ANTIBODY-MEDIATED ENCEPHALOPATHIES IN CHILDHOOD

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Autoantibodies have recently been associated with sub acute, or, more rarely, acute, central nervous system (CNS) symptoms. The clinical spectrum includes seizures, confusion, altered behavior, memory problems, and abnormal movements such as dystonia, tics, or CNS-systems 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 should be considered.

Encephalopathy-associated Abs are produced against the structures of the neuronal membrane: N-methyl-D-aspartate receptor (NMDAR) and voltage-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 is common. The correlation of the severity of symptoms and signs with Ab titers is high index of suspicion from the clinical picture.

LITERATURE


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-antiguo-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 decarboxyla- se (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 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.

Descriptions: ANTIBODY-MEDIATED ENCEPHALOPATHY, IMMUNOGLOBULIN, LIMBIC ENCEPHALITIS


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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 psihiatrijskim simptomima, može nastati zbog razvoja antitijela protiv dijelova stanica središnjeg živčanog sustava (SZS), 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 SZS, kao što su antitijela na N-metil d-aspartat receptor (NMDAR), antitijela na kalijeve ionske kanale ovisne o naponu (VGKC) i antitijela na glutamat dekarboksilazu (GAD). Dio kliničke slike autoimunih bolesti SZS 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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