatment of giant cell arteritis; reduction of an immune response which therefore reduces second eye involvement. They also make suggestions as to possible new techniques in management.

As long as the basic mechanism of action of antiphospholipid antibodies remains obscure, a number of questions must remain unanswered. However, the association of IgG anticardiolipin antibodies with giant cell arteritis mediated AION suggests new directions in which to look for an understanding of this enigmatic disease, and offers a new diagnostic marker.

Keywords: Antiphospholipid antibodies; giant cell arteritis; ischaemic optic neuropathy.

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