

ANTIBODY-MEDIATED ENCEPHALOPATHIES IN CHILDHOOD

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Acute or sub acute, generalized or focal encephalopathy characterized by seizures, confusion, mental deterioration or psychiatric symptoms has been associated with antibodies against nervous system or other antigens such as anti-thyroid or anti-aquaporin-4 (neuromyelitis optica or NMO) antibodies. In addition, novel antibodies against molecules or receptors of the central nervous system such as N-methyl d-aspartate receptor (NMDAR), voltage gated potassium channel (VGKC) and glutamic acid decarboxylase (GAD) have been identified in behavioral, epileptic, or movement disorders of sub acute onset in children. Dyskinesias, sleep disturbances, autonomic symptoms and ataxia can also be part of the clinical picture. MR imaging, EEG and cerebrospinal fluid analysis may point to cerebral parenchymal inflammation, or can be normal. In children, these entities are often non-paraneoplastic. Acute severe epilepsy with a febrile onset and acquired partial epilepsy syndromes, some collected under specific acronyms, have also been associated with an antibody-mediated encephalopathy. All these relatively recently described syndromes require a large index of suspicion and early initiation of immunomodulatory treatment. This group of disorders should be considered in all children with unexplained acute or sub acute central nervous system symptoms.

Descriptors: ANTIBODY-MEDIATED, ENCEPHALOPATHY, IMMUNOGLOBULIN, LIMBIC ENCEPHALITIS

Autoantibodies have recently been associated with sub acute, or, more rarely, acute central nervous system (CNS) symptoms in children. The clinical spectrum includes seizures, confusion, altered behavior, memory problems, and abnormal movements such as dystonia, myoclonia, or tremor. CNS symptoms of multifocal nature developing over a few weeks in a previously healthy child should prompt the clinician to consider this group of disorders. The correlation of the severity of symptoms and signs with Ab titers, and the clinical response to immunomodulatory treatment support the pathogenic role of these Abs.

Encephalopathy-associated Abs are produced against the structures of the neuronal membrane: N-methyl d- aspartate receptors (NMDAR) and volta-

ge-gated potassium channels (VGKC). An Ab against an intracellular enzyme: glutamic acid decarboxylase (GAD) also causes CNS symptoms probably by increasing intracellular glutamate levels and causes a picture of temporal lobe epilepsy or cerebellar ataxia (1). Some, but not all, of these autoAbs are paraneoplastic.

The typical picture caused by NMDAR Abs was initially considered as confined to limbic encephalitis but soon broadened to a variety of CNS symptoms including seizures (usually extratemporal), altered consciousness, movement abnormalities (dyskinesias), or psychiatric symptoms. The association with neoplasms is very low in children: in the national reference centre, only 9% of girls under 14 years with NMDAR Abs old had a neoplasm (2). EEG and MR imaging can be normal. On the other hand, CSF usually shows at least one abnormal finding (cells/protein/oligoclonal bands). The CSF also contains the anti-NMDAR antibodies. A Patient's CSF has been shown to suppress long-term potentiation in mouse hippocampal slices (3).

VGKC Abs have been found to react with 2 major antigens identified to date: the leucine-rich, glioma-inactivated 1 protein (Lgi1) and contactin-associated protein 2 (Caspr2), of whom only Lgi1 Abs have been demonstrated in children. Still, the VGKC Ab group is not common in children: 7/252 samples sent for testing to Mayo referral lab were positive and younger than 18 years. Most were girls, and a family history of autoimmunity was common. Cerebrospinal fluid analysis was usually normal. As in NMDAR Ab-encephalitis, tumors are rarely found in children (4). Brain MR images can show signal changes in the temporal lobe.

The youngest patient reported to date is a 4-month-old girl with epilepsy and developmental delay where the presence of oligoclonal bands in the CSF prompted the search for autoAbs (5). Children who presented movement disorders unexplained with other diagnoses can be found to have anti-VGKC encephalitis. The presence of more than one neurological symptom or sign such as seizures, dystonia, choreoathetosis

or CSF lymphocytic pleocytosis is more likely to point at anti-NMDAR or anti-VGKC mediated disorders.

Anti-GAD IgG has been defined in stiff person syndrome, but the CNS syndromes associated with this Ab: cerebellar ataxia, and temporal lobe epilepsy have been more recently defined. While extratemporal seizures are more likely to be associated with VGKC Abs, GAD Abs have been associated with temporal lobe epilepsy.

Other Abs associated with neurological manifestation are those against the extracellular region of the GABAB1 receptor, reported in 15 patients with refractory seizures and behavioral symptoms. Abs against AMPAR usually do not cause seizures but psychotic symptoms (6).

Anti-Glu3 Abs described in Rasmussen's encephalitis have not been confirmed in further reports: it is possible that they constitute an epiphenomenon not needed to produce the clinical picture which is in fact due to T cell-related and granzyme-mediated mechanisms. Infantile spasms and Landau-Kleffner syndrome are the other epileptic syndromes that have been considered as having an autoimmune etiopathogenesis. Data have been inconclusive so far. However, steroids or intravenous immunoglobulin treatments have shown some effect, suggesting underlying immune-mediated pathways. More recently, acute epileptic encephalopathies have been reported as associated with Abs against glutamate receptor epsilon2 subunit of the NMDA receptor: acute encephalitis with very refractory and frequent partial seizures which evolve into refractory epilepsy (AERPPS), febrile infection-related epilepsy syndrome (FIRES), devastating epileptic encephalopathy in school-aged children (DESC) and new-onset refractory status epilepticus (NORSE). These entities can be difficult to differentiate from each other, and from more frequent causes of epilepsy such as viral encephalitis or Dravet syndrome. Further case descriptions, clinical and serological follow-up are needed to answer questions about these entities (7, 8).

A distinct group of encephalopathies of acute or sub acute presentation is related to anti-aquaporin or neuromyelitis optica (NMO) Abs, initially considered as confined to myelitis and optic neuritis but more recently recognized as the underlying cause of other acute, relapsing or non-relapsing inflammatory and demyelinating events (9). Another well-known antibody-mediated encephalopathy is associated with anti-mitosomal antibodies, or Hashimoto's encephalopathy, now preferably named "steroid-responsive encephalopathy associated with autoimmune thyroiditis".

Treatment in this group of disorders is immunomodulatory: intravenous immunoglobulin, plasma exchange, and corticosteroids in the form of monthly intravenous methylprednisolone pulses or oral high-dose prednisolone. Relapses can follow cessation of immunotherapy. Patients with anti-GAD Abs may show a chronic refractory course (10). Although intravenous immunoglobulin or plasma exchange clear the Abs in the circulation, refractoriness or relapses after these treatments is not unexpected because of plasma cells and B lymphocytes infiltrating the CNS and producing the Abs on site. Rituximab, a monoclonal Ab against CD20 may not be efficient either because CD20 is not expressed by most plasmablasts. Therefore, corticosteroids and other immunosuppressive agents (cyclophosphamide or methotrexate) may be needed in refractory cases (11). The presence of neoplasms should be sought extensively and repeatedly. The versatility of the clinical picture requires a high index of suspicion from the clinician in order to recognize these newly described entities.

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Sažetak

ENCEFALOPATIJE DJEČJE DOBI POSREDOVANE ANTITIJELIMA

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Akutna ili subakutna, generalizirana ili žarišna encefalopatija karakterizirana cerebralnim napadajima, poremećajem svijesti, mentalnim propadanjem ili psihijatrijskim simptomima, može nastati zbog razvoja antitijela protiv dijelova stanica središnjeg živčanog sustava (SŽS), ili zbog razvoja antitijela na druge antigene kao što su anti-tiroidna antitijela ili antitijela na aquaporin 4 (neuromijelitis optika - NMO). Također, kod djece sa subakutnim poremećajima ponašanja, poremećajima pokreta ili epilepsijom otkrivena su antitijela na molekule ili receptore SŽS, kao što su antitijela na N-metil d-aspartat receptor (NMDAR), antitijela na kalijeve ionske kanale ovisna o naponu (VGKC) i antitijela na glutamat dekarboksilazu (GAD). Dio kliničke slike autoimunih bolesti SŽS su i diskinezija, poremećaji spavanja, autonomni simptomi, ataksija. MR snimke mozga, EEG i analiza cerebrospinalne tekućine mogu upućivati na upalne promjene mozga ili nalazi mogu biti uredni. U djece, ti entiteti najčešće nisu paraneoplastični. Epilepsija u febrilitetu te sindromi s parcijalnim epileptičkim napadajima također se mogu povezati s encefalopatijom posredovanom antitijelima. Svi ti, tek nedavno otkriveni sindromi, zahtijevaju rano započinjanje imunomodulatorne terapije. Na njih treba misliti u sve djece s neobjašnjivim akutnim ili subakutnim simptomima središnjeg živčanog sustava.

Deskriptori: ANTITIJELA, ENCEFALOPATIJA, IMUNOGLOBULINI, LIMBIČKI ENCEFALITIS

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