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Do we need broad immunological work-up in all patients with CIS?

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Abstract

Background: The aim of this study was to determine the prevalence of altered immunological tests and their clinical significance in patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS).

Patients and methods: The information was gathered from medical records of patients hospitalized in the Referral Center for Demyelinating Diseases in the 2008-2010 period. All patients had ANA, ENA profile, ANCA, aCl IgG and IgM, C3, C4, CH50, anti-TPO, AST and RF antibodies tested.

Results: From 726 patients with CIS that were reviewed, the complete battery of immunological tests was performed in 418 of them (57.6%), representing our cohort. Altered tests were found in 235 patients (56.2%); 73 (17.4%) had positive antinuclear antibodies, 14 (3.3%) had positive ENA, 47 (11.2%) had positive aCI- IgG, 83 (19.8%) had positive aCIIgM, and 13 (3.1%) had anti TPO antibodies. We found no correlation between ANA, aCl IgG or IgM positivity (ANA vs aCL IgG p=0,554; ANA vs aCL IgM p=0,19; aCL IgG vs aCL IgM, p=0,155). None of the patients had any clinical manifestations other than MS symptoms.

Conclusion: These results indicate that significant number of patients with CIS have altered immunological tests but nevertheless none of them had clinical expression of any other autoimmune disease making them clinically insignificant. In conclusion there is no need to perform expensive immunological work-up in all patients with CIS. Contrary, our results argue for more focused testing rather than a battery of screening tests.

Key words: clinically isolated syndrome, multiple sclerosis, differential diagnosis, autoantibodies

Introduction

The differential diagnosis of multiple sclerosis (MS) is very broad, however most of these MS mimics are rare conditions seldom seen in clinical practice. On the other hand, MS diagnostic criteria have emphasized that alternative explanation for the clinical presentation must be considered and excluded before a diagnosis of MS can be made. Recently a consensus approach on differential diagnosis of MS described an effort to guide the clinical, laboratory, and imaging assessment of patients with a possible diagnosis of MS, so as to help satisfy the requirement for "no better explanation". [1] The International Panel did not recommend extensive testing. Rather, it recommended that alternative diagnoses should be considered and pursued if needed. The special problem in the differential diagnosis of MS represents various laboratory tests that are often used as a screening tool for possible MS mimics. It has been suggested that screening suspected MS patients with an unvarying battery of tests seldom generates a different diagnosis and more often leads to confusing false positive results, this being especially true of many tests ordered for the evaluation of systemic, inflammatory, autoimmune, "collagen vascular" diseases. [2]

The aim of this study was to determine the prevalence of altered immunological tests and their clinical significance in patients with clinically isolated syndrome (CIS) suggestive of MS.

Patients and methods

This was retrospective, observational study. The information was gathered from medical records of patients hospitalized in the Referral Center for Demyelinating Diseases in the 2008-2010 period. Charts of all patients with the diagnosis of CIS were reviewed. All patients

with anti-nuclear antibodies (ANA), extractable nuclear antigen (ENA) profile, antineutrophil cytoplasmic antibodies (ANCA), anticardiolipin (aCl) IgG and IgM antibodies, C3, C4, CH50, anti-thyroid peroxidase antibodies (anti-TPO), anti-streptolysine titer *(*AST), rheumatoid factor (RF) tested were included in the study. All tests were performed in the same laboratory using standardized methods suggested by the manufacturer.

The difference between postitive and negative tests (ANA, aCL IgG and IgM) was analyzed by t test for independent samples. P levels of <0.05 were considered as significant. Statistical analysis was performed using SPSS 19.0 statistical software.

Results

From 726 patients with CIS that were reviewed, the complete battery of immunological tests was performed in 418 of them (57.6%), representing our cohort. Other patients have been referred from first and secondary level centers wirh already performed immunological work-up, so we did not include them in this analysis beacuse of laboratory differences. Altered tests were found in 235 patients (56.2%) (Table 1 and Figure 1). Seventy three patients (17.4%) had positive antinuclear antibodies (6 patients had homogeneous, 54 speckled, 2 nucleolar and 1 cytoplasmatic pattern). ENA was positive in 14 patients (3.3%); ENA profile was: SS-A four patients, Slc 70 one patient, anti-double stranded DNA (dsDNA) one patient, NuMa one patient, DNAtopo-1 four patients, CENP-B one patient, Jo-1 one patient and U1 ribonucleoprotein (U1-RNP) one patient. Furthermore**,** 47 patients (11.2%) had positive aCI IgG, while aCI IgM was positive in 83 patients (19.8%). aCl IgG titers varied from 10 – 38 GPL U/ml (36 patients had weakly positive (10-20 GPL U/ml) and 11 patients had moderately positive titers (21-40 GPL U/ml)). aCl IgM titers varied from 10 – 140 MPL U/ml (65 patients had weakly positive (10-20 MPL U/ml), 8 patients had moderately positive titers

21-30 MPL U/ml and 10 patients had highly positive titers > 30 MPL U/ml). We found no significance between ANA, aCl IgG or IgM positivity (ANA vs aCL IgG p=0,554; ANA vs aCL IgM p=0,19; aCL IgG vs aCL IgM, p=0,155).

Anti TPO antibodies were found in 13 patients (3.1%) in the range from 28 to > 2000 IJ/ml (normal range < 10 IJ/ml). C3 was changed in 63 patients (15.1%) (range 0.58-1.92 g/l, normal values 0.90-1.80), and C4 in 16 patients (3.8%) (range 0.41-0.67 g/l, normal value 0.10-0.40). AST was elevated in 53 patients (12.7%) and 9 (2.1%) had positive RF. None of the patients had any clinical manifestations other than MS symptoms.

Discussion

Many autoantibodies have been identified in both, serum and CSF, of MS patient but unfortunately, there is no autoantibody described being exclusively expressed in MS patients compared to the respective fluids of healthy individuals [3]. Recent proteomic studies on the other hand demonstrated that autoantibody in sera or CSF of MS patients are reactive to a panel of proteins, rather than a single protein, suggesting a MS-specific pattern of autoantibodies [4]. Therefore it is not surprising that many studies have shown present different autoantibodies that are used for the evaluation of systemic, inflammatory, autoimmune, “collagen vascular” diseases in sera of MS patients. Our study is the first to evaluate the presence of these autoantibodies in patients with CIS, and have shown similar percentage of positive autoantibodies in CIS patients compared with previous results in relapsing remitting or primary progressive MS patients.

The frequency of antinuclear antibodies ANA in patients with clinically definite MS varies from 2.5% to 81% of sera according to the study [5-11]. Most of these studies found no correlation between the presence of ANA and symptoms of SLE, although a correlation

between ANA and MS disease activity was observed by Collard *et al* [10]. We have found positive ANA titers in 17.4% of CIS patients, and none of our patients had symptoms of SLE. Recent studies showed a prevalence of aCl in MS patients of 4.8–44% of cases [11-16]. Contrary to our results, some studies have shown higher positivity of aCl IgG than aCl IgM in MS patients [16]. In our CIS cohort, 11.2% patients had positive aCI- IgG, and 19.8% aCIIgM titers. It is interesting that aCl IgG titers were weakly or moderately positive, while 21.7% of patients with positive aCl IgM had moderately to high titers. As well, although we did not find any correlation between ANA and aCl positivity, other have found opposite results [16]. Most of the published studies found no correlation between aCl and age, sex, disease duration, clinical classification, clinical evolution, or peculiar clinical symptoms. Contrary to previous reports showing high titres of anti-TPO antibodies in 21.7% MS patients, we found small percentage of CIS patients with positive titers [17].This may be in line with the observation that these antibodies are associated with clinical disease activity. As well, MRI analysis showed significantly higher T2 lesion volume in patients with positive aCl or anti-TPO antibodies after correction for disease duration [18]. On the other hand some studies have shown that there were no significant differences in autoantibodies (ANA, anti-TPO) frequency or titres between MS and control subjects [19]. Regarding the complement levels, C3 was changed in 15.1% and C4 in 3.8% of our cohort. These changes however were slightly below normal limits for C3, and slightly above normal limits for C4. Previous studies have shown that the mean values of the complement levels of the MS patients did not differ from the values in a normal population [20].

This study has several limitations. This was observational, retrospective study with a referral bias, because all patients came from tertiary center specialized in MS. CIS patients are often stratified for risk for MS based on imaging and CSF findings. All patients in this study had demyelinating lesions on the brain MRI, however we did not correlate the MRI or CSF results

with the results of immunological testing. Other two shortcomings are that the study relied on the documentation of clinical symptoms in the patients' charts and that there were no follow-up data so some patients could have had early or incipient connective tissue disease that declared itself subsequently.

However this is a first study of this kind with CIS patients with a large number of patients included.

Conclusion

These results indicate that significant number of patients with CIS have altered immunological tests but nevertheless none of them had clinical expression of any other autoimmune disease. In conclusion there is no need to perform expensive immunological work-up in all patients with CIS. Contrary, our results argue for more focused testing rather than a battery of screening tests.

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Tables

Table 1. Number and percentage of patients with altered autoantibodies.

Test performed	Number (percentage) of positive tests
ANA	73 (17.4%)
ANA pattern	6 homogeneous, 54 speckled, 2 nucleolar and 1 cytoplasmatic
ENA screen	14 (3.3%)
ENA profile	4 SS-A, 1 Slc 70, 1 dsDNA, 1 NuMa, 4 DNAtopo-1, 1 CENP-B, 1 Jo-1, 1 U1-RNP
aCl IgG	47 (11.2%)
aCl IgM	83 (19.8%)
Anti-TPO	13 (3.1%)
C3	63 (15.1%)
C4	16 (3.8%)
AST	53 (12.7%)
RF	9 (2.1%)

Anti-nuclear antibodies (ANA), extractable nuclear antigen (ENA), antineutrophil cytoplasmic antibodies (ANCA), anticardiolipin (aCl) IgG and IgM antibodies, complement (C3, C4), anti-thyroid peroxidase antibodies (anti-TPO), anti-streptolysine titer *(*AST), rheumatoid factor (RF), anti-double stranded DNA (dsDNA), U1 ribonucleoprotein (U1-RNP)

Figures

Figure 1. Number of patients with normal or altered autoantibodies.