

Pediatric Autoimmune Encephalitis: Practical Aspects

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ABSTRACT

Autoimmune encephalitis is an inflammatory condition of the central nervous system that may involve a widely variable spectrum of clinical features. It can be divided into two main groups: with antibodies against intracellular antigens and with antibodies against surface antigens. The main clinical presentation is characterized by psychiatric symptoms, movement disorders and seizures. The differential diagnosis process should mainly consist of excluding infectious or other causes of encephalitis. Brain imaging, cerebrospinal fluid analysis and serology for a wide range of antibodies should lead to the diagnosis of a specific type of autoimmune encephalitis. Considering the fact that the disease may be paraneoplastic, appropriate tumor screening should be performed. Once the autoimmune etiology is established, treatment consists mainly of escalating immune therapies.

Keywords: autoimmune, encephalitis, clinical, differential, treatment.

INTRODUCTION

Autoimmune encephalitis refers to a group of central nervous system (CNS) inflammatory diseases (1, 2). It includes a variety of neurological and psychiatric syndromes. Autoimmune encephalitis can be divided into two major groups according to their pathophysiology: (a) associated with antibodies against intracellular antigens and (b) associated with antibodies against neuronal cell-surface or synaptic receptors (3).

(a) Autoimmune encephalitis associated with antibodies against intracellular antigens are mainly paraneoplastic and antigens are expressed by both the tumor and nervous system. The antibodies are called onconeural antibodies. The tumors more frequently involved in children are neuroblastoma, teratoma, and Hodgkin’s lymphoma (4). This type of autoimmune encephalitis leads to irreversible neuronal damage and it has a negative prog-

nosis (3, 5). Some examples are limbic encephalitis with anti-Hu antibodies, encephalitis with anti-Ma2 antibodies and encephalitis with anti-GAD (anti-glutamic acid decarboxylase) antibodies. Encephalitis with anti-Hu antibodies may involve the limbic system, brainstem and cerebellum. It may be associated with neuroblastoma, but pediatric patients may not have any underlying cancer (5, 6). Anti-Ma2 encephalitis may involve the limbic system, diencephalon and upper brainstem, and may be associated with testicular germ cell tumor (7). Anti-GAD encephalitis is characterized by refractory seizures originating in the temporal lobes and psychiatric symptoms (8).

(b) Autoimmune encephalitis associated with antibodies against cell surface antigens are directed against ion channels, receptors or other proteins on the neuronal surface. Antibodies are directly pathogenic by altering the synaptic function. Overall prognosis is better than in the case of au-

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Article received on the 14th of October 2020 and accepted for publication on the 8th of December 2020

toimmune encephalitis with antibodies against intracellular antigens. This type of autoimmune encephalitis is less often paraneoplastic, is more responsive to immunotherapy and more prevalent in children and young adults than encephalitis with antibodies against intracellular antigens (3, 9).

Examples of encephalitis with cell surface antigens include anti-GlyR (glycine receptors), anti-GABA-A, anti-GABA-B, anti D1R and anti-D2R (dopamine 1 and 2 receptors), anti-AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, a ionotropic transmembrane receptor for glutamate), anti-NMDA (N-methyl-D-aspartate receptor, a glutamate receptor).

Anti-GlyR encephalitis may associate cognitive dysfunction, seizures, opsoclonus-myoclonus syndrome and stiff-person syndrome (10). Encephalitis with antibodies against GABA-A and GABA-B receptors, the main inhibitory receptors of the brain, may involve severe seizures and status epilepticus (3). Anti-D1R and D2R encephalitis may involve the basal ganglia, while anti-AMPA encephalitis may involve the limbic system (1, 11).

Clinical presentation

The clinical picture in autoimmune encephalitis is heterogeneous and depends on the affected brain area. More areas may be affected at the same time, causing different combinations of symptoms, some of which can be grouped in clinically recognizable syndromes (3).

The onset of symptoms is subacute (< three months) and may be subsequent to events like infections, fever or traumas (11).

The initial presentation may be mainly with psychiatric symptoms (most of which mainly imply that the limbic system is involved) psychosis, hallucinations, aggression, catatonia, bizarre fear, insomnia, memory loss, decreased consciousness, lethargy, mania, etc. Nevertheless, psychiatric symptoms are less common in children with autoimmune encephalitis than adults, and the clinical spectrum is different in younger children, involving temper tantrums, behavioral change, agitation, aggression, progressive speech deterioration, hyperactivity and hypersexuality. Regarding patient management, it is important for the pediatric psychiatrist to be aware of the possibility of autoimmune encephalitis as a differential diagnosis, as patients with this type of initial presentation initially end up in the psychiatry service. The psy-

chiatrist should carefully investigate whether patients have neurological symptoms, particularly those with atypical psychiatric presentations and who do not respond to medical treatment as expected (13).

It is more common for children suffering from autoimmune encephalitis, especially NMDA-R encephalitis, than it is for adults to develop movement disorders or seizures early in the disease course (14). Movement disorders are mainly associated with NMDA-R encephalitis and may include orofacial–lingual dyskinesia, catatonia, tremor, bradykinesia, dystonia, choreoathetosis, and ballism. One or two movement disorders may co-exist. Choreoathetosis tends to be more frequent in children aged < 10. Given that orofacial–lingual dyskinesia may be associated with an ovarian tumor, it must be ruled out, especially in patients >10 years old (15).

Seizures or status epilepticus may occur at any stage in the disease course. It is more common in NMDA-R encephalitis and GABA-A-R encephalitis (14).

Autoimmune encephalitis, mainly GAD65 encephalitis, may also present as cerebellitis with symptoms including ataxia, limb or eye movements, vertigo, nystagmus, dysarthria. It has a negative prognosis, as it may associate irreversible loss of Purkinje neurons. Initial clinical presentation with subacute onset cerebellar syndrome is highly suggestive for an autoimmune etiology (3, 16).

Differential diagnosis

Differential diagnosis of autoimmune encephalitis includes mainly infectious encephalitis, but also metabolic or toxic causes, central nervous system vasculitis or malignancies and psychiatric disorders (13, 14, 17). Infectious encephalitis is the first to be ruled out, as both autoimmune and infectious encephalitis may associate fever and flu-like symptoms. Epidemiological data is of great importance in this situation (18). Bacterial, viral or fungal etiologies can be encountered in infectious encephalitis. Enteroviruses, Epstein-Barr-Virus, Human Herpesvirus-6, arboviruses can be tested through PCR from cerebrospinal fluid. In some cases, serology may be of additional benefit. *Mycoplasma pneumoniae* is particularly involved in infectious encephalitis in children. PCR analysis and serology are both recommended when it is suspected (19).

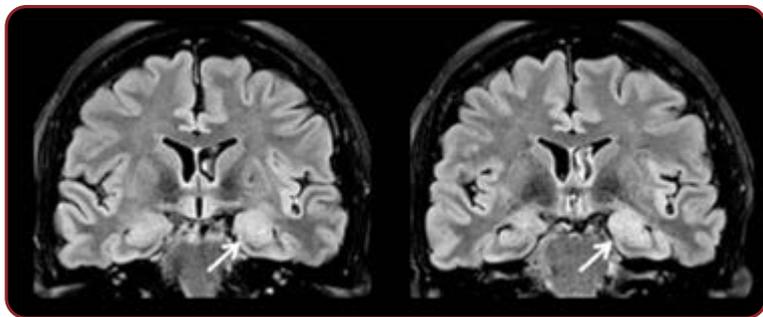


FIGURE 1. Magnetic resonance imaging reveals swelling and hyperintensity of the amygdala (arrow) on serial coronal fluid-attenuated inversion recovery sequences in a patient with limbic encephalitis. Reproduced with kind permission from John Wiley and Sons: Popkirov S, Sebastian S, Ismail FS, Wellmer J. Latent autoimmune diabetes and limbic encephalitis with antibodies against glutamic acid decarboxylase. *Journal of Diabetes* 2018;10(4):338-340.

Neuroimaging

Magnetic resonance imaging (MRI) may present features that are suggestive of autoimmune encephalitis. The affected area may be well defined, e.g., one or both medial temporal lobes with hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences, usually in limbic encephalitis. Hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences may also be found in multifocal areas involving grey and white matter. Nevertheless, MRI findings may also be absent, especially early in the course of disease and especially in NMDA-R encephalitis. In this particular situation, if the clinical suspicion of NMDA-R encephalitis is high, additional imaging proof may be obtained by FDG-PET imaging, that is more sensitive for detecting temporal lobe abnormalities (20).

Electroencephalogram (EEG)

Most of the times, EEG findings are not characteristic in autoimmune encephalopathies. They may present diffuse or focal epileptiform discharges, slow or disorganized activity. In NMDA-R encephalitis, one EEG pattern that is unique for this type of encephalitis was described. The authors called it “extreme delta brush” because it resembles delta brush neonatal EEG pattern (1, 21, 22).

Cerebrospinal fluid analysis and serology

Cerebrospinal fluid analysis may be normal in the first stage of the disease. However, it may bring additional information for diagnosis formulation. It may present lymphocytic pleocytosis, specific oligoclonal bands without evidence for infection or elevated protein levels. Cerebrospinal fluid neopterin may be used as an additional marker of inflammation in pediatric patients (9, 17, 23). Antibody testing should be performed from both serum and cerebrospinal fluid, because testing exclusively serum may lead to false-positive or false-negative results (1). Antibodies that should be tested were described in the introduction of this paper.

Pathogenic treatment

At the present moment, there is no international consensus regarding optimal treatment in pediatric autoimmune encephalitis. First-line therapy that is accepted includes methylprednisolone 30 mg/kg/day in a maximum dose of 1 g daily for 3–5 days, followed by, or combined with, intrave-

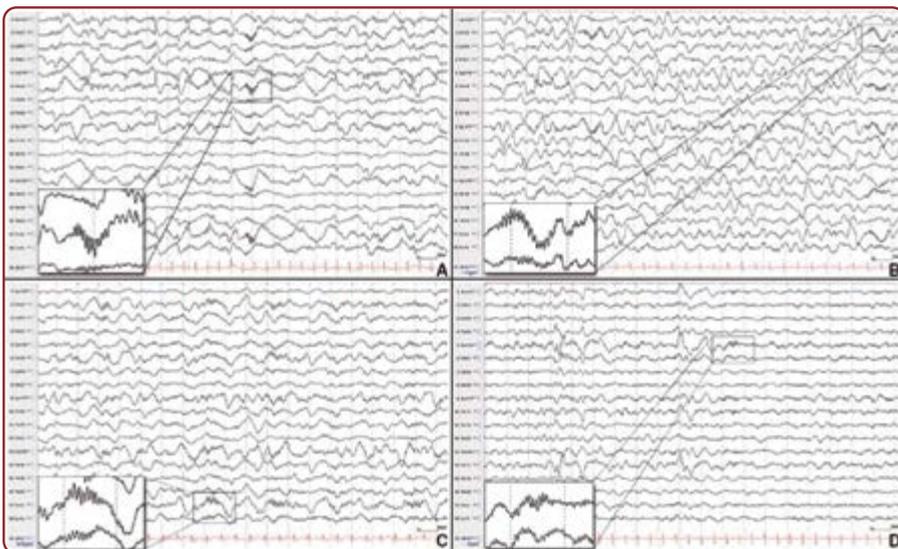


FIGURE 2. Extreme delta brush on a bipolar montage demonstrated in four patients. Reproduced with kind permission from John Wiley and Sons: Farias-Moeller R, Bartolini L, Staso K, Schreiber JM, Carpenter JL. Early ictal and interictal patterns in FIRES: the sparks before the blaze. *Epilepsia* 2017;58(8):1340-1348.

nous immunoglobulins 2 g/kg divided over 2–5 days. Corticosteroids are then tapered using 1–2 mg/kg/day orally for approximately another three months. If symptomatology persists and no amelioration is noted, plasma exchange should be taken into consideration, 3–5 exchanges over 10 days. If symptomatology persists even with corticosteroid treatment and plasma exchange, second-line immunomodulation therapy, consisting of rituximab 375 mg/m² weekly for four weeks, must be considered. Another option would be cyclophosphamide 750 mg/m² monthly (17).

Once the diagnosis of autoimmune encephalitis has been established, tumor screening should also be performed, even though underlying tumors are less frequent in pediatric patients than adult ones. Specific tumors may be associated with specific encephalitides, e.g., NMDA-R encephalitis with ovarian cancer. Identification and adequate treatment of the underlying tumor when applicable is of utmost importance (2).

Symptomatic treatment

Seizures should be appropriately treated. Mood dysregulation may be treated with valproic acid, gabapentin, and lithium, and extreme agitation with phenobarbital, trihexyphenidyl and opioids (24). □

CONCLUSIONS

Patients who are suspected of autoimmune encephalitis should be thoroughly evaluated clinically and a clear history should be taken. Furthermore, the differential diagnosis process should mainly consist of excluding infectious causes of encephalitis. Brain imaging, mostly MRI, cerebrospinal fluid analysis and serology for a wide range of antibodies should lead to the diagnosis of a specific type of autoimmune encephalitis. □

Conflicts of interest: none declared.

Financial support: none declared.

REFERENCES

- Bien PCG, Cellucci T, Cortese I, et al.** A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2017;4:391-404.
- Dalmaj J, Rosenfeld MR.** Autoimmune encephalitis update. *Neuro Oncol* 2014;6:771-778.
- Lancaster E.** The diagnosis and treatment of autoimmune encephalitis. *J Clin Neurol* 2016;1:1-13.
- Alavi S.** Paraneoplastic Neurologic Syndromes in Children: A Review Article. *Iran J Child Neurol* 2013;3:6-14.
- Honnorat J, Didelot A, Karantoni E, et al.** Autoimmune limbic encephalopathy and anti-Hu antibodies in children without cancer. *Neurology* 2013;24:2226-2232.
- Wright S, Vincent A.** Pediatric Autoimmune Epileptic Encephalopathies. *J Child Neurol* 2017;4:418-428.
- Mrabet S, Ben N, Kraoua I, et al.** Anti-Ma2-encephalitis in a 2 year-old child: A newly diagnosed case and literature review. *Eur J Paediatr Neurol* 2015;6:737-742.
- Achour N Ben, Younes T Ben, Rebai I, et al.** Severe dysautonomia as a main feature of anti-GAD encephalitis: Report of a paediatric case and literature review. *Eur J Paediatr Neurol* 2018;3:548-551.
- Li Y, Rae-Grant A.** Autoantibody-mediated encephalitis: Not just paraneoplastic, not just limbic, and not untreatable. *Clin J Med* 2016;1:43-53.
- Swayne A, Tjoa L, Broadley S, Dionisio S, et al.** Antiglycine receptor antibody related disease : a case series and literature review. *Eur J Neurol* 2018;10:1290-1298.
- Hacohen Y, Wright S, Waters P, et al.** Paediatric autoimmune encephalopathies : clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *J Neurol Neurosurg Psychiatry* 2013;7:748-755.
- Olivieri G, Contaldo I, Ferrantini G, et al.** Autoimmune encephalopathies in children: diagnostic clues and therapeutic challenges. *Neuroimmunol Neuroinflammation* 2016;7:147.
- Bost C, Pascual O, de Lyon HC, et al.** Autoimmune encephalitis in psychiatric institutions : current perspectives. *Neuropsychiatr Dis Treat* 2016;12:2775-2787.
- Leypoldt F, Armangue T, Dalmaj J.** Autoimmune encephalopathies. *Ann N Y Acad Sci* 2015;1:94-114.
- Duan B-C, Weng W-C, Lin K-L, et al.** Variations of movement disorders in anti-N-methyl-D-aspartate receptor encephalitis: A nationwide study in Taiwan. *Medicine (Baltimore)* 2016;37:e4365.
- Mitoma H, Adhikari K, Aeschlimann D, et al.** Consensus Paper: Neuroimmune Mechanisms of Cerebellar Ataxias. *Cerebellum* 2016;2:213-232.
- Barbagallo M, Vitaliti G, Pavone P, et al.** Pediatric Autoimmune Encephalitis. *J Pediatr Neurosci* 2017;2:130-134.
- Armangue T, Leypoldt F, Dalmaj J.** Autoimmune encephalitis as differential diagnosis of infectious encephalitis. *Curr Opin Neurol* 2014;3:361-368.
- Venkatesan A, Tunkel AR, Bloch KC, et al.** Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis* 2013;8:1114-1128.
- Kelley BP, Patel SC, Marin HL, et al.** Autoimmune Encephalitis: Pathophysiology and Imaging Review of an Overlooked Diagnosis. *Am J Neuroradiol* 2017;6:1070-1078.
- Schmitt SE, Pargeon K, Frechette ES, et al.** Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;11:1094-1100.
- Tekin HG, Gökben S, Serdaroglu G.** Extreme delta brush activity: Could it be a marker for early diagnosis and prognosis of anti-NMDA (N-methyl-D-aspartate) encephalitis? *Turk Pediatr Ars* 2019;1:61-65.
- Herken J, Prüss H.** Red Flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients. *Front Psychiatry* 2017;8:25.
- Remy KE, Custer JW, Cappell J, et al.** Pediatric Anti-N-Methyl-d-Aspartate Receptor Encephalitis: A Review with Pooled Analysis and Critical Care Emphasis. *Front Pediatr* 2017;5:250