REVIEW

Demyelination in rheumatic diseases

A Theodoridou, L Settas

J Neurol Neurosurg Psychiatry 2006;**77**:290–295. doi: 10.1136/jnnp.2005.075861

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterised by multifocal areas of demyelination in the white matter of the brain and spinal cord. Autoantibodies, for example antinuclear antibodies, can also be present. MS and other demyelinating processes, such as transverse myelitis and optic neuritis (which may be clinically isolated cases or be part of the clinical spectrum of MS), are sometimes difficult to differentiate from CNS involvement in systemic autoimmune diseases like systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), Sjogren's syndrome (SS), and Adamantiades-Behcet disease (BD). An acute isolated neurological syndrome presents the biggest diagnostic problem, since it is common in MS, but can also be the only feature or first manifestation in SLE, APS, SS, and BD. Indeed, the clinical presentation and lesions evidenced by magnetic resonance imaging may be similar.

label of MS.^{1–5} This can sometimes be catastrophic as the treatment for the supposed MS may exacerbate SLE (that is, interferon- β) and of course may be expensive and ineffective.

Other demyelinating processes, such as transverse myelitis (TM) and optic neuritis, may be part of the clinical spectrum of MS or may be isolated syndromes. Optic neuritis usually presents as acute or subacute unilateral eye pain, accentuated by ocular movements and followed by scotomas mainly of the central vision. TM is an acute inflammatory process affecting a focal area of the spinal cord and characterised clinically by acutely or subacutely developing symptoms and signs of neurological dysfunction in motor, sensory, and autonomic nerves and nerve tracts of the spinal cord. TM may be secondary to viral diseases, vaccinations, acute disseminated encephalomyelitis, MS, vascular insults, SLE, spinal arteriovenous malformations, and APS. TM is a monophasic disease and when recurrent raises the possibility of SLE, MS, and APS.³

TM and optic neuritis (as clinically isolated cases) and MS are sometimes difficult to differentiate from CNS involvement in SID such as SLE, APS, SS, and BD. Indeed, the clinical presentation and the lesions evidenced by magnetic resonance imaging (MRI) may be similar. There is no specific diagnostic test for demyelinating diseases, but the most useful are MRI, CSF examination (total leucocyte count and cell type, albumin determination, serological testing for *Borrelia burgdorferi* and other antimicrobial Abs, IgG index, and CSF immunoelectrophoresis), visual evoked potentials (VEP), and autoantibody serology.^{1–6,7} The CSF is grossly abnormal in MS. Total leucocyte count is normal in two thirds of patients, exceeds 15 cells/ μ l in 5%, and only rarely exceeds 50 cells/ μ l (a finding that should raise suspicion of another aetiology). Lymphocytes are the predominant cell type, the vast majority of which are T cells. CSF protein (or albumin) level is usually normal. Albumin determinations are preferable, since albumin is not synthesised in the CNS and therefore gives a better indication of a blood-brain barrier disruption than does total protein, some of which may

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) and is characterised by multifocal areas of demyelination in the white matter of the brain and spinal cord, and axonal loss. The cause of MS is unknown, although viral infections and autoimmune processes have been implicated. There is no specific marker of disease and diagnosis is based on a constellation of clinical and laboratory criteria. MS can only be diagnosed when there is objective evidence of central neurological dysfunction with more than one affected area and more than one episode (other explanations excluded). In many cases, accurate diagnosis can be made after long-term follow up.

An acute isolated neurological syndrome poses the biggest diagnostic problem, since it is the most common symptom in MS but can also be the only feature or first manifestation in antiphospholipid syndrome (APS)/systemic lupus erythematosus (SLE),¹ Adamantiades-Behcet disease (BD), or Sjogren's syndrome (SS), before other features of these diseases, such as thrombosis and/or miscarriages for APS, systemic manifestations for SLE, and mouth ulcers and uveitis for BD, appear. Autoantibodies, for example antinuclear antibodies (ANA), can also occur in MS. Hence a significant number of patients with demyelinating features in the course of APS, SLE, or other systemic autoimmune diseases (SID) may be given the false

See end of article for authors' affiliations

Correspondence to: Athina Theodoridou, Rheumatology Unit of the 1st Internal Medicine department, AHEPA University Hospital, 54006 Thessaloniki, Greece; atheodori@yahoo.gr

Received 17 July 2005
Revised version received 10 October 2005
Accepted 17 October 2005

Abbreviations: aCL, anticardiolipin antibodies; ANA, antinuclear antibodies; AON, autoimmune optic neuropathy; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; BD, Adamantiades-Behcet disease; CNS, central nervous system; CP, cyclophosphamide; LA, Lupus anticoagulant; MP, methylprednisolone; MRI, magnetic resonance imaging; MS, multiple sclerosis; NPLE, neuropsychiatric lupus erythematosus; PAPS, primary antiphospholipid syndrome; SID, systemic autoimmune diseases; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome; TM, transverse myelitis; VEP, visual evoked potentials

be synthesised in the CNS (for example, immunoglobulin). A common finding in MS is elevation of the CSF immunoglobulin level relative to other protein components, suggesting intrathecal synthesis. The immunoglobulin increase is predominantly IgG, although the synthesis of IgM and IgA is also increased. IgG shows an excess of IgG λ and κ light chains. Abnormal CSF IgG production as measured by the IgG index or IgG synthesis rate is found in 90% of clinically definite MS patients.⁷

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with protean manifestations. Neuropsychiatric manifestations are present in up to 60% of patients with SLE. Demyelinating syndrome and myelopathy are two of the 19 recently defined syndromes in neuropsychiatric SLE.⁸

Lupoid sclerosis is a term that has been used to describe a clinical condition in which SLE presents with widespread neurological signs and symptoms suggestive of MS.⁹

McDonald *et al* published revised MS diagnostic criteria, but did not provide guidelines to distinguish MS from other SID including definite SLE/CNS disease. The most common neurological manifestations of SLE (headaches, seizures), symptoms suggestive of peripheral nervous system involvement and psychiatric disorders, are not seen in MS.¹ MRI is the most important diagnostic tool and the MRI criteria from Barkhof *et al*¹⁰ offer the best combination of specificity and sensitivity for MS. The morphology of the lesions is important: the absence of multifocal lesions on brain MRI has a good negative predictive value for later development of MS.¹¹ Small multifocal demyelinating lesions may be produced by MS and by small strokes, as can also happen in SLE and APS, and can be clinically silent.^{1 10 12} Elongated ovoid shaped lesions ("Dawson's fingers") and "black holes" are more characteristic of MS yet are not pathognomonic.^{11 13} Lesion distribution can also be helpful since subcortical lesions predominate in APS and SLE and periventricular and especially corpus callosum lesions are more common in MS.^{2 5 11} The absence of oligoclonal bands in CSF makes a diagnosis of MS unlikely.^{6 14} VEP are particularly helpful when MRI abnormalities are few or have less specificity.⁶ Normal VEP are unusual in MS.^{1 6} In several studies,¹⁵ ANA were found in MS patients at a frequency of 2.5–81%, although no correlation between the presence of ANA and symptoms of SLE was established in most of these studies. Despite these results, when ANA titres are high and persistent, and appear in the context of other autoimmune abnormalities, a diagnosis of SID should be considered.¹

SLE associated TM has become an established clinical entity since the initial series of nine patients were described in the literature in 1968.¹⁶ TM, a demyelinating disease of the spinal cord involving its entire thickness, is very uncommon (1.34/million). SLE is one of the rarest causes of TM, while TM is a rare but serious neuropsychiatric manifestation of SLE (1–2%),¹⁷ with uncertain pathophysiology. Pathophysiological mechanisms suggested in SLE associated TM are vasculitis and arterial thrombosis. The arterial thrombosis hypothesis, the several reports indicative of a significant association of TM-SLE and MS, and the presence and association of antiphospholipid antibodies (aPL) with MS are described in several studies.^{18–23} Concerning the onset TM compared to that of SLE, after an analysis of published cases by Kovacs *et al*¹⁷ determined that TM was the initial manifestation of SLE in 39% and presented in the first 5 years of SLE in 42% of the total cases analysed. As many authors suggest, all patients with TM should be examined for SLE and/or APS by history, clinical examination, and the occurrence of aPL in the blood.^{18 24} SLE should be suspected

in every case of TM with aPL and the patient followed prospectively for several years in case features of SLE develop.²⁴

MRI findings in SLE myelopathy are T1 and T2 signal abnormalities and widening of the cord.²⁵ MRI lesions in SLE myelopathy are longer than those in most cases of MS and similar to those in Devic's syndrome. They may extend over the entire length of the spinal cord.^{19 25 26} Peripheral nervous system involvement, which is absent in MS but sometimes present in SLE and APS, can be investigated by neurographic recording and electromyography.

Outcome is poor^{17 26–28} and not related to disease activity. It has been postulated that starting aggressive treatment early in the course of TM is important to achieve a favourable outcome.^{29–31} Treatments reported in the early and late literature,¹⁷ but not yet confirmed in trials, are iv methylprednisolone (MP), iv MP plus iv cyclophosphamide (CP), and iv MP plus iv CP plus plasmapheresis, with all treatment regimens followed by tapering doses of oral prednisolone.

Optic neuritis is associated with TM in patients with SLE^{17 23 32 33} and was first described by Devic in 1894. Devic's neuromyelitis optica is a CNS disease in which visual involvement (retrobulbar optic neuritis or oedematous papillitis) is associated with longitudinal TM rather than TM of subacute onset; diagnostic criteria have been proposed by Wingerchuk *et al*.³⁴ It has been distinguished from MS³² on the basis of several characteristics (progress more severe, no fever at onset, cerebral and cerebellar lesions absent on MRI, no oligoclonal bands on CSF electrophoresis, and no albumin elevation in CSF).³⁴ The best diagnostic tool is MRI.^{32 34} Devic's syndrome pathophysiology is small vessel vasculitis and white matter demyelination and necrosis.^{32 35} The myelopathy of Devic's syndrome extends over two or more vertebrae and is characterised histologically by necrosis and cavitation. The course of this syndrome is monophasic, relapsing, or chronic,³⁵ and prognosis is often unfavourable. Various treatment regimens have been described in the literature³²: iv CP and/or pulsed iv MP, and a combination of oral prednisone and azathioprine and/or plasmapheresis.

Autoimmune optic neuropathy (AON) was first reported by Dutton in 1982. Frequently patients do not develop a defined collagen disease. AON is a well known complication of SLE, is estimated to occur in 1% of such patients, and appears to be often associated with CNS disease, particularly of the spinal cord.^{36 37} In SLE, visual field loss may precede the reduction in visual acuity. VEP can also be employed in these patients to detect optic nerve damage before it can be demonstrated by visual field examination.³³ The pathogenesis is still unclear: is it due to vasculitis or to thrombosis? According to the review by Giorgi and Balacco Gabrieli,³³ three major criteria can be used to decide which pathogenic mechanism is involved: the first criterion is the monolateral occurrence of optic neuropathy, which is a focal neurological disease, and seems to be more frequent in SLE patients with aPL and clinical manifestations of APS; another criterion is improvement of the optic nerve disease after treatment with immunosuppressive drugs; and finally, the third criterion is association of the optic neuropathy with general CNS disease, which seems to be the main neurological disease seen in SLE patients and to which vasculitis may contribute.

ANTIPHOSPHOLIPID SYNDROME

The interface between MS and antiphospholipid syndrome (APS) is of importance in two common clinical settings: patients clinically diagnosed with MS who are found to have significantly high levels of aPL, and patients clinically diagnosed with APS who are found to have subcortical white matter lesions on imaging studies (table 1).

Table 1 Differential diagnosis between APS, SLE, and MS

	PAPS APS	NP/APS SLE	MS
Clinical			
Thrombosis			
Miscarriages/pregnancy morbidity			
Headaches	May be present	May be present	Absent
Livedo reticularis			
Thrombocytopenia	May be present	May be present	Absent
Raynaud's phenomenon			
Photosensitivity			
Rash	Absent	Usually present	Absent
Arthritis/arthralgia			
Sicca syndrome			
PNS involvement	May be present	May be present	Absent
Optic neuritis	Unilateral, abrupt onset	Usually bilateral	May be bilateral
Laboratory			
aPL	100%	50–60%	± (2–44%)
ANA	Usually negative	98%	± (2.5–25%) low titre
Anti-DNA	Usually negative	60%	Usually negative
CSF oligoclonal bands	Usually negative	15–50%	98%
MRI			
Brain MRI	High-signal lesions Subcortical	High-signal lesions Subcortical	High-signal lesions Periventricular, corpus callosum, brainstem
	Static (may improve after anticoagulation)	Static	Dynamic
Spinal MRI	>4 segments in length Thoracic region more common Cord swelling and atrophy	>4 segments in length Thoracic region more common Cord swelling and atrophy	<2 segments; only part of cross section Cervical region more common No cord swelling
VEP	Normal or reduced wave amplitude	Normal or delayed conduction	Delayed conduction but well preserved wave form

Adopted and modified from Ferreira *et al.*¹

PNS, peripheral nervous system; VEP, visual evoked potentials.

Some patients with APS may have more complex manifestations than a stroke, such as sensory and motor dysfunction, optic neuritis, and TM. MRI studies in these patients frequently show multiple T2 hyperintense brain lesions. This combination – relapsing/remitting multifocal neurological symptoms plus the MRI findings – may closely resemble MS. The prevalence of aPL in MS patients is 4.8–44% of sera according to various studies,^{4 5 14 15 38 39} with a higher frequency in MS patients with TM and optic neuritis. Although aPL are common in MS patients, these antibodies are usually not depended from the presence of serum factors for binding to phospholipids. Karussis *et al* and other authors¹⁴ found an association of aPL in MS with specific clinical features of chronic, slowly progressive myelopathy and optic neuropathy, and concluded that patients with a probable or definite diagnosis of MS and consistently elevated level of anticardiolipin antibodies (aCL) show a slower progression, while Roussel *et al*¹⁵ failed to demonstrate clinical correlates. The pathogenic role of aCL in MS is unknown. The mechanisms by which aPL may induce an MS-like illness may be microvascular thrombotic events, vasculopathy, an autoimmune vasculitis similar to that seen in SLE, and molecular mimicry with myelin or other CNS antigens (cephalin, sphingomyelin).^{14 40 41} Generally, the CNS is a system at particular risk in patients with APS, possibly because the CNS coagulation system has clear differences from those of other organs: the brain endothelium expresses little thrombomodulin compared to other tissues and aPLs may have direct antineuronal activity.⁵ Some studies appear to refute the association between APS and MS-like disease.^{40 41} The editorial by Ruiz-Irastoza and Khamashta² reviews the most important series of patients with positive association of MS and aPL. As no single test can discriminate between ischaemic (secondary to APS) and inflammatory (secondary to MS) white matter lesions, every patient with MS should be routinely tested for aCL, IgG and IgM, and lupus anticoagulant (LA),² even though some authors⁴² say

only MS patients suspected of APS should be evaluated for these antigens. The absence of oligoclonal bands in the CSF should be regarded as evidence against a diagnosis of classic MS,¹⁴ although their presence does not necessarily exclude APS.^{4 14 38 39} Experienced authors in the field say that MRI lesions seen in association with APS are usually static on repeat MRI compared with the dynamic nature of lesions seen in MS.¹ The application of single photon computed emission tomography has been studied in patients with APS where it can show focal low-perfusion areas that improve with anticoagulation.⁴ According to a paper by Rovaris *et al*,¹² magnetisation transfer imaging combined with standard MRI can discriminate MS from APS (but not from SLE).

Based on a positive response to warfarin in case series,^{4 5 38 39} Ruiz-Irastoza and Khamashta² recommended that a trial with anticoagulation therapy should be offered to US patients who are consistently positive for aPL (aCL and IgG and/or IgM at medium to high levels and/or LA) and in particular to those who have atypical forms of the disease (abnormal localisation of lesions, normal brain MRI, epilepsy, unusual progression, absence of oligoclonal bands in CSF, dementia, isolated neurological syndrome), livedo reticularis, previous thrombosis, migraine, obstetric complications, thrombocytopenia, and/or lupus. This trial of anticoagulation with a target INR of 3–4, should last 6 months, and the patient should receive careful counselling of the risks involved.¹

TM is a rare (0.4%) manifestation of APS, either primary or secondary to SLE.^{43–46} The association of TM and APS is not well established and the exact mechanisms are not clearly known. It is not yet clear if aPLs have a pathogenic role in TM. Vascular changes and ischaemic necrosis caused by immune complex mediated vasculitis or vascular thrombosis is a proposed mechanism, while another suggestion is that aPL may interact directly with spinal cord phospholipids.^{18 47} All patients with TM should be examined for SLE and/or APS by history, clinical examination, and the

occurrence of aPL in the blood.^{18–24} SLE must be suspected in every case of TM with aPL and such patients must be followed prospectively for several years in case features of SLE develop.²⁴

The management of these patients is not well established. In recent years, pulses of MP in combination with immunosuppressive drugs, such as CP or plasmapheresis, have been used.^{44–47} Other therapies include anticoagulation.^{31–44–46}

AON was first associated with aCL in Kupersmith's series⁴⁸ and confirmed by several other reports,^{49–50} without demonstration of full blown APS in the vast majority of patients.

Optic neuropathy is a rare manifestation (1%) in the Euro-Phospholipid Project cohort of 1000 European APS patients (primary and secondary).⁴³

PRIMARY SJOEGREN'S SYNDROME

Sjogren's syndrome (SS) is a chronic autoimmune exocrinopathy, which in addition to the two characteristic symptoms of dry eyes and dry mouth, may have extraglandular manifestations in various organs. SS is often unrecognised even though it is probably the most common SID. While most SS patients have positive antibodies (ANA, anti-Ro, anti-La, RF), the absence of antibodies does not exclude a diagnosis of SS.

Between 20 and 25% of SS patients have been reported have to CNS manifestations,^{13–51} but this is a matter of debate as some studies report a negative association.^{52–56} MS and TM are rare events in SS patients and the relationship between SS and MS is ambiguous since SS may mimic MS both clinically and radiologically.^{57–60} Neurological manifestations often precede SS diagnosis at a time when immunological abnormalities are frequently lacking, although xerostomia or xerophthalmia may be present.⁶¹ In fact, many patients have been thought to have MS before a diagnosis of SS was made.^{60–61} In these patients there may be changes in the CSF profile (oligoclonal banding patterns of immunoglobulin) similar to those in MS, but with the difference that MS patients most commonly have multiple bands, whereas SS patients have only one or two bands.⁶⁰

Anti-Ro antibodies can be detected in 2–15% of MS patients.^{55–60–62} Some authors suggest that these antibodies represent cross-reactivity of antibodies against myelin or viral antigens with Ro/SSA molecules and other autoantigens.⁵⁶ Even though anti-Ro, ANA, anti-dsDNA, and aCL are positive in patients with definite MS, these patients should be re-evaluated for SID treatable with maintenance immunosuppression.

TM has been reported in patients with SS^{13–57–60–63–67} and in four patients with primary biliary cirrhosis and SS.^{68–71} Possible aetiologies for TM in SS patients are vasculitis,^{60–63–67–68} immunological injury of spinal vessels and/or spinal cord driven by reactive T cells, and/or the presence of antineuronal antibodies.^{68–69} Patients respond to treatment with high doses of MP and pulses of CP or chlorambucil.^{63–72}

Even though the prevalence of myelopathy in SS is rather low (<1%), it should be considered when the patient first presents with TM and the following procedure followed: a) the patient should be queried about symptoms of SS; b) elevated ESR, positive ANA, a paucity of periventricular white matter lesions, and the presence of marked cord swelling on MRI (unusual in TM) should be considered; c) anti-Ro and anti-La tests ordered; and d) matched oligoclonal bands in the plasma and cerebrospinal fluid noted.⁶³

Optic neuropathy has been described in some patients with primary SS.^{13–60–65–66} In some of these patients neurological signs occurred before or at the same time as the diagnosis of SS.^{60–64} Symptoms of dry eyes and mouth may be mild or even absent. Thus early primary SS should be considered in any patient with unexplained optic neuropathy and serological abnormalities suggestive of a connective tissue disorder,

particularly when criteria for a diagnosis of SLE or other SID are absent.⁶⁴

ADAMANTIADES-BEHCEZ DISEASE

Adamantiades-Behcet disease (BD) is an inflammatory multisystem disorder of unknown cause involving arteries and veins and characterised by uveitis, erythema nodosum, skin lesions, and recurrent oral and genital ulcers. The CNS is affected in 10–49% of patients, and MRI findings and clinical course may mimic MS.⁷³ Some neuro-BD patients have multiple hemispherical white matter lesions^{74–75} and lesions in the spinal cord may be demonstrable if MRI is performed close to attack onset. In the later stages of the disease, atrophy of the brain stem (without cortical atrophy) is almost inevitable, which is more suggestive of neuro-BD than of MS.^{74–75} Patients with BD and CNS involvement have a serum and CSF cytokine and chemokine profile that differs from that of other autoimmune disorders such as MS. There is evidence for lower Th1 related cytokine activity in neuro-BD and a pattern resembling non-specific inflammation such as following neuro-infection, suggesting that a currently unknown infection might be involved in the vasculitic pathology in the CNS.⁷⁶ CSF in neuro-BD may be normal or pathological. The IgG index is usually elevated and sometimes oligoclonal bands may be demonstrated. Reversibility of these bands, which is not the case in MS, has also been reported.⁷⁴ Moreover, the course of MS is more polyphasic, while that of neuro-Behcet is more progressive.⁷⁷ In MS, optic neuritis, acute TM, and internuclear ophthalmoplegia are common, whereas in neuro-BD the main neurological manifestation is progressive pseudobulbar palsy.^{77–78}

Ocular pathology in BD is well recognised to mirror CNS pathology; foci of necrosis and perivascular demyelination with inflammatory cell infiltrate of lymphocytes can occur and there may well be an association between ischaemic demyelination of the optic nerve and the CNS.

A neurological manifestation in a patient fulfilling BD criteria usually does not cause diagnostic dilemmas. However, confusion emerges when a patient presents with an isolated neurological attack preceding the onset of BD. In this case exclusion of MS may not be possible until the extra-neurological manifestations of BD appear.

Neuro-BD should be suspected⁷⁴ if a young male presents with or without symptoms of BD, with predominantly motor/mental rather than sensor clinical symptoms, with more prominent PMN than LYM cells in the CSF, and an MRI showing lesions extending from the brain stem to basal ganglia. Azathioprine with prednisone may be more effective in the long term for optic nerve and CNS involvement than cyclosporine with prednisone.⁷⁸

CONCLUSIONS

In conclusion, every patient with demyelinating events should be queried as to symptoms of SID. If there are such symptoms or if there are atypical forms of MS, a full autoantibodies investigation should be carried out and the patient followed up for several years (even if the autoantibodies are negative in the first investigation) as the possibility of SID occurring is high.

ACKNOWLEDGEMENTS

The authors are grateful to Dr David D'Cruz for careful reading of the manuscript.

Authors' affiliations

A Theodoridou, I Settas, Rheumatology Unit of the 1st Internal Medicine Department, AHEPA University Hospital, Thessaloniki, Greece

Competing interests: none declared

REFERENCES

- 1 Ferreira S, D'Cruz DP, Hughes GRV. Multiple sclerosis, neuropsychiatric lupus and antiphospholipid syndrome: where do we stand? *Rheumatology (Oxford)* 2005;**44**(4):434–42.
- 2 Ruiz-Irastorza G, Khamashta MA. Warfarin for multiple sclerosis? *Q J Med* 2000;**93**:497–9.
- 3 Berman M, Feldman S, Alter M, et al. Acute transverse myelitis: incidence and etiologic considerations. *Neurology* 1981;**31**:966–71.
- 4 Cuadrado MJ, Khamashta MA, Ballesteros A, et al. Can neurologic manifestations of Hughes' (antiphospholipid) syndrome be distinguished from multiple sclerosis. Analysis of 27 patients and review of the literature. *Medicine (Baltimore)* 2000;**79**:57–68.
- 5 Hughes GRV. Migraine, memory loss, and "multiple sclerosis". Neurological features of the antiphospholipid (Hughes') syndrome. *Postgrad Med J* 2003;**79**:81–3.
- 6 McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol* 2001;**50**:121–7.
- 7 McLean BN, Luxton RW, Thompson EJ. A study of immunoglobulin G in the cerebrospinal fluid of 1007 patients with suspected neurological disease using isoelectric focusing and the log IgG-index. A comparison and diagnostic applications. *Brain* 1990;**113**(Pt 5):1269–89.
- 8 The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;**42**:599–608.
- 9 Bluestein HG. Neuropsychiatric disorders in systemic lupus erythematosus. In: Lahita RG, ed. *Systemic lupus erythematosus*. New York: Wiley, 1987:593–614.
- 10 Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997;**120**:2059–69.
- 11 Arnold DL, Matthews PM. MRI in the diagnosis and management of multiple sclerosis. *Neurology* 2002;**58**(suppl 4):23–31.
- 12 Rovaris M, Viti B, Ciboddo G, et al. Brain involvement in systemic immune mediated diseases: magnetic resonance and magnetization transfer imaging study. *J Neurol Neurosurg Psychiatry* 2000;**68**:170–7.
- 13 Alexander GE, Provost TT, Stevens MB, et al. Sjogren's syndrome: central nervous system manifestations. *Neurology* 1981;**31**:1391–6.
- 14 Karussis D, Leker RR, Ashkenazi A, et al. A subgroup of multiple sclerosis patients with anticardiolipin antibodies and unusual clinical manifestations: do they represent a new nosological entity? *Ann Neurol* 1998;**44**:629–34.
- 15 Roussel V, Yi F, Jauberteau MO, et al. Prevalence and clinical significance of anti-phospholipid antibodies in multiple sclerosis: a study of 89 patients. *J Autoimmun* 2000;**14**:259–65.
- 16 Penn AS, Rowan AJ. Myelopathy in systemic lupus erythematosus. *Arch Neurol* 1968;**18**:337–49.
- 17 Kovacs B, Lafferty TL, Brent LH, et al. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. *Ann Rheum Dis* 2000;**59**:120–4.
- 18 Lavelle C, Pizarro S, Drenkard C, et al. Transverse myelitis: a manifestation of systemic lupus erythematosus strongly associated with antiphospholipid antibodies. *J Rheumatol* 1990;**17**:34–7.
- 19 Deodhar AA, Hochenedel T, Bennett RM. Longitudinal involvement of the entire spinal cord and the medulla oblongata in acute catastrophic onset transverse myelitis in SLED. *J Rheumatol* 1999;**26**:446–9.
- 20 Cordeiro MF, Lloyd ME, Spalton DJ, et al. Ischemic optic neuropathy, transverse myelitis and epilepsy in an antiphospholipid positive patient with systemic lupus erythematosus [letter]. *J Neurol Neurosurg Psychiatry* 1994;**57**:1142–3.
- 21 Schantz V, Oestergaard LL, Junker P. Shrinking spinal cord following transverse myelopathy in a patient with systemic lupus erythematosus and the phospholipids antibody syndrome. *J Rheumatol* 1998;**25**:1425–8.
- 22 Smyth AE, Bruce JN, McMillan SA, et al. Transverse myelitis: a complication of systemic lupus erythematosus that is associated with the antiphospholipid syndrome [abstract]. *Ulster Med J* 1996;**65**:91–4.
- 23 Kim JH, Lee SI, Park SI, et al. Recurrent transverse myelitis in primary antiphospholipid syndrome—case report and literature review. *Rheumatol Int* 2004;**24**:244–6.
- 24 Medina-Rodriguez F, Garcia E, Fraga A. Transverse myelitis and antiphospholipid antibodies. *J Rheumatol* 1990;**17**(1):34–7.
- 25 Provenzale JM, Barboriak DP, Gaensler EH, et al. Lupus-related myelitis: serial MR findings. *Am J Neuroradiol* 1994;**15**:1911–7.
- 26 April RS, Vansonnenberg E. A case of neuromyelitis optica (Devic's syndrome) in systemic lupus erythematosus. *Neurology* 1976;**26**:1066–70.
- 27 Kenik JG, Krohn K, Kelly RB, et al. Transverse myelitis and optic neuritis in systemic lupus erythematosus: a case report with magnetic resonance imaging findings. *Arthritis Rheum* 1987;**30**:947–50.
- 28 Tola MR, Casetta J, Granieri E, et al. Systemic lupus erythematosus related transverse myelitis in a patient with myasthenia gravis and multiple sclerosis. *Eur Neurol* 1996;**36**:327–8.
- 29 Harisdangkul V, Doorenbos D, Subramony SH. Lupus transverse myelopathy: better outcome with early recognition and aggressive high-dose intravenous corticosteroid pulse treatment. *J Neurol* 1995;**242**:326–31.
- 30 Noseworthy JH, Bass BH, Vandervoort MK, et al. The prevalence of primary Sjogren's syndrome in a multiple sclerosis population. *Ann Neurol* 1989;**25**:95–8.
- 31 Sherer Y, Hassin S, Shoenfeld Y, et al. Transverse myelitis in patients with antiphospholipid antibodies—the importance of early diagnosis and treatment. *Clin Rheumatol* 2002;**21**:207–10.
- 32 Gibbs AN, Moroney J, Foley-Nolan D, et al. Neuromyelitis optica (Devic's syndrome) in systemic lupus erythematosus: a case report. *Rheumatology* 2002;**41**:470–1.
- 33 Giorgi D, Balacco Gabrieli C. Optic neuropathy in systemic lupus erythematosus and antiphospholipid syndrome (APS): clinical features, pathogenesis, review of the literature and proposed ophthalmological criteria for APS diagnosis. *Clin Rheumatol* 1999;**18**:124–31.
- 34 Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 1999;**53**:1107–14.
- 35 Jennekens FG, Kater L. The central nervous system in systemic lupus erythematosus. Part 2. Pathogenetic mechanisms of clinical syndromes: a literature investigation. *Rheumatology* 2002;**41**:619–30.
- 36 Jabs DA, Miller NR, Newman SA, et al. Optic neuropathy in systemic lupus erythematosus. *Arch Ophthalmol* 1986;**104**:564–8.
- 37 Galindo-Rodriguez G, Avina-Zubieta JA, Pizarro S, et al. Cyclophosphamide pulse therapy in optic neuritis due to systemic lupus erythematosus: an open trial. *Am J Med* 1999;**106**:65–9.
- 38 Scott TF, Hess D, Brillman J. Antiphospholipid antibody syndrome mimicking multiple sclerosis clinically and by magnetic resonance imaging. *Arch Intern Med* 1994;**154**:917–20.
- 39 Ijdo JW, Conti-Kelly AM, Greco P, et al. Antiphospholipid antibodies in patients with multiple sclerosis and MS-like illness: MS or APS? *Lupus* 1999;**8**:109–15.
- 40 Marullo S, Clauvel JP, Intrator L, et al. Lupoid sclerosis with antiphospholipid and antimyelin antibodies. *J Rheumatol* 1993;**20**:747–9.
- 41 Rombos A, Evangelopoulou-Katsiri E, Leventakou A, et al. Serum IgG and IgM anticardiolipin antibodies in neurological diseases. *Acta Neurol Scand* 1990;**81**:43–5.
- 42 Sastre-Garriga J, Reverter JC, Font J, et al. Anticardiolipin antibodies are not a useful screening tool in a nonselected large group of patients with multiple sclerosis. *Ann Neurol* 2001;**49**:408–11.
- 43 Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1000 patients. *Arthritis Rheum* 2002;**46**:1019–27.
- 44 Lee DM, Jeon HS, Yoo WH. Transverse myelitis in a patient with primary antiphospholipid syndrome. *Yonsei Med J* 2003;**44**(2):323–7.
- 45 Shaharao V, Bartakke S, Muranjan MN, et al. Recurrent acute transverse myelopathy: association with antiphospholipid antibody syndrome. *Indian J Pediatr* 2004;**71**(6):559–61.
- 46 Inslight DV, Stein AB, Pomerantz F, et al. Three women with lupus transverse myelitis: case reports and differential diagnosis. *Arch Phys Med Rehabil* 1998;**79**:456–9.
- 47 Andrianakos AA, Duffy J, Suzuki J, et al. Transverse myelopathy in systemic lupus erythematosus: report of three cases and review of the literature. *Ann Intern Med* 1975;**83**:616–24.
- 48 Kupersmith MJ, Burde R, Warren F, et al. Autoimmune optic neuropathy, evaluation and treatment. *J Neurol Neurosurg Psychiatry* 1988;**51**:1381–6.
- 49 Bielory L, Kupersmith MJ, Warren F, et al. Skin biopsies in the evaluation of atypical optic neuropathies. *Ocul Immunol Inflamm* 1993;**1**:231–41.
- 50 Frohman L, Turbin R, Bielory L, et al. Autoimmune optic neuropathy with anticardiolipin antibody mimicking multiple sclerosis in a child. *Am J Ophthalmol* 2003;**136**:358–60.
- 51 Alexander E. MS and Sjogren's syndrome. *Neurology* 1993;**43**:455–6.
- 52 Binder A, Snaith ML, Isenberg D. Sjogren's syndrome: a study of its neurological complications. *Br J Rheum* 1988;**27**:275–80.
- 53 Andrianopoulos AP, Lagos G, Drosos AA, et al. Neurological involvement in primary Sjogren's syndrome: a preliminary report. *J Autoimmun* 1989;**2**:485–8.
- 54 Mok CC, Lau CS, Chan EY, et al. Acute transverse myelopathy in systemic lupus erythematosus: clinical presentation, treatment, and outcome. *J Rheumatol* 1998;**25**:467–73.
- 55 de Andres C, Guillem A, Rodriguez-Mahou M, et al. Frequency and significance of anti-Ro (SS-A) antibodies in multiple sclerosis patients. *Acta Neurol Scand* 2001;**104**:83–7.
- 56 Ioannidis JPA, Moutsopoulos HM. Sjogren's syndrome: too many associations, too limited evidence. The enigmatic example of CNS involvement. *Semin Arthritis Rheum* 1999;**29**(1):1–3.
- 57 Jung SM, Lee BG, Joh GY, et al. Primary Sjogren's syndrome manifested as multiple sclerosis and cutaneous erythematous lesions: a case report. *J Korean Med Sci* 2000;**15**:115–8.
- 58 Sandberg-Wollheim M, Axell T, Hansen BU, et al. Primary Sjogren's syndrome in patients with multiple sclerosis. *Neurology* 1992;**42**:845–7.
- 59 Alexander EL, Beal SS, Gordon B, et al. Magnetic resonance imaging of cerebral lesions in patients with the Sjogren's syndrome. *Ann Intern Med* 1988;**108**:815–23.
- 60 Alexander EL, Malinow K, Lejewski JE, et al. Primary Sjogren's syndrome with central nervous system disease mimicking multiple sclerosis. *Ann Intern Med* 1986;**104**:323–30.
- 61 Lafitte C, Amoura Z, Cacoub P, et al. Neurological complications of primary Sjogren's syndrome. *J Neurol* 2001;**248**:557–84.
- 62 Tourbah A, Clapin A, Gout O, et al. Systemic autoimmune features and multiple sclerosis: a 5-year follow-up study. *Arch Neurol* 1998;**55**:517–21.
- 63 Vincent TL, Richardson MP, Mackworth-Young CG, et al. Sjogren's syndrome-associated myelopathy: response to immunosuppressive treatment. *Am J Med* 2003;**114**:145–8.
- 64 Wise CM, Agudelo CA. Optic neuropathy as an initial manifestation of Sjogren's syndrome. *J Rheumatol* 1988;**15**(5):799–802.
- 65 Alexander EL, Provost TT, Stevens MB, et al. Neurologic complications of primary Sjogren's syndrome. *Medicine* 1982;**61**:247–57.
- 66 Molina R, Provost TT, Alexander GE. Primary Sjogren's syndrome. *Arthritis Rheum* 1985;**28**:1341–7.

- 67 Niemela RK, Hakala M. Primary Sjogren's syndrome with severe central nervous system disease. *Semin Arthritis Rheum* 1999;29(1):4–13.
- 68 Anantharaju A, Baluch M, Van Thiel DH. Transverse myelitis occurring in association with primary biliary cirrhosis and Sjogren's syndrome. *Dig Dis Sci* 2003;48(4):830–3.
- 69 Wakatsuki T, Miyata M, Shishido S, et al. Sjogren's syndrome with primary biliary cirrhosis, complicated by transverse myelitis and malignant lymphoma. *Intern Med* 2000;39:260–5.
- 70 Rutan G, Martinez AJ, Fieshko JT, et al. Primary biliary cirrhosis, Sjogren's syndrome, and transverse myelitis. *Gastroenterology* 1986;90:206–10.
- 71 Sugai S. Sjogren's syndrome associated with liver and neurological disorders, and malignant lymphoma. *Intern Med* 2000;39:193–4.
- 72 Williams C, Butler E, Roman GC. Treatment of myelopathy in Sjogren's syndrome with a combination of prednisone and cyclophosphamide. *Arch Neurol* 2001;58:815–19.
- 73 Akman-Demir G, Serdaroglu P, Tasci B, et al. Clinical patterns of neurological involvement in Behcet's disease: evaluation of 200 patients. *Brain* 1999;122:2171–82.
- 74 Serdaroglu P. Behcet's disease and the nervous system. *J Neurol* 1998;245:197–205.
- 75 Tali ET, Atilla S, Keskin T, et al. MRI in neuro-Behcet's disease. *Neuroradiology* 1997;39:2–6.
- 76 Saruhan-Direskeneli G, Yentur SP, Akman-Demir G, et al. Cytokines and chemokines in neuro-Behcet's disease compared to multiple sclerosis and other neurological diseases. *J Neuroimmunol* 2003;145:127–34.
- 77 Motomura S, Tabira T, Kuojiwa Y. A clinical comparative study of multiple sclerosis and neuro-Behcet's syndrome. *J Neurol Neurosurg Psychiatry* 1980;43:210–13.
- 78 Chavis PS, Tabbara KF. Demyelination of retinal myelinated nerve fibers in Behcet's disease. *Doc Ophthalmol* 1998;95:157–64.

Clinical Evidence—Call for contributors

Clinical Evidence is a regularly updated evidence-based journal available worldwide both as a paper version and on the internet. *Clinical Evidence* needs to recruit a number of new contributors. Contributors are healthcare professionals or epidemiologists with experience in evidence-based medicine and the ability to write in a concise and structured way.

Areas for which we are currently seeking contributors:

- Pregnancy and childbirth
- Endocrine disorders
- Palliative care
- Tropical diseases

We are also looking for contributors for existing topics. For full details on what these topics are please visit www.clinicalevidence.com/ceweb/contribute/index.jsp

However, we are always looking for others, so do not let this list discourage you.

Being a contributor involves:

- Selecting from a validated, screened search (performed by in-house Information Specialists) epidemiologically sound studies for inclusion.
- Documenting your decisions about which studies to include on an inclusion and exclusion form, which we keep on file.
- Writing the text to a highly structured template (about 1500–3000 words), using evidence from the final studies chosen, within 8–10 weeks of receiving the literature search.
- Working with *Clinical Evidence* editors to ensure that the final text meets epidemiological and style standards.
- Updating the text every 12 months using any new, sound evidence that becomes available. The *Clinical Evidence* in-house team will conduct the searches for contributors; your task is simply to filter out high quality studies and incorporate them in the existing text.

If you would like to become a contributor for *Clinical Evidence* or require more information about what this involves please send your contact details and a copy of your CV, clearly stating the clinical area you are interested in, to CECommissioning@bmjgroup.com.

Call for peer reviewers

Clinical Evidence also needs to recruit a number of new peer reviewers specifically with an interest in the clinical areas stated above, and also others related to general practice. Peer reviewers are healthcare professionals or epidemiologists with experience in evidence-based medicine. As a peer reviewer you would be asked for your views on the clinical relevance, validity, and accessibility of specific topics within the journal, and their usefulness to the intended audience (international generalists and healthcare professionals, possibly with limited statistical knowledge). Topics are usually 1500–3000 words in length and we would ask you to review between 2–5 topics per year. The peer review process takes place throughout the year, and out turnaround time for each review is ideally 10–14 days. If you are interested in becoming a peer reviewer for *Clinical Evidence*, please complete the peer review questionnaire at www.clinicalevidence.com/ceweb/contribute/peerreviewer.jsp