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EDITORIAL

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Cognitive Dysfunction in Multiple Sclerosis Patients with Hippocampal Antibodies

Erdil ARSOY[1], Hande YÜCEER[2], Beyzanur YALÇIN[2], Sedat GÜNBEK[2], Melike TEZEL[2] Recai TÜRKOĞLU[1], Erdem TÜZÜN[2]

[1]Department of Neurology, Istanbul Haydarpasa Numune Training and Research Hospital, Istanbul, Türkiye.
[2]Department of Neuroscience, Aziz Sancar Institute for Experimental Medical Research, Istanbul University, Istanbul, Türkiye.

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease causing somatic and cognitive disability in due course due to accumulating neurodegeneration and axonal injury. Although underlying effector mechanisms are poorly understood and considered to be mediated primarily by cellular immunity, accumulating evidence suggests that anti-neuronal antibodies may partake in disease mechanism, as well (1). Notably, serum and cerebrospinal fluid (CSF) antibodies interacting with the axonal projections of hippocampal and cerebellar neurons have been identified in some MS patients (2,3). Moreover, passive transfer of neurofascin antibodies, which may be found in MS patients, have been shown to induce complement-mediated axonal injury in experimental animals (4). Autoantibodies may potentially contribute to disease mechanisms of MS through complement activation and cell-mediated cytotoxicity(1).

Highlights

- **Anti neuronal antibodies are found in MS patients.**
- **Hippocampal antibodies in MS are associated with cognitive impairment.**
- **Neuronal antibodies of MS patients show distinctive binding patterns on brain samples.**

To investigate whether cognitive deterioration in MS could be associated with anti-neuronal antibodies, we collected sera of consecutively recruited 58 patients (41.9±10.7-year-old; 41 women) with relapsing remitting MS (RRMS) fulfilling the revised McDonald criteria and 35 age-gender matched healthy controls and employed a panel of neuropsychological and psychiatric tests listed in Table 1. All RRMS patients were in remission, had not received steroid treatment in the last three months, did not have any co-existing malignant, autoimmune/infectious disorders and were under immunomodulating drug treatment (Table 1). The study was approved by the institutional review board (IRB) and signed informed consents were obtained from all participants.

Well-characterized anti-neural antibodies (NMDAR, LGI1, CASPR2, $GABA_B$ receptor, AMPA receptor, GAD, MOG, Aqp-4) were found negative in sera of all participants by commercial kits (Euroimmun, Luebeck, Germany) utilizing cell-based assay. Indirect immunohistochemistry was used for identification of uncharacterized anti-neuronal antibodies. This assay was performed with frozen 10-µm-thick sections of rat brain fixed in paraformaldehyde overnight, using patient and control sera (1:200, overnight incubation at 4°C), secondary biotinylated anti-human IgG (1:1000, 2 h at room temperature), and the avidin-biotin-peroxidase method (5). Serum IgG of 13 RRMS patients showed remarkable reactivity predominantly with the hippocampal neuropil (Figure 1A,B), whereas sera of remaining RRMS patients and healthy controls showed no reactivity (Figure 1C). End-point titers for hippocampal antibodies were 1:200 (n=4)-1:400 (n=7) for 11 seropositive patients and 1:800-1:1600 for remaining 2 patients.

MS patients with and without hippocampal antibodies showed comparable demographic, clinical features, scores of psychiatric tests assessing increased risk for psychosis (Reading the Mind in the Eyes Test and Interpersonal Reactivity Index) and depression (Beck inventory) and scores of cognitive tests assessing verbal memory, learning (California Verbal Learning Test-II) and language (Boston naming test). By contrast, hippocampal antibody positive patients showed worse scores in Symbol Digit Modalities and Controlled Oral Word Association Tests (Table 1), which assess executive functions including sustained attention, mental processing speed, verbal fluency, and mental flexibility.

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Correspondence Address: Erdem Tüzün, Department of Neuroscience, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Türkiye • **E-mail:** drerdem@yahoo.com
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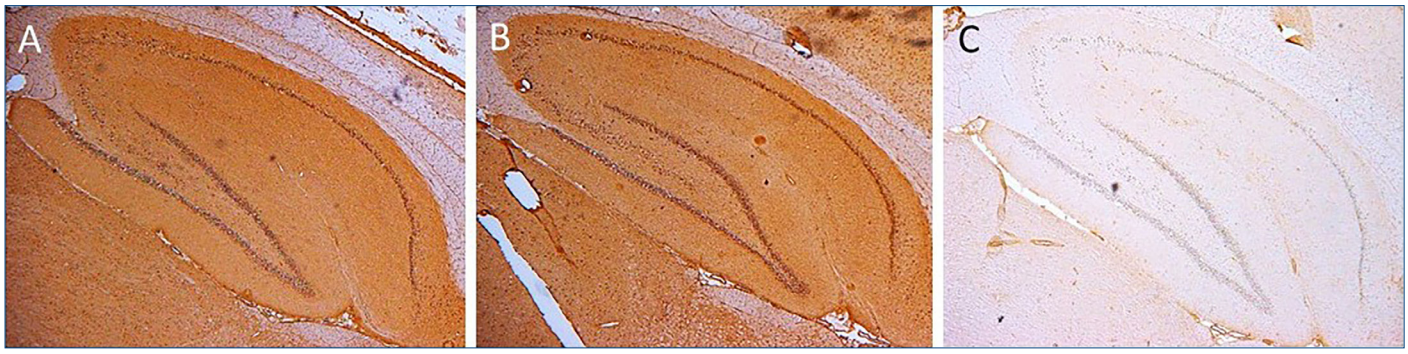

Figure 1. Immunolabeling of frozen rat brain sections with sera of multiple sclerosis (MS) patients. Serum IgG of two MS patients (A, B) shows strong immunoreactivity (brown color) with hippocampus, whereas the that of another MS patient (C) shows no immunoreactivity. Staining was performed with the avidin–biotin–peroxidase technique with hematoxylin (blue color) counterstaining (original magnification 4x).

Table 1. Comparison of the clinical features and cognitive test scores of relapsing remitting multiple sclerosis (RRMS) patients with and without hippocampal antibodies.

	Hippocampal antibody negative (n=45)	Hippocampal antibody positive (n=13)	p value
Age	42.9 ± 10.2	38.4 ± 12.0	0.115
Sex (women/men)	30/15	11/2	0.211
MS duration (years)	9.8 ± 6.6	8.5 ± 7.7	0.285
Number of attacks	4.9 ± 3.0	4.7 ± 2.3	0.378
EDSS	3.0 ± 1.1	2.9 ± 0.9	0.318
Progression index	0.5 ± 0.4	0.8 ± 0.8	0.110
Immunomodulatory drugs			
Interferon beta	6	0	0.722
Fingolimod	9	2	
Teriflunomide	6	2	
Dimethyl fumarate	5	1	
Ocrelizumab	11	5	
Natalizumab	8	3	
California Verbal Learning Test-II			
Total correct words remembered	43.8 ± 11.1	46.7 ± 10.3	0.200
Symbol Digit Modalities Test	39.2 ± 10.0	31.9 ± 10.8	**0.031**
Boston Naming Test			
Spontaneous naming	26.5 ± 3.0	27.1 ± 3.5	0.306
Phonemic cueing	2.4 ± 1.6	2.5 ± 2.1	0.453
Semantic cueing	0.6 ± 1.0	0.3 ± 0.6	0.112
Paraphasia	0.3 ± 0.9	0.2 ± 0.4	0.198
Controlled Oral Word Association Test			
Number of animal words	22.3 ± 9.6	18.3 ± 4.5	**0.023**
Number of K-A-S words	32.5 ± 4.2	27.4 ± 5.2	**0.036**
Total	52.7 ± 12.2	45.5 ± 7.5	**0.040**
Beck Depression Inventory	15.4 ± 10.0	14.1 ± 9.2	0.332
Reading the Mind in the Eyes Test	20.6 ± 5.1	20.9 ± 3.9	0.405
Interpersonal Reactivity Index	63.8 ± 13.2	64.8 ± 12.0	0.393

Numerical values are denoted as mean ± standard deviation. EDSS, expanded disability status scale. p values are obtained by chi-square test for categorical and Student's t-test for continuous variables. Significant p values are denoted with bold characters.

The immunostaining pattern found in our study is highly reminiscent of those found in two previous studies (2,3). We have confirmed the presence of these antibodies and have also found and association with impaired executive functions for the first time. Intriguingly, anti-hippocampal antibodies were not linked to memory loss or psychiatric symptoms that are more typically associated with hippocampal network. Nevertheless, hippocampus is well known to interact with the dorsal attention and central-executive networks and thus hippocampal antibodies might putatively interfere with executive functions through the injury of axonal projections in hippocampal tail, which establishes functional connectivity with other regions and promotes the formation of hippocampus-associated cognitive function (6).

As a limitation, we were unable to test the anti-neuronal antibodies in CSF, since all recruited patients were chronic MS patients with a well-established diagnosis and thus CSF collection was not approved by IRB. Also, target antigens of the established hippocampal antibodies could

not be identified. Nevertheless, our results lend further support to the notion that an autoantibody-mediated subtype of MS may exist or at least anti-neuronal antibodies may contribute to disability accumulation. Further characterization of binding sites and pathogenic actions of these autoantibodies might pave the way to description of novel pathogenic mechanisms of MS.

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