Optic Neuritis and Myelopathy in Systemic Lupus Erythematosus

Stephen Oppenheimer and B.I. Hoffbrand

ABSTRACT: The optic neuritis of systemic lupus erythematosus (S.L.E.) more frequently results in the persistence of a central scotoma or complete blindness after a single attack than demyelinating optic neuritis, although the initial clinical presentations may be identical. A significant number of patients, however, recover normal vision. Optic neuritis may be the presenting symptom of S.L.E. and as myelopathy may also occur in the course of the disease, confusion with multiple sclerosis may result, especially if there are no arthritic, cutaneous nor visceral manifestations. We report a case of lupus optic neuritis associated with anticardiolipin antibodies and a circulating lupus anticoagulant and suggest these may be a marker for vasculitic optic neuritis and play a role in its aetiology.

RÉSUMÉ: La neurite optique et la myélopathie au lupus érythémateux systémique Même si la présentation clinique peut être identique, la persistance d'un scotome central ou de cécité totale est plus fréquemment le résultat d'un seul épisode de névrite optique dû au lupus érythémateux systémique, que d'une névrite optique démyélinisante. Cependant, un nombre important de patients recouvrent une vision normale. La névrite optique peut être le symptome initial d'un lupus érythémateux systémique et, comme la myélopathie, peut aussi survenir au cours de l'évolution de la maladie, d'où la possibilité de confusion avec la sclérose en plaques, surtout s'il n'y a pas de manifestations arthritiques, cutanées ou viscérales. Nous rapportons un cas de névrite optique lupique associée à des anticorps anticardiolipine et à un anticoagulant lupique circulant, et nous suggérons que ces manifestations peuvent être un marquer de la névrite optique vasculaire et jouer un rôle dans son étiologie.

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Ophthalmological manifestations, principally retinopathy, have been reported to occur in 10 - 20% of cases of systemic lupus erythematosus (S.L.E.).[1] However, optic neuritis, presenting as progressive visual loss over a few hours or days, with orbital or supra-orbital pain is a rare complication.[2,3] We report a case of optic neuritis occurring in a patient with S.L.E. who was found to have a lupus anticoagulant and a high titre of anticardiolipin antibodies, an association not previously reported. Anticardiolipin antibodies have been implicated in the etiology of the neurological complications of S.L.E.[4,5,6] and this observation may be of relevance in elucidating the etiology of optic neuritis in this condition. Our case also resembles some of those previously reported, in being associated with a myelopathy at some stage of the clinical course.

Case Report

A 47-year-old woman presented with diffuse arthralgias and alopecia. She had a past history of asthma and hypothyroidism. Physical examination was normal apart from some swelling of the right wrist and a purpuric rash over the left shoulder. She was diagnosed as having S.L.E. on the basis of her clinical presentation and an anti-double stranded D.N.A. titre of 1/640. Her symptoms and signs resolved following a short course of oral steroid therapy.

A year later she complained of the abrupt onset of numbness from the waist downwards with no sphincter or motor symptoms. Examination revealed absent vibration sensation below the knees and absent joint position sensation at the toes. The reflexes were bilaterally brisk in all four limbs and the plantars downgoing. Abdominal reflexes were preserved. No diagnosis was made at the time and she did not undergo any investigations. Her symptoms and signs resolved spontaneously over three weeks.

Thirty months after onset of the initial symptoms she abruptly developed left orbital pain; after one hour there was no perception of light in the left eye which showed an afferent pupillary defect. The disc was normal. Examination of the right eye and of the remainder of the nervous system was unremarkable. There was no clinical evidence of recrudescence of S.L.E. elsewhere. The CBC was normal and the E.S.R. 30 mm/hr (Westergren). Complement levels were within the normal range and the VDRL was non-reactive. The serum IgM was elevated at 4.8 g/L, the other immunoglobulins being normal. The C.S.F. showed no abnormality and no oligoclonal bands. X-rays of the orbits were normal; C.T. scanning revealed an area of low attenuation

From the Department of Medicine, Memorial University of Newfoundland, St. John's, Newfoundland (Dr. Oppenheimer) and the Department of Medicine, The Whittington Hospital, London, England (Dr. Hoffbrand)

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Reprint requests to: Dr. S. Oppenheimer, Department of Clinical Neurological Sciences, University Hospital, 339 Windermere Road, P.O. Box 5339, London, Ontario, Canada N6A 5A5

in the right parietal lobe, which was thought to be consistent with a silent infarct, presumably secondary to cerebral lupus vasculitis. A diagnosis of lupus optic neuritis was made and she was treated with Prednisolone 120 mgs daily by mouth. Within one week, peripheral vision returned to the left eye but she retained a large central scotoma and a visual acuity of finger counting only. Over the next few months, the dose of prednisolone was gradually tapered to a maintenance regimen of 5 mgs daily.

Four years after onset she spontaneously stopped her steroid therapy and, within a few days, developed right supra-orbital pain and a sensation of dark spots and occasional flashes of light in that eye. The visual acuity in the right eye was 6/6; there was no colour desaturation and the pupillary response was normal. The right visual field was normal, as was the disc. The left eye was unchanged from before, with the exception of optic atrophy on fundoscopy. A further attack of lupus optic neuritis was diagnosed and she was treated with methylprednisolone 1 gm intravenously in bolus doses for each of three consecutive days, with complete resolution of her symptoms. She was restarted on oral Prednisolone 60 mgs daily and the dose tapered gradually to a maintenance regimen of 5 mgs as before.

One month later her partial thromboplastin time (PTT) was prolonged at 38 seconds (control 31 seconds) and this did not correct with normal plasma. The prothrombin time and platelets were normal. The presence of a lupus anticoagulant was inferred and, subsequently, very high titres of IgG and IgM anticardiolipin antibodies were found by radioimmunoassay.

After a further six months while on a maintenance dose of prednisolone 5 mgs daily, she suddenly developed pain and blurring of vision in the right eye. The visual acuity of that eye was 6/9 with no colour desaturation and normal pupillary response, visual fields and disc. The left eye was unchanged. A further attack of lupus optic neuritis was diagnosed and she was treated with methylprednisolone 1 gm intravenously daily for three days and a single intravenous dose of cylophosphamide 150 mgs. After one week, her visual acuity improved to 6/6 and her symptoms resolved completely.

DISCUSSION

Although the initial presentation may be identical to that of the optic neuritis of multiple sclerosis (M.S.), it has been suggested that lupus optic neuritis may be clinically differentiated by the persistence of a dense central scotoma, with severe visual loss, after a first attack.[2] This would be unusual in demyelination, where about 90% of patients recover normal or near normal vision after a single episode.[7]

A review of the literature revealed 17 previously published reports of lupus optic neuritis, of which four[8,9,10,11] (cases 1 and 2 in ref. 9) did not fulfill our criteria for the diagnosis of S.L.E. and have consequently been excluded. These criteria are modified from those of the American Rheumatism Association[12] and comprise either 1) the presence of LE cells, anti-double stranded DNA, or ANF *and* evidence of involvement of one or more systems outside the central nervous system *or* 2) no reported immunological abnormality and the involvement of three or more systems outside the central nervous system. April and Vansonnenberg[13] reported a patient with S.L.E. who developed optic neuritis while being treated with ethambutol, which, itself, can cause the condition.[14] This case has also been excluded.

The details of the cases analysed are given in Tables 1 and 2. In four of these, optic neuritis was the initial manifestation of S.L.E.[2,3,9] (cases 2 and 3 in ref. 2, case 3 in ref. 9). There was no difference in the occurrence of anterior (AON) or posterior (PON) forms of optic neuritis at presentation, based on the presence or absence of disc swelling respectively. Thus, we found seven cases of AON and six of PON in the literature. Whereas all the cases of AON presented with a central scotoma, only one third of the cases of PON did so; of the remaining cases of PON, three had no light perception, and one had normal visual acuity. Our patient initially presented with PON and no light perception. Thus, it would appear that a central scotoma occurred in nine of the 13 cases of lupus optic neuritis reported, making it the most common visual field defect.

Eight of the reported cases went on to develop optic atrophy, (the central scotoma persisting in six cases and the remaining two patients being left with no light perception). Complete recovery occurred in the remaining five cases. The presentation as AON or PON had no predictive value for outcome. Therefore, although a persistent central scotoma after a first attack of optic neuritis may be a hallmark of S.L.E., many cases do yet recover after the initial attack; it is in these that a diagnostic difficulty could occur, since their presentations and course would be identical with that of demyelinating disease.

Our patient had two further episodes of supra-orbital pain and blurring of vision, which recovered completely and were unaccompanied by any disc changes or visual field defect. We suggest that, whereas persistent field defects reflect irreversible, vasculitic, ischemic damage to the optic nerve, the less severe episodes represent a reversible optic nerve insult complicating lesser degrees of vasculitis aborted by the very early introduction of steroids. However, once severe visual field defects occur in lupus optic neuritis, there is no conclusive evidence that steroids improve the outcome.

An arcuate scotoma or altitudinal visual field defect is accepted as characteristic of ischaemic optic neuropathy.[23] In this case, large branches of the ophthalmic artery are involved, in either a vasculitic or thromboembolic process. Pathological studies[2,17] suggest that in lupus optic neuritis, there is more widespread infarction of the optic nerve due to arteriolar fibrinoid necrosis which, if focused on the central areas of the nerve, would account for the central scotoma. Therefore, although it has been customary to refer to the condition as 'lupus optic neuritis', owing to its symptomatic similarity to demyelinating optic neuritis, the term 'optic nerve arteriolitis' may be more appropriate.

Table 1: Details of Patients with Lupus Optic Neuritis

Paper and Patient No	Race	Sex	Age at Onset of SLE	VDRL	ANF	LE Cells
Hackett et al[2]						
1	Black	F	16	?	?	Yes
2	Black	F	23	?	?	Yes
3	White	F	26	?	?	Yes
Smith et al[3]						
1	Black	M	17	?	Yes	Yes
2	Black	F	22	?	Yes	?
3	Black	F	28	Pos	Yes	Yes
4	White	F	24	?	Yes	Yes
Dutton et al[9]						
3	?	F	42	Neg	Yes	Neg
Lessell[15]	White	F	41	Neg	Yes	Yes
Cinefro et al[16]	White	M	56	Pos	Yes	Yes
Allen et al[17]	?	F	62	Neg	Yes	Yes
Hayreh[18]						
1	White	M	36	?	?	?
Vitale et al[19]						
1	?	F	10	?	Yes	Yes

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Table 2: Neurological and Ophthalmological Characteristics of Patients with Lupus Optic Neuritis

Paper and Patient No.	Optic Neuritis as Presenting Symptom of S.L.E.	Time to Onset of Optic Neuritis From Diagnosis of S.L.E.	Initial Fundus Appearance	Follow-Up Fundus Appearance	Initial Visual Field Defect	Final Visual Field Defect	Myelopathy	Time to Onset of Myelopathy From Diagnosis of S.L.E.
Hackett et al[2]								
1	No	4 months	Disc Swelling	Optic Atrophy	Central Scotoma	Central Scotoma	No	—
2	Yes	—	Disc Swelling	Optic Atrophy	Central Scotoma	Complete Blindness	Yes	3 yrs.
3	Yes	—	?	Optic Atrophy	Central Scotoma	Central Scotoma	Yes	1 yr.
Smith et al[3]								
1	No	2 months	Normal	Optic Atrophy	Complete Blindness	Complete Blindness	No	—
2	No	6 years	?	Normal	Normal	Complete Recovery	Yes	Presenting Symptom
3	Yes	?	*R eye* Normal	Normal	Normal	Normal Vision	No	—
			L eye Disc Swelling	Optic Atrophy	Central Scotoma	Central Scotoma		
4	No	1 year	*L eye* Optic Atrophy	Optic Atrophy	Complete Blindness	Complete Blindness	No	—
			R eye Blurred Disc	Optic Atrophy	Central Scotoma	Central Scotoma		
Dutton et al[9]								
3	Yes	—	Normal	Normal	Light Perception Only	Complete Recovery	No	—
Lessel[15]	No	10 years	Normal	Optic Atrophy	Central Scotoma	Central Scotoma	Yes	?
Cinefro et al[16]	No	1 year	Blurred Disc Margins	Optic Atrophy	Central Scotoma	Central Scotoma	No	—
Allen et al[17]	No	1 year	?	Optic Atrophy	Complete Blindness	Return of Vision in L Upper Quadrant	Yes	Presenting Symptom
Hayreh et al[18]								
1								
1st Attack	No	13 years	Normal	Normal	Central Scotoma	Complete Recovery	No	—
2nd Attack			Normal	Optic Atrophy	Complete Blindness	Complete Blindness		
Vitale et al[19]								
1								
1st Attack			*R eye* Optic Atrophy	Optic Atrophy	Central Scotoma	Central Scotoma		
2nd Attack 2 years later	No	?	*L eye* Disc Swelling	Normal	Central Scotoma	Complete recovery	Yes	?
3rd Attack 2 years later			*L eye* Disc Swelling	Normal	Central Scotoma	Complete recovery		

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Evidence against the concurrence of S.L.E. and M.S. in these patients comes from post-mortem studies. Hackett et al[2] demonstrated arteriolar fibrinoid necrosis with perivascular lymphocyte and plasma cell infiltrates within the optic nerve of one of their cases. There was marked gliosis with loss of axons. Similar findings were reported by Allen et al[17] in whose case there was no evidence of demyelination within the central nervous system.

The visual evoked response (VER) should be useful in differentiating lupus optic neuritis from demyelination. In the former case, an absent response or a decrease in amplitude would be anticipated rather than conduction delay. Absent VER's have been reported by Dutton et al[9] (case 3) in their case of lupus optic neuritis. Unfortunately, VER recording was technically unsatisfactory in our patient.

Only two of eleven reported patients[8,9] (case 1 in ref. 9) who underwent lumbar puncture at the time of their attack of optic neuritis showed oligoclonal bands in the C.S.F. Neither of these fulfilled our criteria for the diagnosis of S.L.E.

In a patient with optic neuritis, the following features suggest SLE rather than MS as the underlying pathology: 1. The persistence of a severe visual field defect after a first attack; 2. Absent or markedly reduced amplitude of VER's with little or no conduction delay, and; 3. The absence of oligoclonal bands in the C.S.F.

Six of the thirteen reported cases developed a myelopathy during their clinical course, as did our patient. The concurrence of these rare manifestations of S.L.E. may not be fortuitous, suggesting a subgroup prone to vasculitic involvement of the optic nerve and spinal cord.

There appears to be a close association between high titres of anticardiolipin antibodies detected by radioimmunoassay and the neurological manifestations of S.L.E.[4,5,6] A circulating lupus anticoagulant may be detected in at least 70% of cases manifesting anticardiolipin antibodies.[5] The latter can be readily inferred by a prolonged partial thromboplastin time, which does not correct with the addition of normal plasma.[20] In some cases the platelet count may be reduced. Fifty percent of patients manifesting anticardiolipin antibodies have antinuclear factor in their plasma but only 20% are VDRL positive (the VDRL test detects only very high titres of anticardiolipin antibodies).[21] Thus, the presence of anticardiolipin antibodies can be deduced by simple, routine laboratory tests, in most cases. The VDRL result was positive in two of the five cases in which it was recorded,[2,16] suggesting the presence of high titres of anticardiolipin antibodies.

Paradoxically, the presence of the lupus anticoagulant is associated with arterial and venous thrombotic events.[21] This may be due to interference with prostacyclin production by endothelial cells.[22] Both the anticoagulant and anticardiolipin antibodies are thought to be directed against phospholipids.[21] We hypothesize that in those cases of S.L.E. with optic neuritis and myelopathy, these antibodies cross-react with specific phospholipids within the endothelia of optic nerve and spinal cord arterioles, initiating a vasculitic or thrombotic process at these sites, the latter possibly by decreased local prostacyclin production, and the former as a result of an antigen/antibody reaction.

There is a very low incidence of anticardiolipin antibodies and lupus anticoagulant in M.S. and the titres, when positive, are much less than those seen in S.L.E. (C.B. Colaco - personal communication). These factors should be looked for in all cases of isolated optic neuritis in order to distinguish those patients who may have optic neuritis as a single manifestation of S.L.E. from those who have demyelination.

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