Ill-defined Neurological Syndromes with Autoimmune Background: A Diagnostic Challenge

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ABSTRACT. ***Objective.*** To define the diagnostic features of a cohort of patients presenting with autoimmune manifestations and atypical neurological features not fulfilling criteria for a well defined neurological or connective tissue disorder.

Methods. Twenty-nine such patients were referred to our institution for evaluation. Nine were excluded from this study since they were diagnosed with antiphospholipid syndrome. The remaining 20 patients underwent complete clinical and laboratory evaluation, spinal fluid analysis, minor salivary gland biopsy (if sicca features were present), and were tested for evoked potentials. Magnetic resonance imaging (MRI) scans of the brain were performed in all patients and of the spine in 7.

Results. Brain and/or spinal cord MRI abnormalities were found in all 20 patients. Based on morphologic criteria and distribution, these lesions were classified into 3 subsets: (1) multiple sclerosis (MS)-like (4 patients); (2) vasculitic (8 patients); and (3) nonspecific (8 patients). The most frequent underlying abnormality in patients with subgroups 1 and 2 were the presence of homozygous methylenetetrahydrofolate reductase (MTHFR) mutations (5 of 12, 41.6%). The most common findings among subgroup 3 were the presence of antithyroid antibodies (6 of 8 patients, 75%).

Conclusion. Homozygous MTHFR mutations are frequently encountered in patients presenting with neurological features and MS-like or vasculitic type MRI abnormalities in a setting of autoimmune disease. Nonspecific MRI changes are frequently associated with antibodies against thyroid antigens. (J Rheumatol 2007;34:341–5)

Key Indexing Terms:
MULTIPLE SCLEROSIS-LIKE DISEASE
AUTOIMMUNE THYROID DISEASE
MTHFR REDUCTASE MUTATIONS
ILL-DEFINED NEUROLOGICAL SYNDROMES

Central nervous system (CNS) involvement is a recognized feature of various autoimmune disorders including systemic lupus erythematosus (SLE), antiphospholipid syndrome, Behçet's disease, or vasculitides. These diseases often present with similar manifestations, which can be indistinguishable from multiple sclerosis (MS), neurosarcoidosis, and human immunodeficiency virus (HIV) infection[1,2]. Most importantly, there is considerable overlap in the imaging presentations of these disorders, generating dilemmas in therapeutic decisions[3].

We describe a cohort of patients with neurological symptoms and magnetic resonance imaging (MRI) abnormalities in the brain and spinal cord that did not fulfill accepted clinical or imaging criteria of MS or other well defined autoimmune or infectious CNS disorders[4,5]. Clinical, laboratory, and imaging studies are presented to describe this distinct subset of patients and provide insight into the pathophysiology of these ill-defined neurological syndromes.

MATERIALS AND METHODS

A total of 29 consecutive patients were referred to our institution between November 2002 and May 2004 with neurological symptoms and clinical manifestations suggestive of an underlying autoimmune process. Nine patients fulfilled the criteria for antiphospholipid syndrome and were excluded[6]. The remaining 20 (17 women, 3 men), ranging in age from 20 to 64 years (mean 42.1), were further evaluated and represent the body of this report. All patients gave informed consent to participate.

All patients completed a validated questionnaire addressing specifically the presence of neurological syndromes (at presentation or ever) and autoimmune manifestations. In addition, laboratory evaluations were performed, consisting of routine laboratory testing; immunology profile; thrombophilia screening [C, S, antithrombin III, homocysteine, Factor VIII levels, Factor Leiden, prothrombin 20210 and methylenetetrahydrofolate reductase (MTHFR) mutations]; spinal fluid examination for determination of cell count, total protein, IgG index, detection of oligoclonal zones, and cultures (2 patients refused lumbar puncture); testing for objective oral and ocular sicca features; minor salivary gland (MSG) biopsy in the presence of sicca features (1 refused); auditory, somatosensory, and visual evoked potentials (2 patients refused); and brain MRI (all 20 patients) and spine MRI (7) using conventional T1, T2-weighted and flow attenuated inversion recovery (FLAIR) techniques at 1.5 Tesla. Postcontrast scans were acquired from 14 patients after intravenous administration of 0.1 mmol/kg Magnevist (Berlex, Wayne, NJ, USA).

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All brain and spinal cord abnormalities were characterized according to size, distribution, signal characteristics on FLAIR and T2-weighted techniques, and enhancement on the postcontrast scans. Lesions were classified into one of the following categories: (1) MS-like changes (lesions confined to the cerebral white matter indistinguishable in appearance from demyelinating plaques); (2) vasculitic changes (lesions involving cord or cerebral gray matter); and (3) nonspecific changes (< 5 punctuate focal hyperintensities in the cerebral white matter measuring < 3 mm).

RESULTS

Table 1 summarizes pertinent clinical and laboratory abnormalities in the 20 patients. All patients had neurological signs

Table 1. Main clinical and laboratory features in 20 patients.

Patient	Sex/ Age, yrs	History of Neurological Symptoms at Referral (onset)	Autoimmune Manifestations	Autoimmune Profile	MRI Classification	Brain Involvement	Spinal Cord Involvement	Thrombophilia Screening
1	F 40	Bilateral limb weakness (SA)	Arthralgias, palm nodules	Antithyroid antibodies	I	+	NA	None
2	F 51	Seizures, lower limb hyperesthesia/paresthesias (SA)	Not reported	ANA	I	+	NA	MTHFR homozygous
3	M 20	Unsteadiness, slurred speech (A)	Not reported	ANA	I	+	NA	MTHFR homozygous
4	F 40	Optic neuritis (A)	Arthralgias, dry mouth, dry eyes, Raynaud's, hair loss	ANA	I	+	–	MTHFR homozygous
5	F 64	Spastic paraparesis, optic neuritis, lower limb paresthesias (SA)	Dry eyes, facial rash, leukopenia	ANA, anti-Ro/SSA	II	+	+	MTHFR homozygous
6	F 39	Transient hemiparesis on the left, facial numbness (A)	Arthralgias	ANA	II	–	+	MTHFR heterozygous
7	F 37	Optic neuritis, paraparesis (A)	Arthralgias, dry eyes	ANA, anti-Ro/SSA	II	+	+	MTHFR homozygous
8	F 33	Optic neuritis, paresthesias left arm/leg, right face, vertigo (A)	Arthralgias, Raynaud's, oral ulcers	ANA, low C4	II	+	NA	MTHFR heterozygous
9	F 60	Spastic paraparesis, optic neuritis, bladder dysfunction, hyperesthesia lower legs (SA)	Arthralgias	ANA, anti-Ro/SSA	II	+	+	MTHFR heterozygous
10	M 31	Cerebellar syndrome, facial paralysis, face-trunk-limb paresthesias, bowel/bladder dysfunction (SA)	Not reported	ANA, anti-Ro/SSA, low C4	II	+	+	None
11	F 42	Paraparesis, bladder/bowel dysfunction, paresthesias of lower limbs (SA)	Arthralgias, fever, serositis	ANA	II	–	+	None
12	F 52	Spastic monoparesis (A)	Arthralgias, dry eyes	ANA, anti-U1RNP	II	+	+	MTHFR heterozygous
13	F 36	Recent onset migraines (C)	Raynaud's, leukopenia	Antithyroid antibodies	III	+	NA	None
14	F 43	Left hemiparesis (A)	Arthralgias, hair loss, oral ulcers, urticarial rash	Antithyroid antibodies	III	+	NA	MTHFR homozygous low protein S
15	M 39	Dizziness, instability, transient right pyramidal weakness (A)	Photosensitive rash, arthralgias, fever	ANA, anti-U1RNP, low C4	III	+	NA	MTHFR heterozygous high VIII levels
16	F 45	Vertigo, numbness of hands and feet (SA)	Raynaud's fatigue	ANA	III	+	NA	MTHFR homozygous high VIII levels
17	F 29	Optic neuritis (A)	Not reported	Antithyroid antibodies	III	+	NA	None
18	F 49	Left quadrant hemianopia, facial paresthesia (A)	Dry mouth, photosensitive rash	ANA, anti-Ro/SSA, U1RNP, antithyroid antibodies	III	+	NA	None
19	F 42	Face, upper limb paresthesias (SA)	Arthralgias	Antithyroid antibodies	III	+	NA	None
20	F 49	Transient dysarthria, blurring of vision (A)	Raynaud's	ANA, anti-Ro/SSA, antithyroid antibodies	III	+	NA	None

A: acute (onset less than 24 hours; SA: subacute (onset between 24 hours and days); C: chronic (onset between days and months); NA: not available.

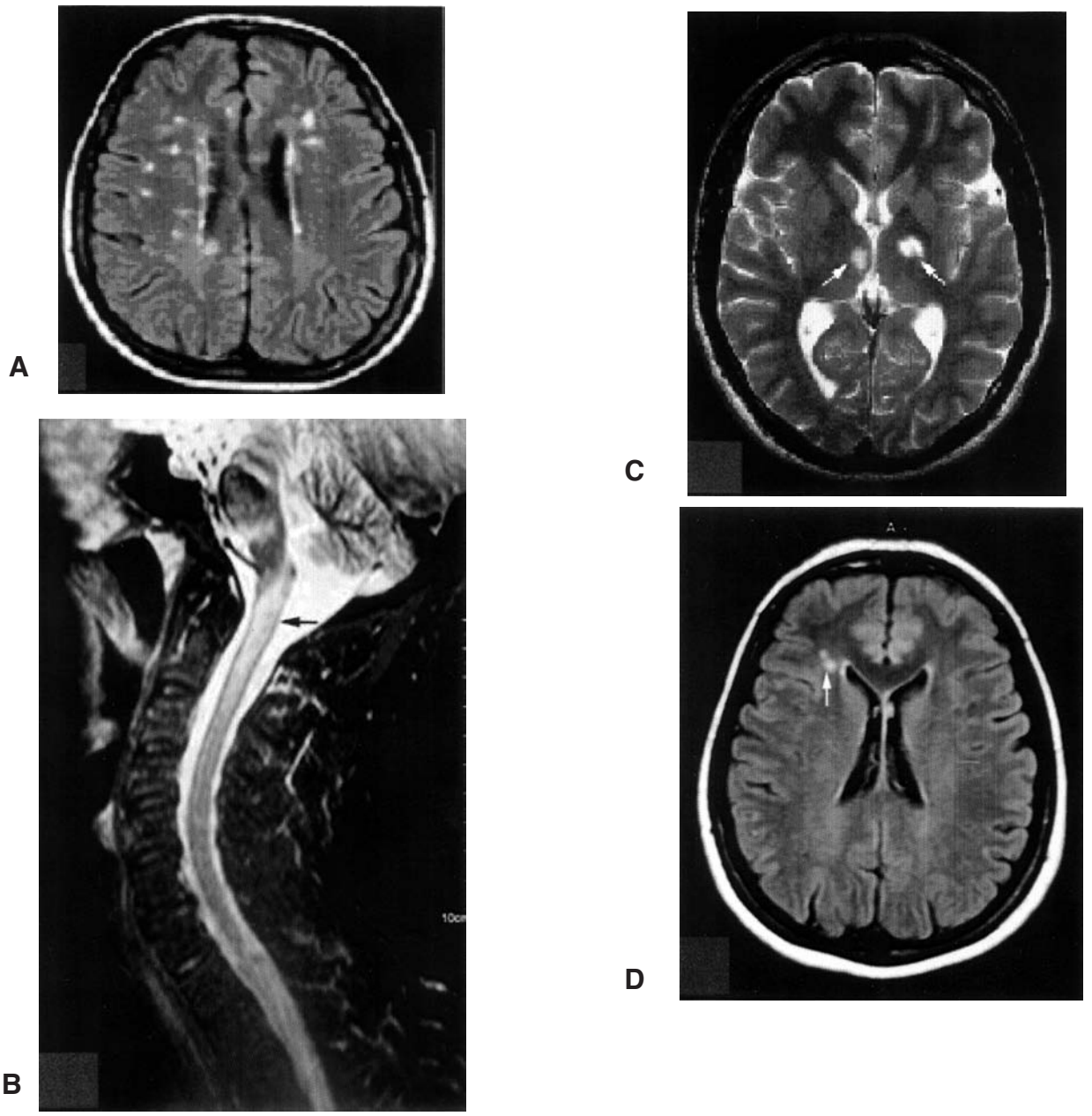

Figure 1. A. MS-like lesions: axial FLAIR MRI scan of brain reveals multiple focal hyperintense lesions in the white matter of both cerebral hemispheres. Similar abnormalities were also present in other tomographic sections (not shown). B and C. Vasculitic lesions: (B) Sagittal T2-weighted image of the cervical spine shows an abnormal area of increased signal intensity in the proximal cervical cord involving both gray and white matter (arrow). (C) Axial T2-weighted image of brain of the same patient. There are 2 small-vessel ischemic lesions in the left globus pallidus and in the right thalamus (arrows). D. Nonspecific brain lesions: axial FLAIR image of the brain reveals 2 punctate lesions of abnormal increased signal in white matter of the right frontal lobe (arrow).

and symptoms. Sixteen patients had clinical manifestations of autoimmune characterization, while all 20 patients were found to have various autoantibodies. No patient who underwent MSG biopsy fulfilled the criteria of Sjögren's syndrome[7]. Five of 18 patients had abnormal evoked potentials (Patients 5, 7, 10, 17, 19), while 4 of 18 who agreed to a lumbar puncture had abnormal findings in cerebrospinal fluid (Patients 5, 8, 12, 17). At the time of referral, erythrocyte sedimentation rate was increased in 1 patient (Patient 18), and C-reactive protein concentrations were above the normal limits in 2 patients (Patients 4, 15). Thrombophilia screening revealed that 12 of 20 patients (60%) had MTHFR mutations, 7 homozygous (35%) and 5 heterozygous (25%). Two patients had increased Factor VIII levels, while 1 patient had low protein C levels.

MRI studies revealed brain abnormalities in 18 of 20 patients. The brain lesions detected were of high signal intensities on FLAIR and T2-weighted scans and measured < 10

mm diameter. The majority of the lesions were in the white matter of the cerebral hemispheres, but in 2 patients cortical and deep gray matter was also affected. The cerebellum and brain stem were normal in all patients. On the postcontrast scans, 2 patients demonstrated abnormal enhancement.

Cervical cord lesions were identified in 7 patients. They were similar in appearance to the brain abnormalities, demonstrating high signal intensities on T2-weighted scans, and involved both gray and white matter. Two patients with cord lesions had normal brain results.

According to the MRI classification criteria, 4 patients were classified in the MS-like group, characterized by the presence of cerebral white matter ranging in numbers from 6 to more than 50 (Group I). None of these patients met the criteria of MS[4] (Figure 1A). Vasculitic lesions were found in 8 patients (Group II; Figure 1B, 1C), while in the remaining 8 of the 20 patients fewer than 5 small punctate lesions were found in the cerebral white matter (Group III; Figure 1D). When MRI abnormalities were analyzed with respect to the underlying thrombophilia and immunology profiles, the following observations were made. MTHFR mutations were found in 3 of the 4 patients in Group I, 6 of 8 patients in Group II, and 3 of the 8 patients in Group III. Interestingly, in Groups I and II, the prevalence of homozygotes for MTHFR was increased by 4-fold compared to the reported prevalence[8] in healthy Greek subjects (41% vs 10%, respectively; $p < 0.0001$). Antithyroid antibodies were encountered in 6 of 8 patients in Group III and in one of the 4 patients in Group I.

DISCUSSION

We have described a group of patients with underlying autoimmunity and neurological manifestations mimicking MS. All patients had MRI brain and/or spinal cord abnormalities involving white or gray matter or combination of both. Thrombophilic conditions such as antiphospholipid syndrome can mimic MS[2], but whether inherited thrombophilic conditions can also be responsible for MS-like disease has not been investigated. The high incidence of MTHFR mutations that was encountered in the subgroups of patients with MS-like and vasculitic lesions suggests that the thrombogenic effects of this mutation play a pivotal role in the pathogenesis of the lesions. MTHFR gene homozygosity (TT genotype) is the most common cause of genetically determined homocysteinemia in the general population and is associated with silent white matter lesions[9]. Of relevance to this is the recent observation that the prevalence of MTHFR mutations follows the same pattern as the incidence of MS from the Equator to the hemispheres[10]. Along with the observation that patients with MS have increased levels of homocysteine[11], this suggests that a number of atypical "MS cases" that do not fulfill the typical MS criteria may represent vasculopathy due to MTHFR mutations. Even though the number of our patients was small, the high prevalence of MTHFR mutations should prompt physicians to screen such patients for an underlying genetic thrombophilic disorder, because the treatment required is different from immunotherapy.

The clustering of thrombogenic MTHFR mutations in a population with vasculitic/MS-like features on MRI in a setting of autoimmune background was surprising and intriguing. In support of this, increasing evidence suggests high prevalence of MTHFR mutations as well as increased homocysteine levels in populations with autoimmune disease such as SLE[12,13]. Taken together, our findings may reveal novel genetic associations in patients with autoimmune disorders that have not yet been studied extensively.

The observation that there was increased association of the nonspecific MRI abnormalities with antibodies against thyroid antigens in Group III is also of interest. Such lesions by themselves are of unclear significance and have been found in asymptomatic patients, especially the elderly, and in patients with vascular risk factors[14]. The mean age of our patients with these changes, however, was less than 50 years, suggesting that aging alone does not account for these abnormalities. It is therefore tempting to propose that in our patients these findings are not epiphenomena, but rather represent the earliest signs of a thyroid-related autoimmune disorder[15].

We conclude that in addition to the standard diagnostic investigations, patients with MS-like clinical manifestations and MRI lesions in the CNS should be carefully evaluated for the presence of MTHFR mutations and antibodies to thyroid antigens. Such information may prove valuable for optimal therapeutic strategies and longterm management.

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