

Is it necessary to perform connective tissue disorders laboratory tests when a patient experiences the first demyelinating attack?

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Background: It may be difficult to differentiate between the first demyelinating attack and the neurological manifestations of connective tissue diseases. **Materials and Methods:** A total of 79 patients with optic neuritis were compared with 79 healthy controls. Their blood samples were tested for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-β2-Glycoprotein I antibody (IgG, IgM), anticardiolipin antibody (IgM, IgG), lupus anticoagulant, anti-double strand DNA (anti-ds DNA), antinuclear antibody (ANA), anti-myeloperoxidase (p-ANCA), and anti-Proteinase 3 (C-ANCA). **Results:** In clinically isolated syndrome group β2-Glycoprotein (IgM) and lupus anti-coagulant were positive in 1.3% of patients whereas ANA was positive in 1.3% and anti-β2-Glycoprotein I (IgM) was positive in 2.5% of control group. No rheumatologic disease was found in objects with positive tests. **Conclusion:** This study shows no specific difference between two groups.

Key words: Clinically isolated syndrome, connective tissue disease tests, multiple sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS). Eighty-Five percent of the patients with MS first presented with a clinically isolated syndrome (CIS), which is an acute or subacute episode of neurologic failure.^[1] As studies show about 21% of patients with CIS present with optic neuritis (ON), 10% have brainstem involvement, 46% show long tract involvement manifestations, and 23% have multifocal deficits.^[2] The diagnosis of MS is made when the dissemination of neurologic disturbances in both time and space have been demonstrated by either clinical, paraclinical, or laboratory findings. The diagnosis can be made when alternate explanations of clinical and paraclinical findings are excluded.^[3-6] First monofocal neurologic sign or symptom (no dissemination in time or space) can be explained by CIS or other differential diagnosis such as systemic rheumatic disease.^[5-9] For example, antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) can explain this finding.^[10-13] SLE is an auto-immune disease which involves multi-organs, 50% of patients with lupus have CNS involvement, which makes their prognosis poor.^[12,14] Lupus CNS involvement can be caused by vasculitis or APS.^[10] This can be true for myelopathy

too.^[14] Antiphospholipid antibodies (APA) can involve CNS, presenting with transient ischemic attack, stroke and other more complex neurologic disturbances, and presence of multifocal white matter lesions on brain magnetic resonance imaging (MRI).^[10,15] Thus, the objective of this study was to determine whether prevalence of positivity of collagen vascular tests such as ANCA (P, C), ANA, dsDNA, and APA differ between patients with ON and healthy subjects.

MATERIALS AND METHODS

This was a cross-sectional study of patients consecutively referred to the MS Clinic in Alzahra Hospital and Neuro-Ophthalmology Clinic in Feiz Hospital in Isfahan for the evaluation of acute ON between July 2010 and July 2011. A total of 79 patients presenting a single, unilateral ON episode, with no history of connective tissue disease were included in the study. The attack was diagnosed as a CIS affecting optic nerve if they showed these clinical findings: Pain on eye movement, decreased visual acuity, and defect in visual field with a compatible fundus examination (mild or no optic disc edema) which was not attributable to other diseases.^[11] MRI of these patients was not compatible with MS according to McDonald criteria 2005.^[6] The

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control group consisted of 79 healthy subjects, with no history of neurologic or connective tissue disease. The study received approval from the Ethics Committee of Isfahan University of Medical Science and informed written consent was obtained from all study subjects. The following clinical data were obtained on the basis of the patients' medical records: Age, gender, and duration of attack. The initial clinical evaluation was performed in all cases by an expert neurologist; symptoms and signs of neurological deficit were recognized and recorded. All subjects were questioned about individual or familial histories of connective tissue diseases, rheumatic manifestations, and APS such as stroke or transient ischemic attack, myocardial infarction, arterial or venous thrombosis, and recurrent abortion.

Sera of patients and controls were tested for ESR, CRP, anti- β 2-glycoprotein I antibody (IgG, IgM), anticardiolipin antibody (IgM, IgG), lupus anticoagulant, anti-dsDNA, antinuclear antibody (ANA), anti-MPO (p-ANCA), and anti-PR3 (C-ANCA). Patients with positive tests were objects of rheumatologic examination to confirm or rule out the connective tissue diseases. Anticardiolipin antibodies (IgM, IgG), anti- β 2-Glycoprotein I antibody (IgM, IgG), ANA, anti dsDNA, p-ANCA, and c-ANCA were detected by enzyme-linked immunoabsorbent assay, Chorus kit. The cutoff values for anticardiolipin antibody IgM were <12 Mplu/ml negative, 12-18 Mplu/ml equivocal, and >18 positive. The cutoff values for anticardiolipin antibody IgG were <12 Gplu/ml negative, 12-18 Gplu/ml equivocal, and >18 positive. The cutoff values for β 2-Glycoprotein I (IgM, IgG) were <12 AU/ml negative, 12-18 AU/ml equivocal, and >18 positive. The cutoff values for ANA were <0.8 U/ml negative, 0.8-1.2 U/ml equivocal, and >1.2 positive. The cutoff values for dsDNA were <12 IU/ml negative, 12-18 IU/ml equivocal and >18 positive. The cutoff values for p-ANCA and c-ANCA were <12 AU/ml negative, 12-18 AU/ml equivocal, and >18 positive. Lupus anticoagulant was detected according to international guidelines and by a manual agglutination assay (Trinity Biotech).

Statistical analysis

Chi-squared test, *t*-test, and fisher exact test were used to test the hypothesis. Statistical power was 80%. The collected data were analyzed by SPSS software version 19 (SPSS Inc., Chicago, IL).

RESULTS

We studied 79 patients with ON and 79 healthy controls. The mean \pm SD of age of CIS cases was 27.5 ± 7.5 and in control group it was 29.4 ± 7.6 ($P = 0.12$). 82.3% (65) of CIS cases and 83.5% (66) of control group were female) $P = 0.83$). Brain

MRI was completely normal in 45 patients and the others had plaques that were not compatible with McDonald criteria 2005.^[6] ANA, p-ANCA, c-ANCA, anticardiolipin antibody (IgG), anticardiolipin antibody (IgM), and anti- β 2-Glycoprotein I antibody (IgG) were not positive neither in case group nor in control group. The results of anti-dsDNA, anti- β 2-Glycorotein I antibody (IgM), lupus anti-coagulant, and CRP are reported in Table 1. The summary of data was shown in Table 1.

A rheumatologist examined patients with positive tests; none of the patients had a rheumatic disorder. The mean ESR level was 9.1 ± 9.5 in case group and 5.7 ± 4.6 in control group ($P = 0.004$) which was statically significant, although both were in normal range but it might show that in a long-term follow-up the mean ESR level in CIS patients was significantly higher than normal population.

DISCUSSION

ON is an inflammation of optic nerve, which is the first manifestation of MS in 30% of MS patients and will show up in 30-70% of them in the disease course.^[1,16-18] ON as a CIS is a differential diagnosis for CNS involvement of some systemic autoimmune disease like SLE, APS and autoantibody serology may help to clarify the issue.^[19]

There is controversy in studies about prevalence of auto-antibodies in MS patients and their clinical associations. ANAs and APAs in MS patients has been reported and a higher prevalence of certain type of APAs in ON and spinal cord involvement of MS has been mentioned.^[20-22]

Barnerd *et al.* reported that 26.7% of relapsing-remitting and 30.4% of chronic progressive MS patients had positive ANA in their study whereas ANA is positive in 2-8% of normal population.^[23] Vasculitis is also a differential diagnosis of ON in MS. Fukazawa *et al.* studied 13 patients with optic-spinal form of MS and 46.2% found to be positive for ANA and 46.2% positive for p-ANCA which was significantly higher than control group consisting of patients with conventional MS. All subjects in two groups were negative for c-ANCA and anti-dsDNA.^[24] In a retrospective study in US, the prevalence of auto-antibodies and APA in MS were 69% and 55% respectively. The prevalence of autoreactive antibodies in CIS was 75%, although mostly

Table 1: Test results

Test	Patients n (%)	Controls n (%)	P value
Anti-ds DNA ¹	1 (1.3)	0	0.99
Anti β 2-Glycoprotein I (IgM)	1 (1.3)	2 (2.5)	0.99
Lupus anticoagulant	0	1 (1.3)	0.99
CRP ²	5 (6.3)	5 (6.3)	1

¹Anti-ds DNA=Anti-double strand DNA; ²CRP=C-reactive protein

were transient.^[25] Collard *et al.* reported a frequency of 22.5% for ANAs in a prospective cohort of MS patients.^[26] Heinzlef *et al.* reported that anticardiolipin antibodies were positive in 15% of patients with MS.^[27]

On the other hand, Rombos *et al.* did not report any higher prevalence of anticardiolipin anti-bodies (IgG or IgM) in MS patients comparing with control group.^[28]

Another study showed a higher prevalence of ANAs and anti β 2-Glycoprotein I antibody (IgM) in MS patients and specific ANAs in CIS patients than in controls whereas anticardiolipin antibodies prevalence was similar in both groups. The study did not show any contribution between the site of neurologic involvement and the presence of autoantibodies.^[29]

CONCLUSION

In the current study, we observed no higher prevalence of positivity of connective tissue disease tests in patients with ON when compared with normal population. Our results suggest that those patients who are experiencing their first demyelinating attack should not be screened for connective tissue disease if they do not have a history of rheumatic disease or symptoms suggesting them.

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