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Autoimmune Encephalitis in Children

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Abstract

The causes of encephalitis are numerous, and extensive investigations for infectious agents and other etiologies are often negative. The discovery that many of these encephalitis are immune mediated has changed the approach to the diagnosis and treatment of these disorders. Moreover, the broad spectrum of symptoms including, psychosis, catatonia, alterations of behavior and memory, seizures, abnormal movements, and autonomic dysregulation usually requires a multidisciplinary treatment approach. This review focuses in several forms of encephalitis that occur in children, and for which an autoimmune etiology has been demonstrated (eg, anti-*N*-methyl-D-aspartate receptor encephalitis) or is strongly suspected (eg, Rasmussen encephalitis, limbic encephalitis, opsoclonus-myoclonus). The authors also review several disorders that may be immune mediated, such as the rapid onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) syndrome and some encephalopathies with fever and status epilepticus. Recognition of novel immune-mediated encephalitis is important because some of these disorders are highly responsive to immunotherapy.

Keywords

autoimmune, encephalitis, limbic, anti-NMDA receptor, NMDA

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Encephalitis refers to an inflammatory disorder of the brain resulting in altered mental status, seizures, or focal neurologic deficits, usually accompanied by signs of inflammation in the cerebrospinal fluid and magnetic resonance imaging (MRI) findings ranging from normal to extensive abnormalities. The causes of encephalitis are numerous, and most patients undergo extensive testing for infectious etiologies without discovery of a causative agent. A study by the California Encephalitis Project, a center focused in the epidemiology and etiology of encephalitis, found that 63% of the patients remained without an etiology after a battery of tests for 16 potential infectious agents.[1] The recent discovery that several forms of encephalitis result from antibodies against neuronal proteins has led to a definitive diagnosis in many of these cases. The antibodies target receptors and cell surface proteins involved in synaptic transmission, plasticity, or neuronal excitability, and associate with syndromes that despite being severe, frequently respond to immunotherapy (Figure 1).[2] The resulting syndromes vary according to the antibody, with phenotypes that resemble those in which the function of the antigen is modified pharmacologically or genetically. The disorder most frequent in the pediatric population is anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis in which the antibodies target the NR1 subunit of the receptor.[3]

The importance of immune-mediated encephalitis is reinforced by the relative frequency of some disorders. A multicenter study in the United Kingdom demonstrated that 4% of patients with encephalitis had NMDA receptor antibodies, making this disorder the second leading cause of immune-mediated encephalitis, after acute disseminated encephalomyelitis.[4] In the California Encephalitis Project the frequency of anti-NMDA receptor encephalitis surpassed that of any viral encephalitis.[5]

This review focuses in autoimmune encephalitis in children, including those with antibodies against cell surface or synaptic proteins, and others that are strongly suspected to be immune mediated, but the immune mechanisms have not been elucidated.

Anti-NMDA Receptor Encephalitis

This disorder has become a leading cause of autoimmune encephalitis in children and adolescents, with 40% of patients being younger than age 18 years.[6] The syndrome is highly predictable

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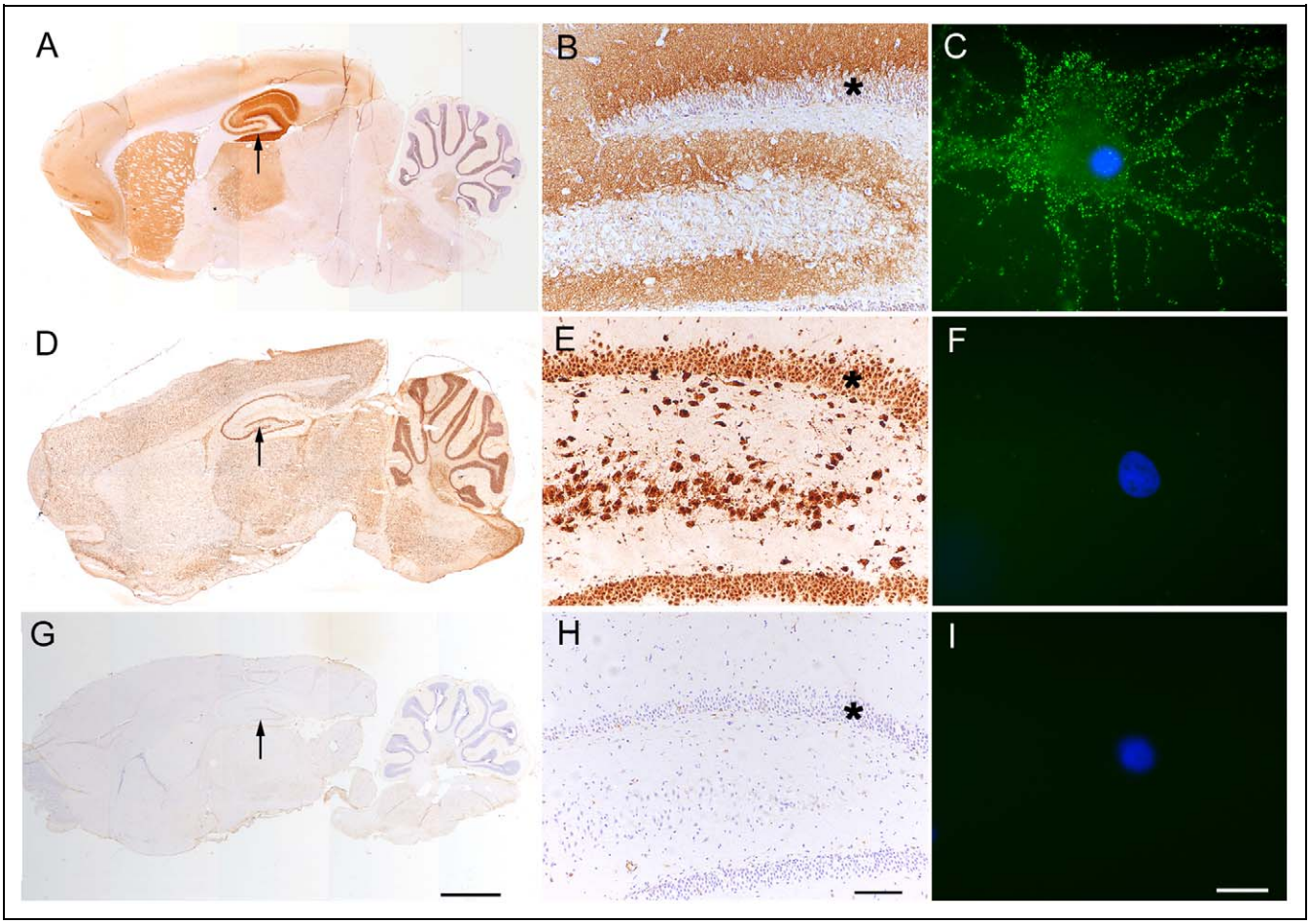

Figure 1. Demonstration of neuronal antibodies with immunohistochemical techniques. Immunohistochemistry of rat brain using cerebrospinal fluid from patients with antibodies to *N*-methyl-D-aspartate (anti-NMDA) receptor (A), Hu (D), and a normal individual (G). The arrows point to areas shown at higher magnification in B, E, and H. Note that the pattern of reactivity of NMDA receptor antibodies (which antigen, NMDA receptor, is expressed on the cell surface and synaptic regions) is different from the pattern of reactivity of Hu antibodies (which target, HuD, is intracellular). In B, E, and H the asterisk indicates the dentate gyrus. C, F, and I show the corresponding cerebrospinal fluids reacting with live nonpermeabilized cultures of rat hippocampal neurons. Only the NMDA receptor antibodies react with the cell surface of live neurons (green staining in C); the Hu antibodies do not show reactivity because the antibodies do not penetrate the cell (F); therefore, there is lack of reactivity similar to that seen with the cerebrospinal fluid control (I). In C, F, and I, the nuclei of the neurons is shown with DAPI. (Bar in G = 2000 μm, bar in H = 100 μm, bar in I = 20 μm.) Careful assessment of novel antibodies using similar techniques is important because antibodies against cell surface antigens usually associate with syndromes that are responsive to immunotherapy whereas antibodies against intracellular antigens associate with disorders that are less treatment-responsive.

in adults and teenagers and usually evolves in stages, including a prodromal phase of fever, headache, or viral-like symptoms that often goes unnoticed. This is followed within a few days or weeks by the onset of psychiatric and behavioral problems including anxiety, bizarre behaviors, paranoid thoughts, grandiose or hyperreligious delusions, and insomnia that progress to decreased level of consciousness, seizures, dyskinesias, choreoathetoid movements or postures, and breathing or autonomic instability.[3,7]

In young children, the syndrome is similar, but the presenting symptoms may be different. A recent study of 500 patients including 180 of ages 18 years or less, showed that the most common presenting symptoms in children under the age of 12 years were abnormal behavior, seizures, and movement disorders.[8] The behavioral changes included new-onset temper tantrums, agitation, aggression, and changes in mood or personality. Many parents report changes in speech, including reduced speech, mutism, echolalia, or perseveration.[9,10]

Regardless of the initial presentation, more than 90% of patients develop at least 3 of the following groups of symptoms within 1 month of disease onset: psychiatric features, memory disturbance, speech disorder, seizures, dyskinesias, decreased level of consciousness, autonomic instability, or hypoventilation.[8] Therefore, one should be cautious diagnosing anti-NMDA receptor encephalitis in patients who after several weeks of disease onset have developed only 1 or 2 of the above symptoms. In these cases, the possibility of a false-positive

serologic test should be considered, in particular when low levels of antibodies are found in serum but not in cerebrospinal fluid (Dalmau, unpublished data).

Autonomic dysfunction that is common in adults occurs less frequently in children. Although more than 42% of adults develop hypoventilation, this occurred in only 16% of one series of children.[8] Other signs of autonomic dysfunction in children include urinary incontinence and episodes of tachycardia, hypertension, or hyperthermia. However, in contrast to adults, severe cardiac dysrhythmia and clinically significant cardiac pauses are less frequent in children.[9] Virtually all patients—children and adults—develop erratic sleep patterns, insomnia, and less frequently hypersomnia.[9,10]

In a series of 100 patients that included children and adults, the MRI of the brain was abnormal in 55% of the cases, including cortical and subcortical T2-fluid-attenuated inversion recovery signal abnormalities, sometimes with transient cortical-meningeal enhancement.[3] Similar findings can occur in the brainstem and cerebellum despite that symptoms related to these structures are rare. In children, the frequency of MRI abnormalities is less than in adults; in a series of 32 patients, 31% had abnormal MRI.[9] In contrast, the cerebrospinal fluid was abnormal in 94% of the cases, showing lymphocytic pleocytosis and less frequently increased protein synthesis or oligoclonal bands. In patients with normal initial cerebrospinal fluid studies (cell count, protein, and glucose concentration), oligoclonal bands may be identified, and repeat analysis performed a few days later often reveals pleocytosis.

The electroencephalogram (EEG) is abnormal in almost all patients. It usually shows diffuse slowing of the background in the delta-theta range, although some patients may have focal slowing. A recent study identified in 30% of adult patients with anti-NMDA receptor encephalitis a unique EEG pattern, called ''extreme delta brush'' because of its resemblance to the delta brush (beta-delta complexes) pattern in premature infants. Although the neonatal pattern is commonly symmetric but not synchronous and is less common in frontal regions, the extreme delta brush pattern typically appears as a nearly continuous combination of delta frequency transients with superimposed fast activity (usually in the beta range) occurring symmetric and synchronous involving all head regions. The extreme delta brush pattern is independent of sedation and episodes of dystonia or abnormal movements.[11] Whether this pattern also occurs in children with anti-NMDA receptor encephalitis is under investigation. Electrographic seizures during continuous EEG monitoring occur in approximately 60% of the patients.[11] Whether continuous monitoring is important has been stressed in several reports of patients with nonconvulsive status epilepticus.[12]

The diagnosis of the disorder is confirmed by demonstrating NMDA receptor antibodies in serum or cerebrospinal fluid. A comparison of normalized IgG levels in serum and cerebrospinal fluid indicates the presence of intrathecal synthesis of antibodies in virtually all patients.[3,13] The levels of antibodies in cerebrospinal fluid correlate better with symptom outcome than those of serum.[14] Studies using cultures of dissociated rat hippocampal neurons and injection of antibodies into the hippocampus of rodents show that patients' antibodies cause a titer-dependent decrease of synaptic NMDA receptor clusters, without affecting cell viability, dendritic complexity, and other synaptic receptors. These effects correlate with the titer of antibodies and are reversible on removing the antibodies from the culture media.[15] These findings and the lack (or minimal involvement) of complement-mediated mechanisms explain the potential reversibility of symptoms even in patients who have been severely ill or with low level of consciousness for several months.[14,16]

In children, the presence of an underlying tumor, teratoma or other, is uncommon. Although approximately 56% of women older than 18 years have unilateral or bilateral teratomas of the ovary, these tumors occur in 30% of women younger than 18 years, and 9% of girls younger than 14 years.[9] In men, the presence of teratoma of the testis is rare, and this tumor has not been reported in young boys with anti-NMDA receptor encephalitis. MRI of the abdomen and pelvis is the test of choice to identify teratomas of the ovary in young girls.

Although no standard of treatment has yet been established, there is evidence that removal of the tumor, when appropriate, and prompt immunotherapy improve outcome.[6] Most children receive first line of immunotherapies including corticosteroids, intravenous immunoglobulin, or plasma exchange. However, because these treatments fail in 30% to 40% of the patients, and because there is an increasing number of reports showing that rituximab is effective, this drug is increasingly being used in combination with intravenous immunoglobulin and steroids, or after first-line immunotherapies.[10,17,18] Rituximab and cyclophosphamide, alone or combined, are often effective in adults, but because of the potential adverse effects of cyclophosphamide (malignancies, infertility, premature gonadal failure) most pediatricians only use cyclophosphamide when the above treatments have failed.[8] In these cases, cyclophosphamide is often effective.[19]

Approximately 80% of patients have substantial or full recovery. An ongoing study assessing the long-term outcome of 500 patients (children and adults) indicates that some patients continue to improve 2 years after symptom presentation.[8] The symptoms that improve first are autonomic instability, dyskinesias, level of consciousness, and seizures. However, after recovering consciousness, the psychiatric manifestations can reemerge, and impulsivity, behavioral disinhibition, problems of attention, planning, social interaction, and memory deficits pose serious problems in the managing of these patients at home or in rehabilitation centers. Most of these centers have limited experience with the disorder, resulting in back-and-forth transfers with the hospital. A multidisciplinary approach involving nursing, psychiatrists, cognitive rehabilitators, and physiatrists among others, is highly rewarding for patients and families.[20-22]

It is not uncommon that fully recovered patients still have detectable levels of antibodies in serum or cerebrospinal fluid, suggesting a potential for reactivation of the immune response.[23] This finding likely explains the occurrence of

Table 1. Differential diagnosis of anti-NMDA receptor encephalitis in children

Disorder	Comments
Viral encephalitis	Usually, this is the first presumptive diagnosis suggested by the acute neurologic change, cerebrospinal fluid pleocytosis and occasional hyperthermia. In general, most viral encephalitides (except rabies) occur with higher levels of cerebrospinal fluid pleocytosis and protein concentration. Psychosis and dyskinesias are significantly less frequent than in anti-NMDA receptor encephalitis.[5]
New onset psychosis	Because most patients with anti-NMDA receptor encephalitis present with psychosis, a primarily psychiatric disorder is frequently considered.[20] As the disease evolves, the development of neurologic symptoms usually reveals the diagnosis. In a study of 100 patients, 77 were initially seen by psychiatrists or admitted to psychiatric centers, and some underwent electroconvulsive therapy before the diagnosis of anti-NMDA receptor encephalitis was made.[3]
Drugs	In young patients, the acute development of personality and behavioral changes, and symptoms suggesting involvement of dopaminergic pathways (rigidity, dystonia, orofacial movements) usually lead to consider drug abuse (eg, ketamine, phencyclidine, among others). Many patients undergo toxicologic screening in emergency departments or at hospital admission.
Neuroleptic malignant syndrome (NMS)	The occurrence of altered level of consciousness, episodes of rigidity, hyperthermia, and autonomic instability often suggest the diagnosis of NMS. In addition, some patients with anti-NMDA receptor encephalitis have elevated serum creatine kinase and signs of rhabdomyolysis (which can occur in the absence of antipsychotic medication). The use of neuroleptics to control the abnormal behavior at early stages of the disease adds further confusion between both syndromes. The presence of dyskinesias and catatonic features suggest anti-NMDA receptor encephalitis.[24]
Limbic encephalitis (LE)	Criteria of LE have been well defined.[25] Patients with LE do not have dyskinesias or central hypoventilation; the MRI usually shows abnormalities restricted to the medial temporal lobes, and the EEG findings (epileptic or slow activity) are also restricted to the temporal lobes.
Encephalitis lethargica	This is an ill-defined entity, likely representing multiple disorders. Criteria include[26]: acute or subacute encephalitis with at least 3 of the following: signs of basal ganglia involvement; oculogyric crises; ophthalmoplegia; obsessive-compulsive behavior; akinetic mutism; central respiratory irregularities; and somnolence and/or sleep inversion. Two studies showed that $\sim$50% of patients categorized as encephalitis lethargica hyperkinetica had in fact anti-NMDA receptor encephalitis.[1,27]
Childhood disintegrative disorder / late onset autism	Children with anti-NMDA receptor encephalitis often show cognitive regression, rapid loss of language function, autistic features, and seizures, suggesting a childhood disintegrative disorder (CDD). Although the prognosis of CDD is poor, most patients with anti-NMDA receptor encephalitis respond to immunotherapy and have substantial clinical recovery.[28]
Kleine-Levin syndrome	Symptoms of hypersomnia, compulsive hyperphagia, hypersexuality, apathy, and childlike behavior, which are typical components of Kleine-Levin syndrome, can occur transiently during the process of recovery of anti-NMDA receptor encephalitis, or as permanent sequelae.[29]
Inborn errors of metabolism	Glutaric aciduria type I can present in previously asymptomatic patients as episodes of encephalopathy with dystonia, coinciding with an infection or febrile process.[30] Several inborn errors of metabolism can also occur with acute or subacute encephalopathy with extrapyramidal signs, including 3-methylglutaconic aciduria, creatine transport deficiency, mitochondrial disorders (Leigh syndrome) and Wilson, Hallervorden-Spatz, and Lesch-Nyhan syndromes.
Monoamine neurotransmitter disorders	Deficiency of dopamine, serotonin, or both can result in encephalopathy, epilepsy, and pyramidal and extrapyramidal symptoms. The diagnosis is established by examining the cerebrospinal fluid for levels of these neurotransmitters.[31]

clinical relapses in 20% of children with anti-NMDA receptor encephalitis. The efficacy of chronic immunosuppression with azathioprine or mycophenolate mofetil in preventing relapses is unknown.

The differential diagnosis of anti-NMDA receptor encephalitis is extensive and varies according to the stage of the disease (Table 1). The most frequently considered disorders are viral encephalitis, neuroleptic malignant syndrome, acute psychosis, and drug abuse.

Limbic Encephalitis

This disorder refers to an inflammatory process of the limbic system, including the medial temporal lobes, amygdala, and

cingulate gyrus.[25,32] Despite being one of the best clinically and radiologically characterized autoimmune encephalitis, it is also one of the most frequently misdiagnosed.[33,34] Unfortunately, any type of encephalopathy resulting in seizures and alteration of memory and behavior is frequently labeled as "limbic encephalitis." As a result, data based on literature searches using the term *limbic encephalitis* are not reliable. This disorder was initially identified in 1968 as a paraneoplastic syndrome associated with small-cell lung cancer.[35] Since then, a number of immune responses, paraneoplastic and nonparaneoplastic, have been identified, all resulting in a similar syndrome, albeit with different pathogenic mechanisms, treatment, and prognosis.[36]

In adults, the most frequent immune-mediated limbic encephalitis occurs in association with antibodies against the neuronal secreted protein called leucine-rich glioma-inactivated 1 (LGI1).[37,38] These antibodies were previously thought to target the voltage-gated potassium channel.[39] LGI1 is a secreted neuronal protein that interacts with the presynaptic and postsynaptic proteins ADAM23 and ADAM22 that act to modulate synaptic transmission. The median age of patients with LGI1 antibody–associated limbic encephalitis is 60 years, and most do not have cancer. In addition to the characteristic severe short-term memory loss typical of all limbic encephalitis, patients with LGI1 autoimmunity often develop hyponatremia, and various types of seizures, including myoclonic-like movements, described as faciobrachial dystonic seizures or more properly as tonic seizures.[40,41] About 70% of the patients improve with corticosteroids, plasma exchange, or intravenous immunoglobulin.[37]

Other less frequent types of autoimmune limbic encephalitis in adults are paraneoplastic and can occur with antibodies against intracellular antigens (eg, Hu, CRMP5, Ma2) or against cell surface or synaptic proteins (eg, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, γ-aminobutyric acid B [GABA(B)] receptor, metabotropic glutamate receptor 5 [mGluR5]).[42-44] Detection of antibodies against intracellular antigens suggests the presence of cytotoxic T-cell–mediated mechanisms and poor symptom response to immunotherapy. In contrast, detection of antibodies against cell surface or synaptic proteins usually associates with syndromes that are more responsive to immunotherapy.[36]

In children, autoimmune or paraneoplastic limbic encephalitis is exceptional. A recent European multicenter study described 10 patients younger than 18 years, 8 of them with antibodies against neuronal proteins (1 Hu, 1 Ma2, 2 glutamic acid decarboxylase 65 (GAD65), 2 voltage-gated potassium channel–protein complex antibodies, and 2 both GAD65 and voltage-gated potassium channel–protein complex antibodies). The patient with Hu antibodies was a 3-year-old girl with an underlying ganglioneuroblastoma; none of the other patients had a tumor.[45] In another report, GAD65 antibodies were identified in a 16-year-old girl with limbic encephalitis and common variable immune deficiency.[46] Prior to these studies, only 5 patients younger than 16 years with limbic encephalitis were reported in the English literature and all were paraneoplastic (2 Hodgkin's lymphoma, 1 leukemia, 1 neuroblastoma and 1 small-cell carcinoma of the ovary).[47-50]

The Ophelia syndrome is a form of limbic encephalitis that occurs in association with Hodgkin's lymphoma, a tumor that can affect children and young adults.[47] The prompt recognition of this disorder is important because it usually precedes the diagnosis of the lymphoma and shows a remarkable response to oncologic and immunologic therapies. A recent study showed that 2 patients with the Ophelia syndrome, one of them a 15-year-old boy, had antibodies against mGluR5, a receptor involved in learning and memory. Both patients had excellent neurologic recovery.[44]

Hashimoto Encephalopathy

This is an ill-defined disorder in which the syndrome and immunological findings are unclear. There are approximately 30 pediatric cases reported in the English literature.[51-55] In a review of 25 patients, 52% had hypothyroidism and 48% normal thyroid function; however, some patients can develop hyperthyroidism.[51,56] For this reason and because not all patients respond to steroids, the term *encephalopathy associated with autoimmune thyroid disease* is considered more accurate than the previous *steroid-responsive encephalopathy associated with autoimmune thyroiditis*.[56,57] Clinical features are not specific and can include stroke-like symptoms, tremor, myoclonus, transient aphasia, sleep and behavior abnormalities, hallucinations, seizures, and ataxia. The cerebrospinal fluid protein level may be elevated, and EEG studies show generalized slowing.[51,58] Brain MRI is usually normal, although it can show diffuse white matter abnormalities and meningeal enhancement that can resolve with steroid therapy.[59]

The disorder is defined by the detection of thyroid peroxidase antibodies in patients with the above symptoms that respond to corticosteroids. These antibodies occur in approximately 10% of healthy adults[60,61] as well as in patients who have more relevant antibody-associated disorders, such as GABA(B), LGI1, or NMDA receptor antibodies.[9,43,62] Therefore, it is not uncommon that patients with these synaptic autoimmune disorders are initially misdiagnosed with Hashimoto encephalopathy. In a study of 303 asymptomatic children, thyroid peroxidase antibodies were identified in 10% of cases (nonencephalopathic and most cases euthyroid); many of these 10% of cases had ultrasound studies suggesting autoimmune thyroiditis.[61] Currently, thyroid peroxidase antibodies should be viewed as a marker of autoimmunity rather than a neurologic disease–specific or pathogenic antibody, and the finding of thyroid peroxidase antibodies should not prevent testing for more relevant antibodies.

Although the disorder is described as steroid-responsive, a review of 25 pediatric patients (85.8% girls) with a median age of 14 years showed that only 55% had complete recovery.[51] In some instances, plasma exchange or intravenous immunoglobulin have been effective.[52,53]

Rasmussen Encephalitis

This is an inflammatory encephalopathy characterized by progressive refractory partial seizures, cognitive deterioration, and

focal deficits that occur with gradual atrophy of one brain hemisphere.[63] The disorder frequently presents in 6- to 8-year-old children, although adolescents and adults can be affected.[64] The etiology is unknown and, therefore, multiple theories have been proposed. In 1994, Rogers and colleagues described the presence of antibodies against the GluR3 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor in a few patients.[65] An animal model with these antibodies and symptoms resembling the disorder triggered enthusiasm for the humoral autoimmune theory, but many patients do not respond to plasma exchange or other immunotherapies, and the presence of GluR3 antibodies has not been reproduced by other investigators.[66] Antibodies against munc 18-1, a protein involved in modulating the release of neurotransmitter vesicles, have also been suggested as potentially pathogenic.[67]

Based on pathologic studies showing infiltrates of T lymphocytes, other investigators have suggested that the disorder is mediated by cytotoxic T-cell mechanisms against neurons expressing MHC class I after perhaps a focal viral infection.[63,68] Granzyme-B, a proinflammatory modulator released by cytotoxic T lymphocytes, would contribute to neuronal degeneration.[69] On the other hand, Bauer et al[70] have proposed that astrocytes could be the target of the autoimmune mechanisms. However, none of these mechanisms satisfactorily explains the unilateral brain involvement characteristic of this disorder.

Treatment with high-dose methylprednisolone and intravenous immunoglobulin can ameliorate symptoms at early stages of the disease, supporting the theory of an autoimmune etiology.[63] Rituximab and intraventricular α-interferon have been effective in a few isolated cases.[71-73] A series of 7 patients treated with tacrolimus showed that compared with a cohort of nontreated patients, patients treated with tacrolimus had better outcomes of neurologic function and slower progression of cerebral hemiatrophy, but not improvement of seizure control.[74]

The only definitive treatment is functional hemispherectomy that consists in surgical disconnection of the affected hemisphere.[63,75]

Other Encephalitis Associated With Epilepsy or Status Epilepticus

The discovery of treatment-responsive encephalitis associated with antibodies against cell surface or synaptic proteins has resumed the interest for a potential autoimmune basis of several devastating encephalopathies with refractory seizures that are suspected to be induced by fever or an inflammatory process. Some of the terms used to describe these disorders include "Acute Encephalitis with Refractory Repetitive Partial Seizures (AERRPS),"[76] "Fever-Induced Refractory Epileptic Encephalopathy Syndrome (FIRES),"[77] and "Devastating Epilepsy of School-aged Children (DESC)."[78] The biphasic clinical course of these disorders has suggested a possible infection-triggered autoimmune process.[77,79] Although cerebrospinal fluid oligoclonal bands, or serum antibodies to GAD65, GluR-epsilon2, voltage-gated potassium channel, and GluR3 have been found in a few patients, the significance of these antibodies in this clinical context is unclear. The lack of response to most treatments, including immunotherapy, casts doubts on an autoimmune pathogenesis. This is supported by a recent report of 10 patients with FIRES who were examined for mutations on sodium channel alpha1 subunit (SCN1A) and also for antibodies to voltage-gated potassium channel–associated proteins, and were found negative for both.[80]

A recent study of 10 children with unexplained encephalitis presenting with encephalopathy and status epilepticus showed that 4 patients had antibodies to protein complexes related to voltage-gated potassium channel (LGI1 and Caspr2 negative) without identifying the target antigen. Only 1 of these 4 patients responded to immunotherapy, suggesting that the antibodies were against intracellular epitopes or pathogenically unrelated to the disease. Residual symptoms included cognitive impairment, temporal lobe epilepsy, and mesial temporal sclerosis.[81]

Opsoclonus-Myoclonus

This disorder occurs in children and adults although it probably represents different diseases and pathogenic mechanisms. In children, the syndrome usually develops in the first 2 years of life (mean, 20 months), presenting with irritability, ataxia, falling, myoclonus, tremor, and drooling. Additional symptoms can include refusal to walk or sit, speech problems, hypotonia, and the typical features of opsoclonus characterized by rapid, chaotic, multidirectional eye movements without saccadic intervals. Because opsoclonus may be absent at symptom presentation, patients can initially be diagnosed with acute cerebellitis or labyrinthitis.[82] At least 50% of pediatric patients have an underlying tumor, mostly a neuroblastoma.[82] The autoimmune etiology is suggested by the rapid development of symptoms, accompanied by cerebrospinal fluid abnormalities suggesting B-cell activation, and the rapid, albeit frequently incomplete response to various forms of immunotherapy, including corticosteroids, intravenous immunoglobulin, rituximab, and cyclophosphamide.[82-84] The presence of antibodies against neuronal proteins has been suggested in several studies, although the identification of a specific autoantigen has been elusive.[85,86]

Although treatment often improves opsoclonus-myoclonus, residual behavioral, language, and cognitive problems persist in the majority of patients, requiring special education.[82,87,88] Speech problems include word-finding difficulties, expressive aphasia, and dysarthria.[87] In the largest study focused on residual symptoms or sequelae, 79% of the patients had episodes of rage, 65% oppositional-defiant behavior, 58% obsessions-compulsions, 47% hyperactivity, 29% depression, and 19% deficit of attention. In addition, insomnia and abnormal response to pain were common.[82] Relapses occur in 50% of the patients, usually as a result of intercurrent infections or drug tapering. Delay in treatment appears to associate with a worse neurologic outcome; therefore, in cases with neuroblastoma, removal of the tumor should not delay the start of immunotherapy.[82,87]

Although the disorder probably results from an inflammatory or immune mediated process involving the cerebellum and

brainstem, the pathogenesis of the alterations of behavior, cognition, speech, and sleep is unclear. The role of a cerebellar dysfunction (eg, cognitive-affective syndrome) in some of these symptoms is a matter of debate.

Late Onset Central Hypoventilation With Hypothalamic Dysfunction

This disorder, also known as rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD), usually affects children who had normal development until 2 to 4 years of age, and then develop rapid onset of hyperphagia, gain of weight, and abnormal behavior (social disinhibition, irascibility, impulsivity, lethargy, outburst of euphoria and laughing, impaired concentration), followed by autonomic dysfunction (abnormal pupillary responses, thermal dysregulation, gastrointestinal dysmotility), and central hypoventilation.[89] Other symptoms of hypothalamic dysfunction can include hyperprolactinemia, hypernatremia due to adipsia, hypothyroidism, hypersomnia, growth hormone deficiency, hypogonadotropic hypogonadism and glucocorticoid deficiency.[90] Depending on the series, the frequency of an underlying neural crest tumor (ganglioneuroma, neuroblastoma, or ganglioneuroblastoma) ranges from 33% to 100%.[89,90]

A possible genetic origin has been suggested because of the similarities of this syndrome with the congenital central hypoventilation syndrome (or Ondine's curse) related to a *PHOX2B* mutation, which also associates with autonomic problems (Hirschsprung disease) and neural crest tumors.[89,91] However, congenital central hypoventilation syndrome usually presents in the neonatal period with central hypoventilation during sleep, and unlike ROHHAD does not associate with behavioral and hypothalamic symptoms. There is no clear evidence that ROHHAD has a genetic cause, although the disorder has been reported in siblings.[91] Several studies for mutations in candidate genes, such as *PHOX2B*, *TRKB*, *BDNF*, *ASCL*, and *NECDIN* did not found genetic alterations.[89,91]

An autoimmune or paraneoplastic etiology of ROHHAD syndrome is supported by the frequent association with neural crest tumors, the identification in some patients of genetic factors predisposing to autoimmunity,[91] and the finding of extensive infiltrates of lymphocytes and histiocytes in the hypothalamus of some patients.[92,93] The paradigm would be similar to the pediatric opsoclonus-myoclonus syndrome, which can occur with or without neuroblastoma, and neuropathologic and cerebrospinal fluid studies reveal variable signs of inflammation. In a patient with ROHHAD, treatment with intravenous immunoglobulin improved the change of behavior and adipsia, but did not affect the endocrinologic dysfunction.[94] Another patient experienced transient improvement with rituximab and long-term response to cyclophosphamide.[95]

Twenty-five percent of patients with ROHHAD die of central hypoventilation.[89] Prompt recognition of this disorder is important for early tumor screening, appropriate management of endocrine deficits, and close monitoring for the need of respiratory support.

Future Advances in Pediatric Autoimmune Encephalitis

Future advances in this group of disorders depend on a challenging approach to many ill-defined encephalitides known with descriptive terms or acronyms because of the limited knowledge on their etiology or pathogenic mechanisms. Rasmussen encephalitis, Hashimoto encephalitis, encephalitis lethargica, ROHHAD, even opsoclonus-myoclonus should all be viewed as umbrella terms likely representing different disorders and pathogenic mechanisms. A major lesson from the study of autoimmune limbic encephalitis in adults has been the discovery that this syndrome is the result of many disorders. This has been critical for the classification of limbic encephalitis according to the presence or absence of a tumor, predominant B- or T-cell immune mechanisms, different responses to immunotherapy (ranging from refractory to highly responsive), and different long-term prognosis.

In encephalitic processes of unclear etiology, autoimmune mechanisms should be considered when symptoms develop rapidly (in a few days or weeks), accompanied with signs of inflammation in the cerebrospinal fluid or neuroimaging studies, and the clinical and immunological features respond to immunotherapy. If serum and cerebrospinal fluid are negative for clinically relevant antibodies, they should be investigated in research laboratories. These criteria when applied to carefully selected groups of patients have led to the discovery of most of the relevant autoantibodies and target antigens discussed in this chapter, and will lead to the identification of new forms of pediatric autoimmune encephalitis.

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Author Contributions

TA and MP have reviewed the literature, developed the figures, and written the manuscript. JD has coordinated this work and supervised the writing.

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Ethical Approval

This review has been approved by the Ethics Committee of Hospital Clinic, University of Barcelona.

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