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An evolving redefinition of autoimmune encephalitis

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ABSTRACT

Autoimmune encephalitis encompasses a wide variety of protean pathologic processes associated with the presence of antibodies against neuronal intracellular proteins, synaptic receptors, ion channels and/or neuronal surface proteins. This type of encephalitis can also involve children with complex patterns of seizures and unexpected behavioural changes, which jeopardize their prompt recognition and treatment. Many epidemiological studies have shown that numerous immune-based forms of encephalitis can be encountered, almost surpassing the rate of postinfectious encephalitides. However, the overall exact prevalence of autoimmune encephalopathies remains underestimated, and the definition of diagnostic algorithms results muddled. The spectrum of neuropsychiatric manifestations in the pediatric population with autoimmune encephalitis is less clear than in adults, but the integration of clinical, immunological, electrophysiological and neuroradiological data is essential for a general approach to patients. In this review we report the most relevant data about both immunologic and clinical characteristics of the main autoimmune encephalitides recognized so far, with the aim of assisting clinicians in the differential diagnosis and favouring an early effective treatment. Correlations between phenotype and autoantibodies involved in the neurological damage of autoimmune encephalitis are largely unknown in the first years of life, because of the relatively small number of pediatric patients adequately studied. Future multicenter collaborative studies are needed to improve the diagnostic approach and tailor personalized therapies in the long-term.

1. Introduction

Acute encephalitis is a complex of neurological syndromes with relevant morbidity and crucial impact on patients, families and society, occurring in subjects of all ages, although more common in children [1]. In a review dealing with prospective studies carried out in the Western industrialized countries, a minimum annual incidence of 10.5 per 100.000 cases for children and 2.2 per 100.000 for adults was calculated, with a mean value of approximately 6 per 100.000 [2]. For years, the etiology of encephalitis remained unknown in > 50% of cases. However, as a trigger infectious agent, mainly Herpes simplex virus (HSV) was found in the cerebrospinal fluid (CSF) and blood of many cases, leading to conclude that at least most encephalitides might be infectious diseases [3]. This rationale explained why criteria for the diagnosis of encephalitis were mainly based on the characteristics of an infection.

The Consensus Statement of the International Encephalitis Consortium reported that diagnosis of encephalitis required evidence of an altered mental status lasting ≥24 h with no alternative cause identified (major criterion) along with 2 or more minor criteria, including fever ≥38 °C within the 72 h before or after presentation, generalized or partial seizures that were not fully attributable to a pre-existing seizure disorder, a new onset of focal neurologic findings, CSF pleocytosis (white blood cell count ≥5/mm^3), abnormality of brain parenchyma on neuroimaging, and abnormality on electroencephalography (EEG) not ascribable to other causes [4]. Two of these minor criteria were needed for a possible diagnosis of encephalitis and ≥ 3 for a probable or confirmed diagnosis. However, in the last 10 years, there have been significant advances in the identification of encephalitis etiologies. A number of studies has demonstrated that autoimmunity might play a role in conditioning the development of encephalitis [5]. Antibodies against central nervous system (CNS) and

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peripheral nervous system (PNS) components have been identified, and their presence has been associated with both signs and symptoms of neurological diseases also in children. An autoimmune pathogenesis has been supported by the evidence that administration of human antibodies to animals reproduced aspects of human diseases, that reduction in antibody levels was associated with significant clinical improvement and, finally, that these antibodies could be detected in the CSF of patients.

Analysis of clinical, radiological and laboratory characteristics of autoimmune encephalitides revealed that the criteria used to define encephalitis should be revised, as cases from autoimmunity processes frequently had a different clinical picture. Some manifestations differed greatly from those usually found in infectious encephalitis, whereas both CSF and neuroradiologic findings could even result normal [6]. Aim of this paper is to describe the immunologic and clinical characteristics of the main autoimmune encephalitides recognized so far to assist clinicians in the differential diagnosis and favour a prompt effective treatment.

1. Autoimmune encephalitis: a complex interplay of autoimmune phenomena and inflammation

It is established that autoimmune-mediated CNS damage can derive from the production of several different autoantibodies targeting various neuronal antigens. According to the location of these antigens, three different types of diseases have been identified: those in which antibodies are directed against intracellular antigens, those secondary to the production of antibodies against synaptic receptors, and those based on antibodies targeting ion channels and/or other cell surface proteins (Table 1) [6].

Antibodies against intracellular antigens are frequently observed in patients with cancer, mainly small-cell carcinoma, and are typical of adult patients: they are defined as paraneoplastic antibodies, but are unlikely to be the only cause of neurological manifestations [7]. On the other hand, in experimental animals, the active and passive transfer of antibodies does not always induce a clear neurological damage [7]. The evidence of antibodies against intracellular antigens is only exceptionally associated with the development of CNS or PNS disease in patients with cancer [8]. Moreover, antibody concentrations are not correlated with overall outcome, tumour evolution, or response to different treatments [8].

In general terms, we observe a significantly less effective response to immunosuppressive therapies in patients with autoimmune encephalitis who display the production of antibodies against extracellular antigens. Although the possibility that, at least in some cases, the intracellular antigens can be exposed to the autoantibodies within the synaptic cleft [9], a cytotoxic T-cell mediated immune response against neurons is more likely to be the main mechanism that leads to a specific damage. The most important antibodies included in this group are against Ma2, Hu (also defined type 1 anti-neuronal nuclear autoantibody, ANNA1) and glutamic acid decarboxylase (GAD) [6]. In all these forms the response to therapy is generally poor.

The pathogenesis of neuronal damage and patterns of response to therapy in autoimmune encephalitis, in which the immune response targets proteins that are part of synaptic receptors, ion channels or cell surface, is different. In this case, antibodies are the true cause of damage as they disrupt the target antigen. Several findings support this conclusion. The passive transfer of antibodies to experimental animals can reproduce a similar brain damage, as shown in humans [10]. The same phenomenon may occur when drugs or genetic mutations cause disruption of the target antigen. Synaptic receptor antigens involved in the determination of autoimmune encephalitides include *N*-methyl-D-aspartate (NMDA), γ-aminobutyric acid A and B ($GABA_AR$, $GABA_BR$), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), the metabotropic glutamate receptor 5 (mGluR5), and the dopamine 2 receptor [5,6,10]. Antigens that are part of ion channels or part of the cell surface are leucine-rich glioma inactivated-1 (LGI1), contactin-associated protein-like 2 (Caspr2), dipeptidyl-peptidase-like protein 6 (DPPX), myelin oligodendrocyte glycoprotein (MOG), aquaporin 4 and ganglioside GQ1b [5,6,10–13].

However, the identification of antibodies that are involved in different forms of autoimmune encephalitis is complex, as it requires complicated laboratory methods that are not readily accessible in many institutions [14]. Consequently, antibody identification cannot be considered as an initial step for the diagnosis of these diseases. The same is true for the response to immunosuppressive therapy, that is ethically prescriptible only after abnormal immunity processes are demonstrated.

Based on these premises, it seems clear that diagnosis of autoimmune encephalitis should be suspected following a combination of disease signs and symptoms. Initial assessment should consider neurological evaluation and standard diagnostic tests and take into account that specific clinical manifestations and radiological abnormalities might frequently occur in some autoimmune encephalitides. Moreover, other neurologic disorders than can mimic autoimmune encephalitis should also be considered (*i.e.*, CNS infections, septic encephalopathy, metabolic encephalopathy, drug toxicity, cerebrovascular diseases, neoplastic disorders, Creutzfeldt-Jakob disease, Kleine-Levin syndrome, Reye syndrome, mitochondrial diseases, inborn errors of metabolism, and rheumatologic disorders) and excluded [15–20]. According to Graus et al. [6], the diagnosis of autoimmune encephalitis should be suggested in all ages when the following criteria are met: 1) subacute onset of working memory deficits (short-term memory loss), altered mental status (decreased or altered level of consciousness, lethargy or personality change), or psychiatric symptoms; 2) at least one of the following: new focal CNS findings; seizures not explained by a previously known seizure disorder; CSF pleocytosis with white blood cell count of > 5 cells per mm^3; 3) magnetic resonance imaging (MRI) of the brain and spinal cord showing abnormalities suggestive of encephalitis (hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes [as in limbic encephalitis], or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation).

In the following sections the characteristics of the best-known autoimmune encephalitides are reported with focus on immunologic and clinical details. In several cases, the knowledge of clinical presentations can lead to the suspicion of a presumed diagnosis, favouring a rapid

Table 1
Immunological mechanism of autoimmune encephalitides.

Mechanism	Antigens involved
Production of antibodies directed against intracellular antigens	Hu, MA2, glutamic acid antibodies against Hu (also defined type 1 anti-neuronal nuclear autoantibody, ANNA1), Ma2, glutamic acid decarboxylase (GAD)
Production of antibodies against synaptic receptors	*N*-methyl-D-aspartate (NMDA), γ-aminobutyric acid A ($GABA_AR$), γ-aminobutyric acid B ($GABA_BR$), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), metabotropic glutamate receptor 5 (mGluR5), dopamine 2 receptor
Production of antibodies targeting ion channels and cell-surface proteins	Leucine-rich glioma inactivated-1 (LGI1), contactin-associated protein-like 2 (Caspr2), dipeptidyl-peptidase-like protein 6 (DPPX), myelin oligodendrocyte glycoprotein (MOG), aquaporin 4, ganglioside GQ1b

initiation of treatment before antibody detection.

2. Clinical sceneries with multi-faceted presentations

3.1 Anti-glutamic acid decarboxylase (GAD) encephalitis.

GAD is an intracellular enzyme that can be found in both neural and pancreatic cells [21]. Two isoforms of GAD have been identified, GAD 65 and GAD 67: both can be detected in the CNS, where they catalyze the synthesis of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter; pancreatic islets contain only GAD 65, that exerts paracrine functions [21]. Antibodies against GAD are associated with both type 1 diabetes and several neurological manifestations, including limbic encephalitis (LE), stiff person syndrome (SPS), cerebellar ataxia, ocular movement disorders and refractory epilepsy [22–24]. Very few cases have been reported in children. In particular, LE is characterized by rapidly progressive short-term memory loss, psychiatric symptoms and seizures [25], which, in patients with anti-GAD 65 antibodies, tend to have a chronic course with poor response to immunotherapy and marked resistance to antiepileptic drugs [26,27]. SPS is characterized by fluctuating muscle rigidity in the trunk and limbs and heightened sensitivity to different stimuli, such as noise, touch and emotional distress, which can set off muscle spasms. Abnormal postures, often hunched over and stiffened, are characteristic of this disorder. Patients with anti-GAD 65 antibodies develop SPS or overlapping syndromes more frequently than do those with anti-glycine receptor antibodies, and have a worse outcome [28]. Cancer (thymoma or small-cell lung carcinoma) is associated with approximately 25% of cases of anti-GAD 65 encephalitis [6].

As data comparing antibody titers in patients with brain disorders and type 1 diabetes seem to indicate an intrathecal synthesis of autoantibodies, the titer of these antibodies may remain stable and significantly high during a long observation period [29]. However, further studies capable of explaining the true pathogenesis of this form of autoimmune encephalitis with or without cancer are needed. A very recent report related to a 9-year-old girl with refractory seizures, behavioural and severe fatal autonomic imbalance including dysrythmia, bradycardia/tachycardia, hypotension/hypertension, hypothermia/hyperthermia and hyperhidrosis, showed the possibility of extralimbic brain involvement in children with anti-GAD 65 antibodies [30].

3.2 Anti-*N*-methyl-D-aspartate receptor encephalitis.

NMDARs are ligand-gated ion channels that mediate excitatory neurotransmission, included in a group of ionotropic glutamate receptors, which are made of tetrameric complexes of large transmembrane subunits forming a central ion channel pore [31]. Three different NMDAR subunits that are ubiquitously expressed have been identified: NR1, NR2 and NR3. NR1 has eight different subtypes generated by alternative splicing from a single gene. In addition, there are four different NR2 subunits (A-D) and two NR3 subtypes (A, B). Tetramers are composed of two NR1 subtypes and two NR2 subtypes or a combination of NR2 and NR3 subtypes. The final structure of tetramers varies with age: NR2B (and NR2D) subunits are abundant at early stages of development, and NR2A or NR2C subunits are progressively added during growth [32–34].

The distribution of NMDARs in the nervous system is not uniform as well as their functional activity. These findings could explain why signs and symptoms of NMDAR encephalopathy vary among subjects, particularly between children and adults. The simultaneous binding of glycine and glutamate activates NMDAR, which results in cation (mainly Ca^{++}) influx into the cell, provided that a sufficiently strong depolarization is present. This process initiates signal transduction cascades and results in a longlasting pattern of synaptic strength modulation. Signalling through NMDAR is critical for activity-dependent synaptic plasticity and hippocampal long-term potentiation [35]. Moreover, NMDARs modulate excitotoxicity, as an excessive cation influx can cause neuronal death [36]. The reduction in NMDAR activity can have dramatic effects. Mice with reduced NR1 subunit expression [37] or NR2A subunit deletion [38] show behavioural changes characteristic of schizophrenia. Furthermore, drugs blocking NMDAR can cause psychotic symptoms, and NMDAR dysfunction has been implicated in a variety of diseases, including stroke, schizophrenia, epilepsy, dementia, Parkinson's disease and Huntington's disease [39].

Anti-NMDAR encephalitis is the most common autoimmune encephalitis. > 1.000 subjects with this disease have been described, and it is likely that a relevant portion of cases with undefined etiology, if properly studied, might recognize a pathogenesis mediated by anti-NMDAR antibodies [40–42]. Although this type of encephalitis can affect people of any age, it predominates in young women and children, among whom it has been found to occur with a frequency surpassing all individual viral encephalitides [40]. In a relevant number of patients both neurological signs and symptoms are associated with those of a tumour, most commonly an ovarian teratoma [41], although testicular immature teratoma [42] and lymphoma [43] have been also described.

In anti-NMDAR encephalitis the main epitope targeted by antibodies is the extracellular N-terminal domain of the NR1 subunit of the receptor [44], and this autoimmune process causes a selective and reversible decrease in both NMDAR surface density and synaptic localization, that leads to disruption of the synaptic structure and function, strictly dependent on the patient's antibody titer [45]. Patients with a higher proportion of consciousness disturbances, autonomic dysfunction, central hypoventilation, epilepsy and involuntary movements have more frequently a strong positive anti-NMDAR antibody titer in the CSF (48.7% *vs* 29.2%) [46]. In tumour-associated cases the presence of tissue expressing NMDAR in the tumour mass explains the development of autoimmune phenomena [44,47]. In cases without any association with malignancies, it is hypothesized that viruses can trigger the disease. A high prevalence of prodromal viral-like symptoms can be demonstrated in these patients. An autoimmune response to the NR1 subunit of NMDAR has been shown in children to be triggered by various infectious agents, and different reports have suggested that anti-NMDAR encephalitis may be associated with HSV, *Mycoplasma pneumoniae*, measles virus, mumps, group A hemolytic *Streptococcus* and *Toxoplasma gondii* infection [48–50]. There is evidence that 20% of patients with HSV encephalitis develop anti-NMDAR autoantibodies [51], and may have a relapse of neurological manifestations with clinical signs resembling those of anti-NMDAR encephalitis [52]. Finally, anti-NMDAR antibodies has been detected in children suffering from influenza A/H1N1 infection [53], though a role of genetic predisposition to autoimmunity cannot be excluded [47].

From a clinical point of view, anti-NMDAR encephalitis is characterized by psychiatric symptoms, behavioural dysfunction, decreased consciousness, speech and movement disorders, autonomic instability, central hypoventilation, cognitive impairment and seizures. The clinical scenery is different between adults and children. First, the association with a tumour is less common in children. Zhang et al. [46] reported that 9% of subjects younger than 18 years had a tumour compared to 27% of older patients ($p < .0001$). Conversely, in adults, at onset, neuropsychiatric manifestations such as psychosis, memory loss and hallucinations are the rule. In contrast, only 60% of children present with exclusively psychiatric symptoms, whereas movement disorders and seizures are significantly more common. Abnormal movements can be severe and lead to hypertonia and opisthotonic posturing. The most commonly described movements are chorea, athetosis, tremors, ataxia, limb or oromandibular dystonia, limb or facial myorhythmia, blepharospasm and opisthotonus [54,55]. Seizures are generally, but not exclusively, focal. Children have usually a better outcome ($p = .0064$) with a low frequency of central hypoventilation and reduced admission rates to the pediatric intensive care units [46].

From a laboratory point of view, CSF pleocytosis is significantly less common in children than adults (43% of children *vs* 63% of adults; $p = .0163$) [46]. In addition, the presence of pleocytosis or oligoclonal bands supports this diagnosis. EEG and MRI findings seem independent from age, although their relevance is different. Contrarily to cranial

MRI, which is abnormal in approximately half of cases, almost all patients with anti-NMDAR encephalitis have an abnormal EEG both at onset and at peak stages of the disease. Diffuse slowing is the most common presentation on EEG in both children and adults: this finding can significantly contribute to diagnosis, particularly in adults who only exhibit psychiatric symptoms at onset [56]. Moreover, at the peak stage, focal slowing, epileptiform discharges, polymorphic delta rhythm, diffuse beta activities, and extreme delta brush can also be detected [57]. Significantly, MRI findings are less useful. A recent systematic review has shown that, when pathological findings are present, they include T2/FLAIR medial temporal and frontal hyperintensity and leptomeningeal contrast enhancement [58]. However, subcortical white matter changes seem as common as those of cortical grey matter. The only prognostic marker seems is related to the progressive cerebellar atrophy, which has been associated with length of hospital stay ($p = .002$, 11.1 *vs* 2.4 months), need for ventilation ($p = .04$; 5 out of 5 *vs* 4 out of 10 patients), and serious complications ($p = .004$; 4 out of 5 *vs* 0 out of 10 patients) [59]. Positron emission tomography (PET) seems to be more precise than MRI in assessing brain disease that might accompany anti-NMDAR encephalitis. Indeed, PET can show CNS abnormalities in cases with normal MRI. However, very few studies have used this diagnostic tool in patients with anti-NMDAR encephalitis, and further research is needed to evaluate the role of PET in both diagnosis and monitoring of this syndrome [58].

As previously reported, manifestations of anti-NMDAR encephalitis are slightly less severe in children than in adults. However, in both cases, the final prognosis is generally good. Most patients, independently from age, respond to immunosuppressive treatment and, if present, to tumour resection. Although no predefined protocol is presently available, first-line immunotherapy is based on corticosteroids, intravenous immunoglobulin (IVIG) or plasma exchange alone or combined, whereas second-line immunotherapies include rituximab and cyclophosphamide alone or combined. These second-line drugs are recommended if no sustained improvement occurs within four weeks after initiation of immunotherapy or tumour removal [41]. In a study involving 252 patients, including one third of children and adolescents followed for 24 months after diagnosis, mortality rate was limited to 9.5%, and 83% had a favourable outcome [41]. Factors associated with better prognosis included no need for intensive care unit admission ($p < .0001$), early treatment ($p = .009$), and low disease severity within four weeks from onset ($p = .011$). Similar results were obtained in another study including 111 patients aged between 13 and 72 years [41]. In this case, mortality rate within 6 months was 4.5%. Recovery was slower in severe cases, but at 6 months after treatment initiation there were no significant differences in outcome between severe and non-severe cases. Approximately 5 years after therapy, a follow-up of 93 patients revealed that about 90% of them had Rankin scale evaluation within the normal range. However, in some patients, cognitive impairment, personality changes, epileptic seizures and involuntary movements might persist for several months, and sometimes neurological manifestations can also recur. Persistence of neurological deficits and recurrences also occur in children, affecting their transition into adulthood with subsequent cognitive, emotional and behavioural abnormalities [60].

2.3 Voltage-gated potassium channels (VGKCs)-positive group of encephalitides.

VGKCs are present on the membrane of neurons in both CNS and PNS, where they mediate repolarization after an action potential. Antibodies against VGKCs have been associated with LE [61], some types of epilepsy including facio-brachial dystonic seizures [62,63], Morvan's syndrome [64] and neuromyotonia [65]. However, more recently, it was shown that these antibodies did not target the VGKC itself, but some associated proteins, as LGI1 and Caspr2 [13,66,67], causing slightly different clinical manifestations [68].

3.3.1 Anti-LGI1 encephalitis.

LGl1 (leucine-rich glioma inactivated-1) is a protein mainly expressed in the hippocampus and neocortex [66], that connects the presynaptic disintegrin and metalloproteinase domain-containing protein 23 (ADAM23) to postsynaptic disintegrin and metalloproteinase domain-containing protein 22 (ADAM22), essential for inhibitory signal transmission from the presynaptic potassium channel to the postsynaptic α-amini-3-hydroxy-5-methyl-4 isoxazolepropionic (AMPA) receptors [69]. Animal studies have found that mutations in the LGI1 gene abrogate AMPA-mediated synaptic signalling, whereas *in vitro* studies have revealed that antibodies against LGI1 inhibit the binding of this protein to ADAM22 and ADAM23, resulting in a decrease in postsynaptic AMPA receptors. In turn, a decrease in AMPA receptor function is strongly associated with the development of seizure disorders [70].

In humans anti-LGI1 encephalitis occurs mainly in approximately 60-year-old males presenting with LE: > 300 cases have been described. The clinical spectrum is relatively homogeneous: seizures and subacute progressive alteration of memory; behaviour and space orientation abnormalities are the most common signs of this disorder. In some cases seizures precede the cognitive decline, but in 10–15% of patients cognitive dysfunction occurs without seizures [71,72]. The most characteristic seizures, detectable in approximately 50% of cases, are facio-brachial dystonic seizures (FBDS). However, autonomic seizures and different motor events can also occur. FBDS are considered pathognomonic of anti-LGI1 encephalitis and are involuntary unilateral contractions of the face and arm (or leg) that last for < 3 s and occur up to 100 times a day. Motor events different from FBDS can be automatisms or vocalizations, although in the late stage of disease; generalized tonic-clonic seizures can also be seen. Both subclinical and clinical seizures are frequently accompanied by EEG changes. Aurangzeb et al. reported that EEG changes were detected in 37 of 53 seizure episodes with the same frequency in both clinical and subclinical manifestations [73]. Moreover, multifocal interictal epileptiform discharges, from temporal, frontal and parietal regions, and interictal slow-wave activities can be observed. Multiple seizures, in addition with numerous subclinical seizures and interictal epileptiform discharges, are considered hallmarks of anti-LGI1 encephalitis. A tumour may be found in up to 11% of patients, with thymoma and lung cancer being the most common [27,66,67,74].

Different autoantibodies can be detected in both serum and CSF while hyponatremia is present in approximately 60% of cases. At disease onset brain MRI is normal in approximately 25% of patients: if abnormalities are present, they are mostly characterized by T2 hyperintensity in the mesio-temporal lobe, consistent with LE. However, long-term assessment of the disease might also reveal hippocampal atrophy or sclerosis in 41–95% of patients [75].

Although the effect of immunotherapy has not been studied in randomized controlled trials, data collected in small patient groups seem to indicate that response to treatment is good in most cases, particularly in those who start early. Corticosteroids and IVIG alone or in combination are the first-line drugs, inducing a rapid reduction of seizures. Cognitive improvement may be significantly slower. In the study by van Sonderen et al., at a follow-up longer than 2 years, most surviving patients reported mild residual cognitive deficits with spatial disorientation [75]. A total of 86% of patients had persistent amnesia. Relapses were common (35%) and presented up to 8 years after disease onset. The two-year case fatality rate was 19% [75].

3.3.2 Anti-Caspr2 encephalitis.

Caspr2 (contactin-associated protein-like 2) is an adhesion molecule expressed in CNS and PNS, essential for potassium channel clustering of myelinated axons [13,76]. Anti-Caspr2 autoantibodies recognize multiple target epitopes in the extracellular domain of Caspr2 [77], and cause damage to both brain and nerves. > 80% of the approximately 200 reported cases are in elderly men (approximately 80 years). A tumour, mostly a thymoma, may be detected in up to 32% of cases

[66,78,79]. The clinical spectrum is significantly less homogeneous than that due to anti-LGI1 encephalitis. Cognitive decline, including amnesia, behavioural disorders, hallucinations and psychosis is the most common CNS symptom, which might progress very slowly, mimicking dementia [80]. In approximately 50% of cases seizures can be observed and cerebellar ataxia is frequently associated [81]. However, due to PNS involvement, muscular pain, fasciculations and cramps are present in many patients. Hyperhidrosis is common. The simultaneous presence of CNS and PNS manifestations associated with autonomic dysfunctions and insomnia defines the so-called Morvan's syndrome [82]. CSF pleocytosis can be also detected in 30–40% of cases.

Diagnosis is strongly supported when three or more of the following symptoms can be detected: encephalopathy (cognitive deficits/seizures), cerebellar dysfunction, PNS hyperexcitability, dysautonomia, insomnia, neuropathic pain and weight loss. Brain MRI is normal in most patients. When MRI abnormalities are observed, bilateral T2 hyperintensity of the medial temporal lobes is the most common finding. Resection of the tumour is essential to assure improvement and cure. Immunotherapy seems effective in patients without malignancy. However, relapses may be very common, occurring even several years after the initial episode and involving other areas of CNS [83]. The presence of autoantibodies directed against the synaptic protein LGI1 and adhesion molecule Caspr2 has not been found in children with acute infectious encephalitis and the role of these autoantibodies in pediatric sceneries is still debated. Brimberg et al. have demonstrated that male mice exposed *in utero* to a monoclonal antibody binding to Caspr2 display abnormal cortical development, decreased dendritic complexity of excitatory neurons, reduced numbers of inhibitory neurons in the hippocampus and behavior abnormalities, suggesting that *in utero* exposure to maternal brain-reactive anti-Caspr2 antibodies might have a role in the autism spectrum disorder [84].

3.3.3 Voltage-gated potassium channels (VGKCs)-positive encephalitis in the absence of anti-LGI1 and Caspr2 antibodies.

The clinical relevance of antibodies against VGKC in patients lacking anti-LGI1 and anti-Caspr2 antibodies is not precisely defined. In these patients a wide clinical spectrum has been observed, including pain syndromes, LE, epilepsy, polyneuropathy and cramp fasciculation syndromes, all associated with the demonstration of anti-VGKC autoantibodies [85–87]. The lack of syndrome specificity and detection of high-titer anti-VGKC-complex autoantibodies even in patients without autoimmune phenomena seem to indicate that different disease entities might be included in this group [88]. Recently, an acute and isolated psychotic presentation of anti-VGKC encephalitis has been reported in a 16-year-old girl [89], but further studies are needed to identify potential new antibodies against neuronal structures and determine which of these patients have a real autoimmune disease.

3.4 Anti-glycine receptor (GlyR) encephalitis.

Glycine receptors (GlyRs) are ligand-gated chloride channels that mediate fast inhibitory transmission, predominantly located in the spinal cord and brainstem where they are agonized by glycine, taurine or alanine, leading to neural hyperpolarization through a selective flux of chloride down the electrochemical gradient. GlyRs are essential for muscle tone, coordination, respiratory rhythm, and sensory processing [90]. The genetic modification of GlyRs is associated with hypertonia, hyperekplexia, development delay and apnoea [91]. Patients with neurological manifestations associated with anti-GlyR antibodies have more frequently a progressive encephalomyelitis with rigidity and myoclonus (PERM), though with variations in severity and clinical expression [92]. PERM is a rare variant of SPS, characterized by brainstem symptoms, stiffness, rigidity, muscle spasms, myoclonus, autonomic dysfunction and hyperekplexia. Compared to classifying SPS associated with anti-GAD antibodies, PERM is generally more severe but also more responsive to immunotherapy [93]. However, various combinations of signs and symptoms have been described. Carvajal-Gonzalez et al. studied the clinical characteristics of the disease in 45 patients, among whom 4 were children, and 9 had a tumour. They reported that at onset, spasms, which were often painful, and stiffness/rigidity of the neck, trunk or limb muscles could be evidenced in 69% of cases, whereas diplopia, ptosis and nystagmus were found in 40%. Sensory symptoms such as pruritus, dysesthesia and hyperaesthesia were detected in 22% of patients. Finally, cognitive disturbance was evidenced in 29% and seizures in 13% [94]. There has not been a systematic evaluation of autoantibodies in pediatric patients with anti-GlyR encephalitis, though the relationship of specific antibody detection with treatment or outcomes is still far to be unraveled [95].

3.5 Anti-γ-aminobutyric acid receptors (GABARs) encephalitis.

GABARs are a class of receptors that respond to the neurotransmitter γ-aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the vertebrate CNS. $GABA_A$Rs are ligand-gated ion channels that allow the flux of Cl^- and fast synaptic inhibition; $GABA_B$Rs are metabotropic receptors expressed in both the CNS and PNS, which predominantly couple to Gi/o proteins: the effect is primarily inhibitory *via* inhibition of presynaptic voltage-gated Ca^{2+} channels, activation of postsynaptic K^+ channels, and inhibition of adenylyl cyclase [96]. Knockout mice lacking functional $GABA_B$Rs have spontaneous seizures leading to premature death, decreased pain threshold, increased locomotor activity and cognitive deficits [97]. The genetic modification of $GABA_B$R genes is associated with the development of temporal lobe epilepsy [98], schizophrenia [99] and obsessive-compulsive disorders [100]. High serum and CSF titers of anti-$GABA_A$R antibodies that cause a selective reduction of the target antigen have been associated with severe forms of encephalitis characterized by seizures, refractory status epilepticus, or both. A portion of patients with anti-GABAR encephalitis might have a favourable response to immunotherapy [101].

Regarding the clinical manifestations of anti-$GABA_B$R encephalitis in humans, the first report was by Lancaster et al. [102], who found an association between these autoantibodies and the development of LE with severe seizures. Cerebellar ataxia, opsoclonus-myoclonus, and brainstem involvement were also described [103–105]. A recent study by Cui et al. [106], referred to 11 adult patients, showed that the disease occurs mainly in males (7/11), being associated with cancer in approximately 50% of cases (5/11), and is characterized by cognitive decline (9/11), epilepsy (10/11), mental and behavioural disorders (6/11), involuntary movements (4/11), sleep disorders (2/11), hearing loss (1/11), disturbance of consciousness (4/11) and fever (3/11). At the EEG, abnormal discharge and epileptiform activities were also observed in 10/11 and 5/11 patients, respectively. Moreover, brain MRI revealed abnormalities in the hippocampal region, parahippocampal gyrus, temporal lobe and occipital lobe in 4/11 cases. The response to first-line therapy was good in 8/11 cases. Substantially similar results were reported by Qiao et al. [106] in a smaller study sample, confirming that anti-$GABA_B$R encephalitis is diagnosed mainly in males with cancer. Seizures were the most common initial symptom, and all patients developed a typical LE during their disease course. Response to immunosuppressive therapies was good in tumour-free patients. Recently, a previously healthy child presenting with catatonia and encephalopathy without seizures due to antibodies against the $GABA_A$R has been reported [107].

3. Conclusive remarks

Although clinical manifestations of autoimmune encephalitides can significantly vary and different autoantibodies have been associated with similar phenotypes, the global evaluation of clinical picture, EEG and brain MRI can predict a well-defined disorder in a significant number of cases. As one of the cerebral areas more frequently involved in autoimmune encephalitis is the limbic system, the presence of limbic alteration at MRI is frequently associated with rapidly progressive short-term memory loss, psychiatric symptoms and seizures, leading to the consideration of LE and autoantibodies against intracellular antigens or against LGI1 or Caspr2. A prominent psychosis should lead to

Table 2
Main general features of autoimmune encephalitides in the pediatric age.

Disease	*Clinical features*	*EEG abnormalities*	*Brain MRI findings*	*Response to treatment*
Anti-glutamic acid decarboxylase encephalitis	Limbic encephalitis, stiff person syndrome, cerebellar ataxia, ocular movement disorders, refractory epilepsy, dysautonomia, transient global amnesia	Interictal epileptiform discharges	Asymmetric bilateral T2 or FLAIR hyperintensities in the hyppocambus, amygdala and temporal lobes	Poor
Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis	Abnormal movements (chorea, athetosis, tremors, ataxia, limb or oromandibular dystonia, limb or facial myorhythmia, blepharospasm, opisthotonus), seizures; psychiatric symptoms (catatonia, hallucinations) are less frequently observed in children	Abnormal nonspecific focal or diffuse slowing; epileptiform discharges, polymorphic delta rhythm, diffuse beta activities and extreme delta brush	Negative in up to 50–70% of patients; T2 or FLAIR hyperintensities in the hippocampus, frontobasal and basal ganglia regions	Full recovery in most patients
Anti-voltage-gated potassium channel (VGKC)-complex encephalitis	Limbic encephalitis, epilepsy, polyneuropathy, fasciculations, autonomic symptoms, cognitive impairment	Multifocal interictal epileptiform discharges and interictal slow-wave activity	T2 hyperintensity in the temporal lobes	High rate of recurrences
Anti-glycine receptor (GlyR) encephalitis	Encephalomyelitis with rigidity and myoclonus (PERM), stiffness, muscle spasms, myoclonus, hemiballism, autonomic dysfunctions and hyperekplexia	Epileptiform discharges	No abnormal features in most cases	Good
Anti-γ-aminobutyric acid type A receptor ($GABA_AR$) encephalitis	Severe encephalitis, seizures and/or refractory status epilepticus	Refractory status epilepticus, epileptiform activities	Multifocal T2/FLAIR hyperintensities involving the temporal lobes	Favourable
Anti-γ-aminobutyric acid type B receptor ($GABA_BR$) encephalitis	Limbic encephalitis, severe seizures, cerebellar ataxia, opsoclonus-myoclonus, cognitive decline, behavioural disorder	Abnormal discharge, epileptiform activities	Abnormalities in the hippocampal region, parahippocampal gyrus, temporal and occipital lobes	Favourable

identify anti-NMDAR encephalitis or AMPA-related encephalopathy, while cerebellar degeneration is indicative of the involvement of Yo, Hu, VGKC, $GABA_BR$, Caspr2 or GAD 65 antigens.

An attempt to define diagnostic criteria for the different types of autoimmune encephalitides has been made by Graus et al. [6], who concluded that it is possible to proceed through a logical differential diagnosis even in the absence of antibody identification. This method allows the decision to start therapies before results of antibody tests become available. Indeed, prognosis of autoimmune encephalitides seems strictly associated with early start of therapy [41]. However, a logical differential diagnosis of these disorders using clinical, laboratory and radiological findings seems possible mainly for adults and not for children. As previously reported for anti-NMDAR encephalitis, signs and symptoms of autoimmune encephalitis can differ significantly in the pediatric age (see Table 2). Screening for malignancy is mandatory also in children to rule out a neoplastic syndrome.

There are no evidence-based treatment standards for autoimmune encephalitides, though many clinicians have become confident with the prompt use of high-dose methylprednisolone in combination with IVIG. Differently than in other pediatric rheumatologic conditions like Kawasaki disease, in which IVIG has a proved clear effectiveness [108], its efficacy through different regimens of administration has been reported in only few children with autoimmune encephalitis with potential benefits related to the supply of idiotypic antibodies or complement inhibition [109]. Other types of immunotherapies could also be considered in the postinfectious cases, such as immunoadsorption (antibody-removing therapy), which should be started as promptly as possible to warrant the best results in terms of neurological outcome, though several weeks or months might be required to show a clear effectiveness [18,110].

More research on differential blood-brain barrier permeability would resolve many questions about autoantibody entry and pathogenesis of autoimmune encephalitides, clarifying the usefulness of biologic treatment. Differently than in other multidrug-resistant vasculitic syndromes with CNS or SNP involvement, like pediatric-onset Behçet's disease, in which biologic therapies have been administered with encouraging results [111], there are no data about anti-cytokine therapies in young patients with refractory autoimmune encephalitis. The only available results using drugs targeting the chemokine system in neurology are related to the treatment of multiple sclerosis [112], but these successful experiences cannot drive the use of specific biologic tools in patients with autoimmune encephalopathies. General outcomes are usually good in younger patients with autoimmune encephalitis, including children, and recovery rates over 80% have been reported also in pediatric patients [113].

In the end, the correlation between phenotype and autoantibodies involved in the neurological damage observed in younger patients with autoimmune encephalitides remains only partially defined, probably because the total number of children adequately studied is relatively small. This means that future multicenter studies on the pediatric population with longer-term evaluation of outcome are needed in order to improve the diagnostic approach and personalize therapies specifically in the younger patients with autoimmune encephalopathies.

4. Take-home messages

- The hallmark of autoimmune encephalitis is antibody-mediated central nervous system autoimmunity, which is related to the development of antibodies recognizing neuronal receptors or synaptic proteins as foreign proteins.
- The pathogenic mechanisms that underlie autoantibody-triggered autoimmune encephalitides are poorly understood and how autoantibodies breach the blood-brain barrier remains obscure for almost all these disorders.
- Although clinical manifestations of autoimmune encephalitides can significantly vary and different autoantibodies can be associated

with similar phenotypes, the global evaluation of clinical symptoms, EEG findings and brain/spinal cord MRI can strongly suggest the diagnosis of a well-defined disorder in a relevant number of cases. However, many of these conditions remain considerably underdiagnosed in children.

- Various clinical features can herald the onset of encephalitic syndromes, but the dominating modality of onset is characterized by movement and psychiatric disorders.
- Seizures and movement disorders along with psychosis, confusion or additional behavioural changes are the most relevant initial manifestations in all age groups.
- There are few reports of pediatric autoimmune encephalitis in the medical literature and wide variations can be noted in both diagnostic procedures and treatments.
- The general approach to children with autoimmune encephalitis has been driven by global information related to adult patients.
- A host of autoantibodies has been found in the sera of patients with autoimmune encephalitis, and screening for malignancy is essential to rule out a neoplastic syndrome.
- Anti-glutamic acid decarboxylase (GAD) 65 encephalitis has been mostly reported in adults, variably presenting as limbic encephalitis, stiff person syndrome, cerebellar ataxia, ocular movement disorders, epilepsy, but also with extralimbic manifestations.
- Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is the most frequent autoimmune encephalitis in children: several infectious agents have been implicated in its pathogenesis, and its overall outcome is largely favourable.
- Voltage-gated potassium channels (VGKCs)-positive group of encephalitides starts as limbic encephalitis with cognitive impairment, seizures and variable neuropsychiatric symptoms.
- Facio-brachial dystonic seizures can be considered pathognomonic of anti-LGI1 encephalitis, which prevalently occurs in the elderly.
- Anti-glycine receptor (GlyR) and anti-γ-aminobutyric acid receptors (GABARs) encephalitides are phenotypically diverse neurobiological entities which have been mostly reported in adults.
- Future multicenter studies on the pediatric population with autoimmune encephalitis are needed to identify whether the phenotype clusters may direct therapy or predict treatment response and outcome.

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