Autoimmune Encephalitis. Case Report in the Infectious Diseases Intensive Care Unit, High-Specialty Medical Unit, La Raza National Medical Centre

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Case report

Neurology

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Background: Autoimmune encephalitis refers to progressive, acute or subacute cerebral inflammation associated with antibodies against neuronal cell-surface antigens and synaptic proteins, the most common form being N-methyl-D-aspartate receptor encephalitis. It is frequently associated with an underlying malignancy and therefore requires appropriate screening. The condition usually responds to immunotherapy, with better outcomes when treatment is started early in the clinical course. [1] Certain neuronal antibodies have very high specificity for autoimmune encephalitis and have improved its recognition. [2] Many patients are seronegative (up to 50%), which further emphasises the importance of a detailed clinical history, careful examination and supportive paraclinical investigations, such as magnetic resonance imaging and inflammatory cerebrospinal-fluid parameters. Different antibody types, IgG subclasses and epitope specificities produce distinct pathogenic effects. [3] The most common targets include antibodies against NMDA, GABA(B) and glycine receptors, as well as proteins such as CASPR2, DPPX and LGI1. [4] The clinical manifestations of autoimmune encephalitis are diverse and include abnormal psychiatric behaviour, cognitive dysfunction, speech dysfunction, seizures, movement disorders, reduced level of consciousness, autonomic dysfunction and central hypoventilation. [5] A recent epidemiological study in the United States showed that autoimmune encephalitis is as common as infectious encephalitis, with a prevalence of 13.7 per 100,000. [6]

Keywords: Autoimmune encephalitis.

The term encephalitis refers to an inflammatory process involving brain tissue, producing a clinical syndrome usually characterised by impairment of mental functions associated with variable neurological findings. [7,8] The causes of encephalitis may be classified as infectious, post-infectious, paraneoplastic and autoimmune; however, approximately 60% of cases remain without a precise diagnosis. [9] Autoimmune encephalitis is a severe autoimmune disease characterised by rapid progression and variable neuropsychiatric symptoms. Although infectious causes remain among the most recognisable, recent years have seen the development of a different diagnostic approach to these conditions, based on clinical algorithms and paraclinical studies aimed at avoiding delays in diagnosis and treatment. Autoimmune encephalitis has been associated with different antibodies against cell-surface antigens, including NMDAR, leucine-rich glioma-inactivated 1 (LGI1), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), contactin-associated protein-like 2 (CASPR2), gamma-aminobutyric acid receptor type B (GABABR), and antibodies against intracellular proteins such as Hu, Ma2 and glutamic acid decarboxylase 65 (GAD65). Differentiating these two groups is relevant because the latter generally respond poorly to immunomodulatory treatment. [10]

The Olmsted study suggested that the incidence of autoimmune encephalitis (0.8 per 100,000) was almost equal to that of infectious encephalitis (1 per 100,000), and that the incidence of autoimmune causes increased over time as these entities were increasingly identified and tested. [11] In the study Clinical Characteristics and Functional Prognosis in Patients with Possible Autoimmune Encephalitis in a Neurological Emergency Department, among 9,046 patients, 31 (0.3%) met criteria for possible autoimmune encephalitis. Mean age was 28.4 +/- 12.1 years, and 51.6% were women. Cognitive impairment (90.3%), psychosis (74.2%), abnormal movements (71%), catatonia (67.7%), seizures/status epilepticus (64.5%/19.4%) and

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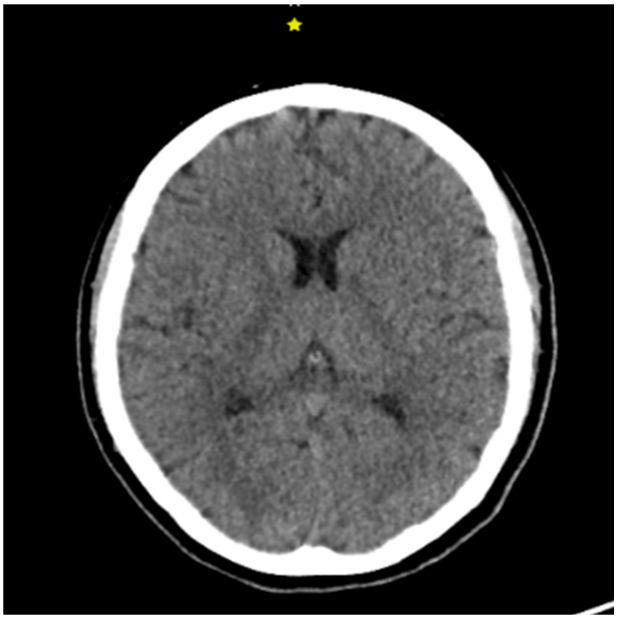
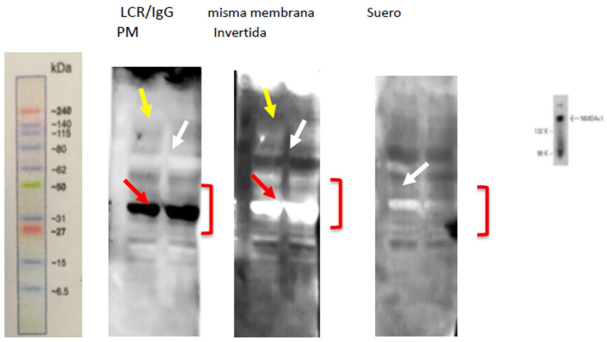


Figure 1. Axial computed tomography of the skull.



In cerebrospinal fluid, recognition of auto-IgGs against neuronal proteins of 80-62 kDa (white arrow) was observed, and recognition was greater against proteins of 50-31 kDa molecular weight (red arrow).

dysautonomia (58.1%) were observed. Good functional prognosis at discharge was reported in 58.1%. Factors associated with poor prognosis included age (24.8 +/- 5.0 vs 33.4 +/- 16.8 years, p = 0.049), status epilepticus (0% vs 46.2%, p = 0.002) and headache (61.1% vs 15.4%, p = 0.025). [12]

The causes of encephalitis may be grouped as follows: (1) infectious origin, including viral encephalitis (herpes) and viral meningitis; (2) post-infectious; (3) paraneoplastic, including breast, lung, renal and thyroid cancer, ovarian teratoma and B-cell lymphoma; and (4) autoimmune. [147]]

We present the clinical case of a female patient in her fourth decade of life diagnosed with autoimmune encephalitis, with positive testing for auto-IgGs against intramembrane proteins.

Case report

A 34-year-old woman with no relevant chronic degenerative history presented with a current illness that began on 11 October 2025 with headache, noise intolerance and photophobia, with partial improvement after analgesic medication. On 25 October 2025, she developed an altered level of consciousness characterised by euphoria, tachylalia, tachyphemia, anxiety and aggressiveness. On 26 October 2025, she attended her General Zone Hospital because of up to 10 seizure episodes, which were treated with phenytoin sodium and magnesium valproate. Lumbar puncture was performed and reported leukocytosis with polymorphonuclear predominance. A superimposed infection due to nosocomial pneumonia was reported, and she was referred to the High-Specialty Medical Unit, Infectious Diseases Hospital, Infectious Diseases Intensive Care Unit. On 6 November 2025, computed tomography showed cytotoxic oedema of the right parietal lobe.

An electroencephalogram was performed and reported severe generalised dysfunction. Based on these findings, autoimmune encephalitis was suspected. A new lumbar puncture was performed, and immunohistochemistry studies were requested to search for anti-neuronal surface autoantibodies (anti-NMDA, anti-GABA A, anti-AMPA and anti-GAD65) at the Medical Research Unit for Neurological Diseases of the High-Specialty Hospital, Siglo XXI National Medical Centre. The report showed the presence of auto-IgGs against surface proteins (in hippocampus) and, to a greater extent, intramembrane proteins (cerebellum). These findings were compatible with the presence of auto-IgGs against intramembrane proteins. A diagnosis of autoimmune encephalitis was established.

In the intensive care unit, the patient remained under sedation with midazolam 105 mg in 100 cc of 0.9% sodium chloride solution at 0.23 microg/kg/h, as well as propofol calculated at 2 mg/kg/h; levetiracetam 1.5 tablets via nasogastric tube every 12 hours; magnesium valproate 600 mg, half a tablet via nasogastric tube every 12 hours; and lacosamide 100 mg tablets, one-quarter tablet every 12 hours.

On admission, the following laboratory results were reported: glucose 111 mg/dL, creatinine 0.52 mg/dL, uric acid 1.4 mg/dL, total cholesterol 280 U/L, alkaline phosphatase 117 U/L, gamma-glutamyl transferase 143 U/L, lactate dehydrogenase 1263 U/L, Na 146 mmol/L, K 4.2 mmol/L, Cl 103 mmol/L, Mg 2.1 mmol/L, Ca 8 mmol/L, haemoglobin 12.2 g/dL, haematocrit 38.7%, leukocytes 11.3 x 10^3/microL and platelets 305,000 x 10^3/microL.

Given the patient's poor clinical course, cerebrospinal-fluid culture was requested; it showed no growth. The meningitis/encephalitis panel was not detected. India ink staining was negative.

The viral panel (HIV, HBV and HCV) was negative. Cerebrospinal fluid was colourless and transparent, with 80 cells, 60 lymphocytes, 40 neutrophils, glucose 115, glucose CSF/serum ratio 0.6 (normal), LDH 45 U/L proteins 41 U/L and CPK 1434 U/L. 80 cells, 60 lymphocytes, 40 neutrophils, glucose 115, glucose CSF/serum ratio 0.6 (normal), LDH 45 U/L, proteins 41 U/L and CPK 1434 U/L.

Discussion

Descriptions of autoantibodies against voltage-gated potassium channels (VGKC) in limbic encephalitis in 2001 [13], aquaporin-4 (AQP4) in 2004 [14] and N-methyl-D-aspartate receptors (NMDAR) in 2007 [15], together with responses to immunotherapy, catalysed the identification of further autoantibodies. [16] To establish a relationship between seropositivity and disease, autoantibodies must be detected in the patient's serum and/or cerebrospinal fluid (CSF), clinical improvement should be demonstrated after autoantibody removal, disease phenotypes should be reproduced in in-vivo models, and functional alteration of the target antigen should be shown in vitro.

B-cell development

The presence of high concentrations of IgG antibodies against autoantigens in the serum or cerebrospinal fluid of patients with autoimmune encephalitis indicates failure of immune tolerance mechanisms. To understand the pathophysiology more clearly, it is crucial to determine the point in B-cell development at which tolerance mechanisms fail and autoreactivity develops.

Central tolerance

B-cell autoreactivity is counteracted by central and peripheral tolerance mechanisms in order to prevent autoimmune responses. In the bone marrow, central tolerance eliminates autoreactive B cells through three processes: clonal deletion, receptor editing and induction of anergy. Clonal deletion removes highly autoreactive B cells through apoptosis. Receptor editing involves secondary V(D)J recombination to generate non-autoreactive B-cell receptors. Induction of anergy makes autoreactive B cells biochemically and genetically less responsive to activation. [21] Approximately 20% of autoreactive B cells escape elimination. [22]

A critical question is whether naive B cells already exhibit CNS autoreactivity or whether such autoreactivity is acquired later through somatic hypermutation in germinal-centre reactions. One way of addressing this question is to sequence patient-derived BCR genes and compare mutated autoantibodies with their unmutated germline counterparts. These germline configurations, known as unmutated common ancestors, can be analysed to determine their binding and pathogenic properties together with their mutated versions. If the unmutated common ancestors exhibit autoreactivity, central tolerance mechanisms have failed to eliminate these B-cell clones. In NMDAR encephalitis, evidence suggests that central tolerance checkpoints are defective.

Germinal-centre reactions

Mature naive B cells migrate to secondary lymphoid organs, where several peripheral tolerance mechanisms mitigate potential autoimmune reactions. These checkpoints include the absence of co-stimulatory, pro-inflammatory or survival signals, as well as active suppression by regulatory T cells. [21] Germinal centres within secondary lymphoid organs are the sites where B cells undergo clonal expansion and somatic hypermutation. These B cells are selected according to their affinity for antigens involving follicular helper T cells and follicular dendritic cells. Affinity-matured and class-switched B cells ultimately leave the germinal centre as plasmablasts or memory B cells. To prevent autoreactivity, germinal centres use at least two primary peripheral tolerance checkpoints. [23] Negative selection eliminates B cells that strongly recognise self-antigens; these cells undergo activation-induced cell death if they receive strong BCR signals without additional survival signals. A process known as clonal redemption allows autoreactive B cells to acquire additional somatic hypermutation, enabling them to mutate away from autoreactivity by reducing binding to self-antigens and increasing affinity for pathogen-derived antigens.

It has been suggested that autoantibodies in autoimmune encephalitis originate from germinal-centre reactions. First, histopathological studies of associated tumours from patients with NMDAR encephalitis frequently show dense lymphocytic infiltrates comprising T and B cells, as well as mature dendritic cells surrounding neuronal tissue, resembling germinal centres. [24,25]

Overall levels of somatic hypermutation in the variable regions of these NMDAR autoantibodies were significantly lower than in CSF antibodies from the same patients that did not target the NMDA receptor. These findings challenge the conventional assumption that germinal-centre reactions are the only pathway for pathogenic autoantibody production, at least in NMDAR encephalitis.

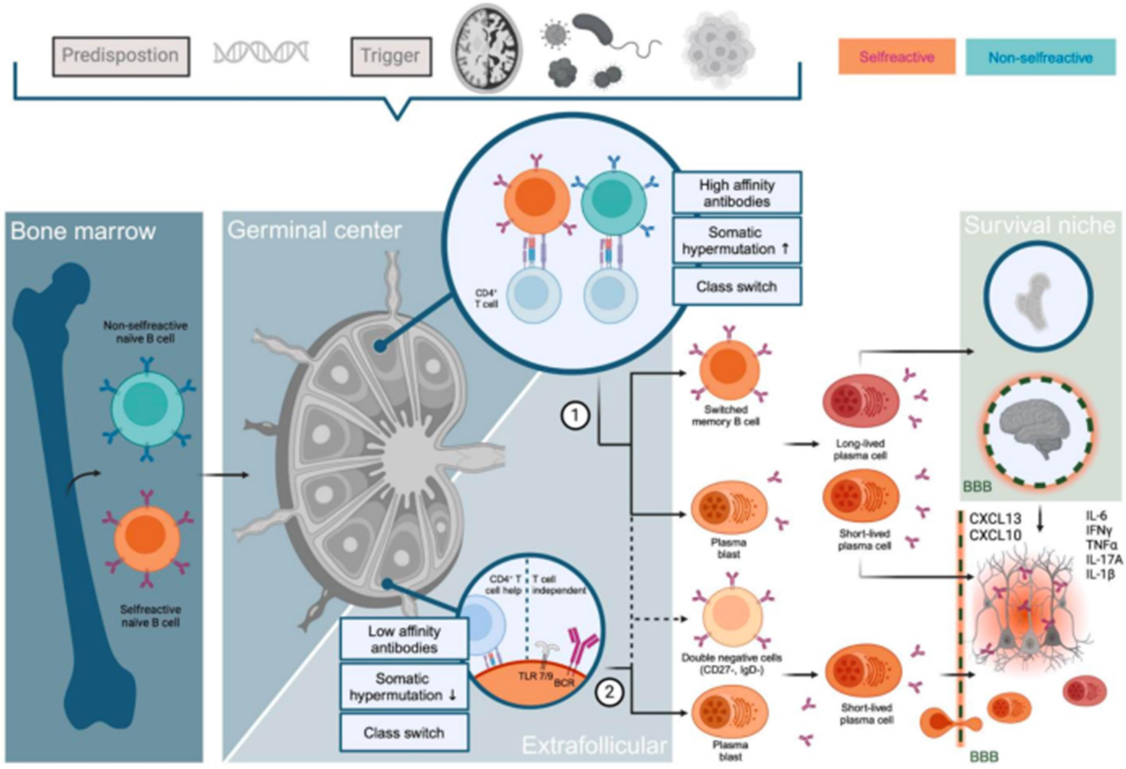


Figure 2. Pathways of autoreactive B-cell development in autoimmune encephalitis. Naive B cells may be autoreactive after evading central tolerance mechanisms, or non-self-reactive. In germinal-centre reactions, autoreactive and non-autoreactive B cells interact with CD4+ follicular helper T cells to undergo class-switch recombination and acquire somatic hypermutation. Previously non-autoreactive naive B cells may acquire autoreactivity through somatic hypermutation, or autoreactive naive B cells may further mature their affinity. These cells ultimately leave the germinal centre as memory B cells or plasmablasts secreting autoantibodies. In extrafollicular reactions, autoreactive naive B cells may acquire limited somatic hypermutation and may class-switch with T-cell help or independently of T cells through strong B-cell receptor signalling enhanced by Toll-like receptor signalling. Extrafollicular reactions generate lower-affinity, short-lived antibody responses, whereas germinal-centre reactions can produce higher-affinity antibodies and long-lived plasma cells that persist in survival niches such as the bone marrow or behind the blood-brain barrier in the central nervous system. Elevated CSF cytokine levels may promote the entry and survival of these cells. Genetic predisposition and triggers such as neurodegeneration, infection and tumours may initiate this autoimmune process. Image source: Homeyer MA, Falck A, Li LY, Prüss H. From immunobiology to intervention: Pathophysiology of autoimmune encephalitis. Seminars in Immunology. 2025;78:101955. Created in BioRender.

Some forms of autoimmune encephalitis, particularly LGI1 encephalitis, are strongly associated with certain HLA class II genes. [31-34] Germinal-centre affinity maturation involves CD4+ follicular helper T cells that recognise peptides presented by MHC II. Therefore, the association of disease with genes encoding MHC II suggests T-cell-dependent B-cell maturation and antibody production. Interestingly, HLA association studies in NMDAR encephalitis have been inconsistent. Consequently, the pathophysiology of NMDAR encephalitis may differ from that of other HLA class II-associated forms of autoimmune encephalitis and may not depend on T-cell reactions in the same manner.

Extrafollicular reactions

Class switching and somatic hypermutation were once considered exclusive hallmarks of germinal centres; however, these processes may occur before germinal-centre differentiation [35] and at extrafollicular sites. [36] B cells can migrate to extrafollicular regions, where they differentiate into short-lived, class-switched antibody-secreting cells. Although the germinal-centre pathway presumably generates high-affinity antibodies through a slower and more complex process, the extrafollicular pathway provides a rapid, short-lived and less refined antibody response. This rapid response is crucial in early defence, but it has also been implicated in autoantibody development in autoimmune diseases. [37-39]

The finding of class-switched IgG autoantibodies with low levels of somatic hypermutation in NMDAR encephalitis [18], without a clear HLA class II association, together with reduced frequencies of NR1-specific Th cells [40] and evidence of autoreactive naive precursors [18,40], may be explained by participation of extrafollicular responses in antibody production.

These precursor cells may be activated in extrafollicular pathways through the combination of specific stimuli, such as infection or tumour, and genetic predisposition. In systemic lupus erythematosus, extrafollicular pathways have been

linked in multiple studies to the generation of pathogenic autoantibodies. [41]

Central nervous system immunity and lymphocytic infiltration

For autoantibodies to exert pathogenic effects within the CNS, they must cross the cerebral barriers. The CNS, long regarded as an immune-privileged site, is now understood to actively regulate the passage of immune cells through the blood-brain barrier, the blood-leptomeningeal barrier and the blood-CSF barrier. [42]

Autoantibodies may passively diffuse through regions with barrier disruption. [43] However, in many cases of autoimmune encephalitis, the blood-brain barrier remains intact, indicating that B cells and antibody-secreting cells actively infiltrate the CNS and produce autoantibodies locally.

Evidence of B-cell/antibody-secreting cell infiltration into the CNS has been described in autoimmune encephalitis. In clinical practice, pleocytosis and oligoclonal bands are markers of immune-cell infiltration and intrathecal antibody production. In addition, a positive specific autoantibody index indicates intrathecal synthesis of antigen-specific antibodies by CNS-resident antibody-secreting cells. In non-melanoma autoimmune encephalitis, many patients have pleocytosis and oligoclonal bands. [44,45]

Patient-derived CSF cells and/or peripheral-blood mononuclear cells are stained for B-cell or plasmablast/plasma-cell markers, and their respective antibodies are recombinantly expressed and analysed to determine antigenic reactivity. [18]

Peripheral blood, lymph-node and BCR sequencing studies suggest that initial immunisation takes place in the periphery and that CNS infiltration is secondary.

Cytokines

Cytokines play a central role in regulating the maturation, proliferation and chemotaxis of immune cells into the brain. In NMDAR encephalitis, intrathecal elevation of CXCL13 has been consistently observed [48-51] and has been proposed as a biomarker of disease activity and treatment response. [51] Produced mainly by stromal and follicular dendritic cells, [52] CXCL13 recruits B lymphocytes to B-T-cell interaction zones in lymphoid tissue, is a key chemoattractant for short-lived plasmablasts migrating to the CNS and is associated with tertiary lymphoid structures. [53,54] Patients with NMDAR encephalitis and elevated CXCL13 levels showed greater intrathecal autoantibody production, poorer treatment responses and higher relapse rates. [51] Elevated CXCL13 levels have been observed in LGI1 and CASPR2 encephalitis; however, unlike NMDAR encephalitis, CXCL13 levels did not correlate with treatment response in these subtypes. [55,56] Other cytokines involved in B-cell survival, such as BAFF and APRIL, which are relevant in neuromyelitis optica spectrum disorder and multiple sclerosis, [57] were rarely elevated during the acute phase of NMDAR encephalitis [58], and other studies found no elevation beyond acute settings. [48,50]

Cytokine profiles provide information about T-cell involvement in autoimmune encephalitis. Elevated TNF-alpha and interferon-gamma levels in NMDAR encephalitis indicate Th1 involvement. [48,50] Th17 cells also appear to contribute to the pathogenesis of NMDAR encephalitis, consistent with Th17/Treg ratios observed in other autoimmune diseases. [59,60] IL-6, a pleiotropic cytokine that increases blood-brain barrier permeability and promotes differentiation of B cells into antibody-secreting cells, while also driving Th17 development, [61] was elevated in the CSF of patients with NMDAR encephalitis and correlated with poor clinical outcomes. [48,49,62-64] The Th17-derived cytokines IL-1 beta and IL-17A were elevated in the CSF of patients with NMDAR encephalitis. [64-66] IL-17A, which among other effects increases blood-brain barrier permeability to leukocytes, [67] was associated with limited treatment response and higher relapse rates. [64] In LGI1 encephalitis, Th17-associated cytokines are less frequently elevated.

T cells

Unlike other autoimmune diseases, such as multiple sclerosis or paraneoplastic autoimmunity, in which T cells are strongly implicated in pathogenicity, [68,69] they have classically not been considered a primary trigger in autoimmune encephalitis. Histopathological studies have rarely identified CD3+ T cells around small vessels or within the brain parenchyma, [56,68,70] and these cells were commonly negative for CD8 or cytotoxic markers such as granzyme B. [27,46]

T cells are now increasingly recognised for their role in supporting B-cell maturation and promoting inflammation in autoimmune encephalitis. In NMDAR encephalitis, several findings suggest a T-cell contribution: histopathological studies show scattered CD4 T-cell infiltration [27,46,70], and cytokine signatures, particularly Th1 and Th17 cytokines, are elevated throughout the disease, especially in more severely affected patients. [50] In addition, in an active immunisation mouse model, [19] TCR-alpha knockout mice, which lack mature CD4 and CD8 T cells, did not develop the disease.

CD4 follicular helper T cells are particularly relevant in supporting B-cell maturation and class switching during germinal-centre reactions. [71] In

addition, CD4+ T cells can transiently open the blood-brain barrier, allowing lymphocytes to enter immune-privileged sites. [72] Given this role, an increase in antigen-reactive CD4 T cells in the peripheral blood of patients with NMDAR encephalitis might be expected. A multicentre single-cell study in patients with LGI1 and CASPR2 encephalitis identified activated and clonally expanded CD4 T cells, and to a lesser extent CD8 cells, [47] with shared clones in both CSF and peripheral blood. These cells could promote intrathecal B-cell expansion and class switching; however, the same study found that B cells in LGI1 and CASPR2 encephalitis matured mainly in the periphery before CNS infiltration.

Interestingly, the same study also revealed a reduction in mucosal-associated invariant T cells in both peripheral blood and CSF. MAIT cells, a T-cell subtype with innate-like features, have been associated with numerous autoimmune diseases. The authors therefore hypothesised that a deficit in peripheral innate regulatory mechanisms could trigger interaction between autoreactive B cells and autoreactive T cells, which would in turn lead to intrathecal infiltration and autoantibody production. These studies show that distinct T-lymphocyte subsets, previously underestimated, may have a more relevant and differentiated role in the different forms of autoimmune encephalitis. Detailed investigation of each subset within specific forms of autoimmune encephalitis is warranted and may reveal new therapeutic targets.

Microglia

Resident immune cells of the CNS [73] contribute to neuroinflammation, for example through chemokine secretion. [74] Histopathological studies in NMDAR encephalitis have demonstrated pronounced microglial activation, with upregulation of activation markers such as HLA-DR and CD68. [46] In the CSF of patients with NMDAR encephalitis (n = 29), markers of microglial activation were elevated compared with controls. [75] In a brain biopsy from a patient with NMDAR encephalitis, perivascular microglia and macrophages expressed CXCL13, a chemokine critical for recruiting immune cells into the CNS, suggesting an active role in immune-cell trafficking. [51] In addition, a neuron-microglia co-culture model showed that patient-derived NMDAR autoantibodies bound to microglia through Fc receptors, leading to phagocytosis of autoantibody-tagged NMDA receptors. [76]

Tumor

Tumors are often associated with autoimmune encephalitis, and their prevalence varies by subtype. [20] Ovarian teratomas are found in 30-40% of cases of NMDAR-associated autoimmune encephalitis [17] and have been shown to contain germinal-centre-like structures with lymphocytes producing anti-NR1 autoantibodies. [26,30] Although ovarian teratomas may contain ectopic nervous tissue, which could trigger antineuronal immune responses in the inflammatory tumour environment, [77] 40-66% of ovarian teratomas in neurologically healthy individuals also contain nervous tissue, suggesting that its mere presence is insufficient to break tolerance. [24] Autoantibody development may involve tumour-intrinsic factors, such as abnormal neuroglial features or NMDA receptor composition, [24] although a recent cohort study found no genetic or histopathological differences except for germinal-centre formation in encephalitis-associated ovarian teratomas. [78] Alternatively, susceptibility to developing an autoimmune response to ovarian teratomas may also be due to genetic changes, such as a polymorphism in a gene regulating type I interferons, which has been associated with tumour-associated but not non-tumour-associated cases. [79] Concomitant infection of tumour tissue acting as an adjuvant may also be considered. [80]

Another mechanism of tumour-associated tolerance breakdown is exemplified by thymomas. These tumours are strongly associated with autoimmune diseases, particularly myasthenia gravis, [69] and patients frequently exhibit a broad immune defect with multiple autoantibodies. [81,82] The thymus is central to negative selection of autoreactive T cells, and this mechanism may be disrupted by thymomas through altered presentation of autoantigens, allowing autoreactive CD4+ T cells to evade tolerance checkpoints and support germinal-centre B cells, while also reducing Treg cells. [83] Some forms of autoimmune encephalitis, including GABAAR, [84] AMPAR, [85] LGI1 [86] and CASPR2 encephalitis, [28] may have underlying thymomas, although no such link has been described for NMDAR encephalitis.

Viruses

With the increasing use of specific autoantibody testing, a growing number of antigen-specific autoantibodies have been described after viral infections, providing one explanation, apart from persistent infection or persistent organ damage, for post-viral sequelae. [87] Among these, NMDAR autoantibodies stand out because of their frequent and consistent associations with multiple viruses. Approximately 30% of patients develop NMDAR encephalitis within three months after HSV1 encephalitis, with NMDAR autoantibodies in CSF, absent before infection, negative HSV PCR ruling out

persistent infection, and response to immunosuppressive therapy ruling out virus-induced organ damage. [88,89] NMDAR autoantibodies have also been reported after infections with other members of the Herpesviridae family, [90] HIV, [91] influenza A, [92] Japanese encephalitis virus [93] and tick-borne encephalitis virus. [94] Less frequently, other associations have been reported, such as GABAAR autoantibodies after HSV1 and HHV6 infections [95] or dopamine-2 receptor autoantibodies after HSV1 infections. [96] Three main hypotheses have been proposed regarding how viruses trigger the autoimmune response in autoimmune encephalitis.

Molecular mimicry: this mechanism occurs when viral proteins share structural similarities with self-antigens, which may induce cross-reactive autoantibodies. [97] An example is the presence of EBV autoantibodies in multiple sclerosis that cross-react with a glial-cell adhesion molecule. [98] Although similar molecular mimicry has been hypothesised for HSV1 and the NMDA receptor, there is no direct evidence supporting this hypothesis.

Antigen exposure through tissue damage: HSV1 infection can cause direct neuronal injury and disrupt the blood-brain barrier, exposing previously hidden NMDAR antigens. [99] This damage, together with transient abnormal antigen expression and inflammatory signals, could trigger an autoimmune response. [100]

Genetics: association with HLA class II

Autoantibody-mediated autoimmune diseases are often strongly associated with HLA class II genes, which encode MHC class II molecules. These are expressed on antigen-presenting cells and present peptides to CD4+ T cells. Specific alterations in this interaction may include escape of autoreactive T cells from thymic selection, preferential antigen presentation in the binding groove leading to cross-reactivity of T-cell receptors with microbial and self-antigens, or preferential binding of modified neoantigens. [101] Some HLA associations confer protective effects, which may be explained by correct thymic T-cell selection. [102] HLA polymorphisms have also been linked to preferential production of IL-10 and IgG4. [103] Although the exact mechanisms are complex, HLA class II associations in autoantibody-mediated autoimmune disease suggest a contribution of T-cell and B-cell interactions in autoantibody production. LGI1 encephalitis is a notable example of an HLA class II association.

Studies have consistently reported a strong association with HLA-DRB1*07:01, with up to 90% of patients with LGI1 encephalitis testing positive across different ethnic groups. [31-34] In CASPR2 encephalitis, HLA-DRB1*11:01 has been suggested. [31,104] In IgLON5 disease, 85% of patients carry HLA-DQ5 haplotypes, and DRB1*10:01 has again been reported. [29,104,105] Notably, carriers of HLA-DRB1*10:01 were more likely to show intrathecal IgG4 production than non-carriers, [29] highlighting the need for experimental studies to establish causal explanations.

Genetics: susceptibility genes outside the HLA region

Genetic risk factors for autoimmune encephalitis extend beyond HLA associations. With thousands of loci involved in the immune system, [107] mutations or variations in one or more of these loci may predispose individuals to autoimmune diseases. Next-generation sequencing now allows identification of such genetic alterations at an unprecedented scale. [108] These genetic associations differ from classical genetic diseases, in which a single mutated gene produces a phenotype. Instead, they lower the threshold for breakdown of immune tolerance, so that triggers such as viral infections or tumours may induce autoimmunity in genetically predisposed individuals, while those without such predispositions or without exposure to triggers remain unaffected. [109] In NMDAR encephalitis, risk loci have been identified in B-cell development and in pathways related to pro-inflammatory cytokine production by microglia and astrocytes, associated with blood-brain barrier integrity. [110]

Other studies in NMDAR encephalitis detected genetic variations in type I interferon signalling pathways, innate immunity [106] and genes specifically associated with cancer, herpesvirus infections and B-cell differentiation. [79] Non-HLA risk loci in LGI1 encephalitis were located in pathways of B-cell activation and Th17-cell differentiation. [111]

Diagnosis requires evaluation of cerebrospinal fluid. Findings include moderate lymphocytic pleocytosis, elevated protein and oligoclonal bands in 60% of cases. Definitive diagnosis is based on demonstration of antibodies against N-methyl-D-aspartate in cerebrospinal fluid and serum. [115]

Autoimmune encephalitis has been associated with different antibodies against cell-surface antigens, including NMDAR, leucine-rich glioma-inactivated 1, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, contactin-associated protein-like 2, gamma-aminobutyric acid receptor type B, and antibodies against intracellular proteins such as Hu, Ma2 and glutamic acid decarboxylase 65. Differentiating these groups is relevant because intracellular-antigen syndromes are less likely to respond to immunomodulatory treatment. [116]

In approximately 50% of cases, magnetic resonance imaging may be normal. When abnormal, findings include hyperintensities in cortical or subcortical regions, the medial temporal lobe, or

punctate areas in the frontal or parietal cortex, insula or basal ganglia. [131,132]

Electroencephalography is abnormal, with slow and disorganised delta/theta activity and superimposed seizure activity. [133] In women, computed tomography or ultrasound screening should always be performed because of the possibility of ovarian teratoma. [134] The study by Shu et al. described the relationship between reduced lipid and bilirubin metabolism and decreased HDL in the early stages of disease, with subsequent recovery after treatment. Tumour markers (CA-125, beta-hCG, alpha-fetoprotein or testosterone) are negative in most patients. [135,136]

Intravenous corticosteroids are first-line treatment for autoimmune diseases of the nervous system. Corticosteroid administration in autoimmune diseases may improve cognition and reduce seizure frequency, as in faciobrachial dystonic seizures. [137] The dose, duration and tapering of corticosteroids depend on the type of autoantibody involved. In anti-NMDAR encephalitis, corticosteroid induction without tapering may be successful, whereas in LGI1 encephalitis a prolonged corticosteroid course is required. [138]

To reduce corticosteroid adverse effects while improving effectiveness and safety, a 3- to 12-month corticosteroid course is recommended. [139]

Second-line therapy: intravenous immunoglobulin

Second-line treatment is initiated when first-line therapy does not show a clear benefit, or when the disease course is severe or recurrent.

Derived from pooled polyclonal IgG from donor serum, intravenous immunoglobulin has shown effective anti-inflammatory and immunomodulatory effects in several neurological diseases. [140] In autoimmune encephalitis, intravenous immunoglobulin is often recommended together with corticosteroids. [141] In the study by Tao-Ran Li et al. on anti-GAD65 encephalitis, intravenous immunoglobulin appeared to have a slightly better therapeutic effect than intravenous methylprednisolone among patients with stiff-person syndrome or cerebellar ataxia. [142]

Intravenous immunoglobulin mitigates inflammatory responses by acting on cells and processes involved in innate and adaptive immune responses. This includes inhibition of monocyte and macrophage activation; induction of anti-inflammatory cytokines such as IL-1 receptor antagonist, TGF-beta and IL-10; cytotoxic effects on neutrophils; and enhanced clearance of pathogenic antibodies through FcRn receptor saturation. [143] Common adverse effects include mild to moderate headache, fever, chills, chest or back pain during the first hours of infusion and post-infusion fatigue. Rare cases of pulmonary thromboembolism, acute myocardial infarction and cerebrovascular disease have been reported after intravenous immunoglobulin treatment.

Plasma exchange involves removing blood plasma from the body, separating it and replacing it with a human albumin solution. It is a relatively safe, tolerable and effective treatment for autoimmune neurological diseases. Plasma exchange is typically used after steroids and intravenous immunoglobulin. Patients receiving first-line immunological therapy combining plasma exchange with steroids, with or without intravenous immunoglobulin, have higher recovery rates than those receiving other treatments without steroids. [144]

The American Society for Apheresis concluded that plasma exchange is probably effective in the treatment of autoimmune encephalitis, such as LGI1 and CASPR2 encephalitis. [145] A pilot study indicated that plasma exchange was more effective for patients with neuronal surface autoantibodies (NMDA, LGI1, CASPR2 and mGluR5) than for those with intracellular-synaptic antigens (Hu and GAD). [146]

Third-line therapy: monoclonal antibodies, proteasome inhibitors, interleukin antagonists and folate-synthesis inhibitors

A minority of patients with autoimmune encephalitis do not respond to first- and second-line treatments and are considered refractory. These patients may have severe disability, prolonged intensive-care admission and a high relapse rate, and require more effective treatments based on agents such as monoclonal antibodies, proteasome inhibitors and interleukin antagonists.

Conclusion

The increase in cases of autoimmune encephalitis requires further investigation into the factors associated with its presentation. Timely identification of autoimmune encephalitis cases and appropriate treatment substantially improve morbidity and mortality. Antibodies against neuronal membrane-surface structures are usually the main pathogenic mediators. In the case presented, identification of auto-IgG antibodies against neuronal membrane surfaces was greater against proteins of 50-31 kDa molecular weight (red arrow), involving the hippocampus, which is responsible for memory, learning, spatial navigation and emotional regulation, and the cerebellum, which is crucial for coordination, balance and posture and integrates sensory information. This demonstrates the clinical course typical of encephalitis. Delayed aetiological differentiation often delays treatment administration. It is important to consider the presence of tumours, prion diseases and metabolic disorders. Initial treatment should consist of corticosteroids

because of their immunomodulatory function, most often associated with plasma exchange because of its direct action in clearing autoantibodies and replacing plasma with human albumin solution. In severe disease, alternative options include monoclonal antibodies, proteasome inhibitors, interleukin antagonists and folate-synthesis inhibitors.

Conflicts of interests

The authors declare that there are no financial, personal, or institutional conflicts of interest that could have influenced the work reported in this manuscript.

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