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Original Research Article

Autoimmune diseases related to anti-N-methyl-D-aspartate receptor encephalitis, a descriptive study in a third level center

Juan José Gómez-Piña[1]*, Emanuel Rodriguez Chavez[2], Olga Lidia Vera Lastra[1]

[1]Department of Internal Medicine, Hospital de Especialidades "Dr. Antonio Fraga Mouret" La Raza National Medical Center of the Mexican Institute of Social Security, CDMX, Mexico
[2]Department of Neurology, Hospital de Especialidades "Dr. Antonio Fraga Mouret" National Medical Center La Raza of the Mexican Institute of Social Security, CDMX, Mexico

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***Correspondence:**
Dr. Juan José Gómez Piña,
E-mail: drjgomezp@gmail.com

ABSTRACT

Background: Epiphenomena in neurological disorders can lead to subsequent autoimmune diseases such as autoimmune encephalitis (AE), but research on this condition is limited. There is a lack of knowledge about the development of autoimmune diseases in AE patients due to its rarity. The objective of this study is to investigate the association between the development of autoimmune diseases and patients with anti-NMDA autoimmune encephalitis.
Methods: A cross-sectional study was conducted from 2015 to 2022 at UMAE La Raza Antonio Fraga Mouret to investigate the relationship between autoimmune diseases and anti-NMDA AE. 194 patients were tested for anti-NMDA antibodies in cerebrospinal fluid (CSF), and 50 were found to meet the criteria for AE based on clinical, laboratory, and imaging tests. Follow-up evaluations assessed for rheumatological diseases and various additional tests were conducted before and after the AE event. The study was approved by the ethical and investigation committee.
Results: Our analysis included 50 patients with autoimmune encephalitis. Of these, 62% were women aged 18-51 years (mean age 31.97 years) and 38% were men aged 19-72 years (mean age 39.2 years). Fifty-two percent of patients had positive antibodies for autoimmune diseases, but only 12% met ACR criteria for autoimmune disease. The CSF was negative for infections. Electroencephelography (EEG) showed abnormalities in 42% of patients, and Magnetic resonance imaging (MRI) showed hyperintensity in the medial temporal lobes, cortico-subcortical regions, and white matter. False positives were excluded.
Conclusions: Among patients with autoimmune encephalitis, 12% had associated autoimmune diseases, most of which developed after the diagnosis of encephalitis. The observed diseases were 3 cases of lupus, 1 of rheumatoid arthritis, 1 of thyroiditis, and 1 of vasculitis. There is an epiphenomenal relationship between autoimmune encephalitis and subsequent development of autoimmune diseases.

Keywords: Encephalitis, Autoimmune encephalitis, Autoimmune diseases, NMDA, Prevalence

INTRODUCTION

Autoimmune encephalitis is an inflammatory disorder characterized by the presence of autoantibodies targeting synaptic proteins located on the surface of neuronal cells, including the NMDA receptor.[1]

Neurological disorders such as neuromyelitis optica (NMO) and myasthenia gravis (MG) are known to involve epiphenomena associated with autoimmune diseases in their pathogenesis. These epiphenomena arise as a consequence of primary autoimmune diseases such as systemic lupus erythematous (SLE), rheumatoid arthritis (RA), and thyroiditis. As a result, associations have been

reported between these disorders and other autoimmune diseases, including SLE and Sjogren's disease (SD), which may exhibit positivity for anti-aquaporin-4 (AQP4-IgG).[2]

Positive antibodies for associated diseases, such as anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), complement, immunoglobulins A, G, and M, anti-double-stranded DNA (dsDNA), anti-Smith (Sm), anti-SRP, anti-Ro, anti-La, rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), anti-insulin, and anti-GAD65, are commonly found in NMO and MG.[3] Anti-aquaporin-4 (AQP4) antibodies are detected in as many as 60% of individuals with neuromyelitis optica (NMO), whereas in systemic lupus erythematosus (SLE), this figure is less than 10%. Correspondingly, 11% of patients with NMO exhibit the presence of anti-acetylcholine receptor (AChR) antibodies.[4]

The presence of ANA positivity may be observed in female patients with co-occurrence of SLE and MG.[5] Furthermore, the presence of MG has been reported in conjunction with various autoimmune disorders, including hypothyroidism, pernicious anemia (PA), ulcerative colitis (UC), sclerosing cholangitis (SC), autoimmune thrombocytopenia (AT), antiphospholipid syndrome (APL), SD, and SLE.[6]

The confirmation of the diagnosis of anti-NMDA receptor encephalitis involves the detection of IgG antibodies targeting the GluN1 subunit of the NMDA receptor in the cerebrospinal fluid (CSF). To aid in the diagnosis of probable anti-NMDA encephalitis, a set of criteria based on clinical examination and commonly available diagnostic tests has been proposed.[7]

The detection of IgG antibodies against the N-methyl-D-aspartate (NMDA) receptor in CSF is considered to be highly sensitive and specific for the diagnosis of anti-NMDA receptor encephalitis. However, it is important to note that false positive and negative results may occur if only serum detection is tested.[8] In the context of antibody detection for anti-NMDA receptor encephalitis, it is important to note that CSF antibodies are consistently detected at the disease's nadir. Even in cases where treatment has been administered or the disease has advanced, CSF antibody levels typically remain elevated in the absence of clinical improvement. Conversely, serum antibodies may decrease substantially following treatment.[9]

The primary symptoms observed in patients with the disease are headache, fever, and various psychiatric manifestations, including anxiety, agitation, abnormal behavior, hallucinations, delusions, disorganized thinking, and psychosis. Other symptoms include sleep disturbances, memory impairments, seizures, catatonia, and dyskinesias such as choreoathetosic movements, dystonia, rigidity, and opisthotonic postures. In addition, patients may experience dysautonomia, characterized by hyperthermia, fluctuations in blood pressure, tachycardia, bradycardia, cardiac pauses, and, in some cases, hypoventilation requiring mechanical ventilation.[10,11]

In the initial stages, the CSF may appear normal, while electroencephalogram (EEG) may reveal epileptic activity, but slow and disorganized activity is often observed. Brain magnetic resonance imaging (MRI) typically shows transient fluid-attenuated inversion recovery (FLAIR) or contrast-enhancing abnormalities in cortical or subcortical regions, predominantly in the hippocampus, basal ganglia, and white matter. Although not performed routinely, positron emission tomography (PET) reveals a characteristic increase in the frontal-occipital gradient of cerebral glucose metabolism, which correlates with the severity of the disease.[12]

The administration of glucocorticoids, intravenous immunoglobulin, mycophenolate mofetil, and/or plasma exchange has been shown to produce significant clinical improvement in 70 to 80% of patients. Early initiation of immunotherapy in patients with seizures has been found to reduce the incidence of cognitive impairment, leading to improved long-term outcomes.[13]

METHODS

A cross-sectional ambispective analytical study was conducted from 2015 to 2022, with approval from the ethical and investigation committee (registration number R-2022-3501-114). Initially, 194 patients were screened for anti-NMDA antibodies in the CSF, of which 106 were negative and 92 were positive. Among the positive cases, 50 patients met the criteria for AE based on clinical, laboratory, electroencephalography and/or brain MRI assessments, and were further evaluated for rheumatological diseases through clinical or laboratory examinations.

Inclusion criteria comprised patients over 18 y.o exhibiting positive anti-NMDA antibodies and either suspected or confirmed rheumatological diseases based on clinical presentation or laboratory findings, the latter contingent upon the assessment of anti-NMDA antibodies in CSF. Exclusion criteria encompassed patients lacking physical or electronic medical records, those transferred to another healthcare facility; incomplete diagnostic protocols for AE, and lacking anti-NMDA antibody determination. The patients were tested for various autoantibodies including ANA, ANCA, anti-dsDNA, anti-Sm, Anti-Ro, Anti-La, C3, C4, RF, anti-CCP, anti-centromere, anti-TSH, anti-TPO, anti-thyroglobulin, anti-Scl70, lupus anticoagulant, anticardiolipin and anti-b2 glycoprotein. CSF parameters were also evaluated, including glucose, LDH, proteins, cells, bacterial, fungal, and tuberculosis cultures. In addition, thyroid panel (T3, T4, TSH), tumoral markers (CA 125, Alfa fetoprotein, Ca 19.9, Carcinoembrionary antigen, viral panel for B and C hepatitis, HIV) and TORCH panel (Toxoplasm, Rubeola, Cytomegalovirus, Herpes virus type 1 and 2, and Epstein-Barr) were assessed 1 month prior and after the AE event.

All patients underwent electroencephalography during the first and second week of the AE event, as well as brain MRI. The patients were also evaluated for rheumatological diseases according to the 2019 European League against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus criteria, and a test for Rheumatological activity was performed. A clinical examination was conducted by a rheumatologist to diagnose rheumatological disease during hospitalization for AE event or within 1 year of follow-up after hospital discharge. Data were analyzed using IBM statistical package for the social sciences (SPSS) statistics: version 25.

RESULTS

In the final analysis of our study, we observed that 31 women (62%) with ages ranging from 18-51 years and a mean age of 31.97 years, and 19 men (38%) with ages ranging from 19-72 years and a mean age of 39.2 years, met the criteria for autoimmune encephalitis. Of these patients, 52% had positive antibodies for autoimmune diseases, with 14% of patients having high titers over 1:160 for ANA, anti-dsDNA, ANCA, anti-SSA/Ro, anti-SSB/La, and anticardiolipin antibody, while 2% had titers over 20 U/ml for anti-Smith, anti-CCP, and anti-TPO. None of the patients tested positive for anti-Smith, RNP, Scl 70 or anti-jo1 markers. However, only 12% of the included patients had higher antibody titers and met ACR criteria for autoimmune disease, which included patients with SLE in 3 patients (6%), rheumatoid arthritis in 1 patient (2%), ANCA with associated vasculitis in 1 patient (2%), and Hashimoto's thyroiditis in 1 patient (2%). The SLE patients all had titers over 1:320 with a fine mottling pattern, the rheumatoid arthritis patient had titers of anti-CCP of 87 U/ml (<20 U/ml), the ANCA with associated vasculitis (AAV) in 1 patient (2%) with c-ANCA over 20 U/ml, and otorhinolaryngological affection; and finally, 1 patient with Hashimoto's thyroiditis (2%) with positivity of anti-TPO with titers of 58 U/ml (<20 U/ml).

Table 1: Antibody positivity of patients with diagnosis of autoimmune encephalitis according to sex.

Antibody positivity	Females N (%)	Males N (%)
Anti-Cardiolipin IgG	2 (4)	1 (2)
Anti-Cardiolipin IgM	2 (4)	1 (2)
Anti-Ro/SSA	3 (6)	1 (2)
Anti-La/SSB	1 (2)	1 (2)
Anti-CCP	1 (2)	0
Anti-Sm	0	1 (2)
ANA	3 (6)	3 (6)
Anti-mithocondrial	1 (2)	0
Anti-dsDNA	13 (26)	4 (8)
ANCA	3 (6)	3 (6)

Table 2: Patients with encephalitis who fulfilled ACR-EULAR criteria and time until development of rheumatic disease after the diagnosis of autoimmune encephalitis.

Diagnosis	ACR-EULAR criteria met	Time until the development of the rheumatological disease
Patient 1		
Systemic Lupus Erythematosus	ANA Hep-2 IF 1:320, leukopenia, thrombocytopenia, low C3 and C4 complement, anti-dsDNA antibody, joint involment, proteinuria >0.5 g/24 hours (23 points)	4 months
Patient 2		
Systemic Lupus Erythematosus	ANA Hep-2 IF 1:320, leukopenia, low C3 complement, anti-dsDNA antibody, pericardial effusion (18 points)	2 months
Patient 3		
Systemic Lupus Erythematosus	ANA Hep-2 IF 1:160, thrombocytopenia, low C3 and C4 complement, anti-dsDNA antibody, proteinuria >0.5 g/24 hours (18 points)	5 months
Patient 4		
Rheumatoid arthritis	3 small joints affected, Anti-CCP positive, elevated ESR, duration >6 weeks, (7 points)	8 months
Patient 5		
Hashimotos's thyroiditis	Hypothiroidism (TSH:7.9 mUI/l, T4:0.21 mUI/l, T3:43 ng/dl), anti-TPO 21 mcg/dl, asthenia, adynamia	4 months
Patient 6		
ANCA associated vasculitis	Hearing loss, cANCA/PR3 positive, masthoiditis, proteinuria >0.5 g/24 hours	5 months

ACR-EULAR: American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), ANA HEP-2 (antinuclear antibodies targeting human epithelial cells), anti-dsDNA (double-stranded DNA), Anti-CCP (cyclic citrullinated peptide), ESR (erythrocyte sedimentation rate), TSH (thyroid-stimulating hormone), Anti-TPO (thyroid peroxidase), cANCA/PR3 (anti-neutrophil cytoplasmic antibodies targeting proteinase 3).[21-24]

In the remaining panels that were evaluated, our analysis revealed that there were 3 patients with subclinical hypothyroidism, 2 patients with untreated hypothyroidism, and 1 patient with untreated hyperthyroidism. Among the main immunoglobulins, IgG was found to be elevated in 2 patients, with serum levels exceeding 1850 mg/dl (<1600 mg/dl). However, no clinical manifestations were observed. C3 complement was elevated in 6 patients with titers over 163 mg/dl (<152 mg/dl), and C4 was elevated in 8 patients with titers over 47 mg/dl (<38 mg/dl). Only 3 patients met the ACR criteria for SLE. The CSF was tested for bacterial, fungal, viral, and tuberculosis infections, but no infections were detected. Glucose levels were low in 12 patients (50-75 mg/dl), while LDH was higher in 12 patients with levels over 102 UI/L (<25 UI/l). Proteins were elevated in 15 patients with levels over 132 mg/dl (<60 mg/dl). Erythrocytes were elevated in 9 patients with an erythrocyte count over 4800 cells (<900 cells), and only 4 patients had a red-aspect of CSF. Leukocytes were higher than 70 cells in 5 patients (<3 cells).

In 21 patients (42%), electroencephalography revealed slow and disorganized brain activity, and one patient showed epileptic activity in the temporal lobes. Brain magnetic resonance imaging (MRI) predominantly revealed hyperintensity in the medial temporal lobes in 16 patients, cortico-subcortical hyperintensity in 7 patients, and homogeneous hyperintensity in the white matter in 13 patients, as detected by T2 and FLAIR sequences. While only 36 patients showed neuroimaging findings that were suggestive of autoimmune encephalitis, we excluded several false positive cases. Specifically, we excluded one case of cavernous angioma, four cases of multiple sclerosis, five cases with a history of previous stroke, one case of meningeal reinforcement meningitis, one case of NMO, and one case of Susac syndrome. Within our analysis, we identified 6 patients with autoimmune diseases, comprising 3 cases of SLE, 1 case of RA, 1 case of Hashimoto's thyroiditis, and 1 case of microscopic polyangiitis vasculitis (Table 2).

DISCUSSION

Autoimmune diseases arise from immunological intolerance to an individual's antigens. However, several factors contribute to the predisposition and precipitation of this immunological intolerance, with epiphenomena playing a critical role in neuroimmunological disorders. The coexistence of autoimmune diseases is the most significant factor contributing to this intolerance.[14] The co-occurrence of neuroimmunological diseases with other autoimmune diseases, such as an epiphenomenon, has been observed to be associated with systemic viral infections or with antibodies against autoantigens with pathogenic characteristics that induce disease. These epiphenomena have been observed in several diseases, including multiple sclerosis (MS), myasthenia gravis, and Guillain-Barre syndrome.[15]

The most widely accepted method for diagnosing anti-NMDAR encephalitis is to detect antibodies in the CSF that target the GluN1 subunit of the NMDA receptor. In addition to this, neuroimaging studies and electrophysiological studies are also used as complementary methods. According to the diagnostic criteria for autoimmune encephalitis, the presence of antibodies in CSF is necessary, and all the patients included in our analysis had these antibodies.[16] Brain MRI is the preferred diagnostic modality in the evaluation of autoimmune encephalitis, particularly with regards to identifying signal enhancement in FLAIR and T2 sequences, with temporal lobe involvement being a key feature. However, in a subset of cases, MRI findings may be normal in approximately 30% of cases or demonstrate unilateral changes.[17] On the contrary, the electroencephalogram has a low sensitivity in detecting abnormalities, with less than 50% of cases showing abnormal results. In our study, we found an abnormal EEG in 42% of patients.[18]

Interestingly, certain serum markers related to AE, such as ANA or TPO antibodies, have been described in the literature. Nevertheless, our patients with these markers exhibited clinical manifestations and met the ACR criteria for the respective rheumatological disorder.[19,20]

This study provides an opportunity for the diagnosis of patients with AE, as this disease has been described as an independent phenomenon, but is associated with other autoimmune diseases that must be considered during the AE approach. Additionally, AE mainly affects young adults and early treatment improves functional prognosis. Despite the numerous etiologies of encephalitis, it is crucial to characterize the clinical and paraclinical manifestations of diseases associated with AE, which can guide diagnosis, particularly when the CSF anti-NMDA test is inaccessible.

CONCLUSION

The early diagnosis plays a critical role in improving the prognosis of AE, especially given the limited availability of anti-NMDA antibodies testing. This highlights the importance of characterizing the clinical and paraclinical manifestations of diseases associated with AE, such as electroencephalographic and imaging studies, for prompt diagnosis and treatment. While the prevalence of AE in adults may be low, its diagnosis raises the risk of developing autoimmune diseases, particularly SLE, RA, HT, and vasculitis. Taking into account rheumatological diseases in the approach to AE is significant since it can help identify both new and previously known disorders associated with AE. Furthermore, the association between AE and diseases such as MS and MG, although sharing a similar mechanism of autoimmunity, has not been previously reported, and this relationship may aid in identifying potential patients with AE or those at risk of developing other autoimmune diseases.

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