

Pediatric autoimmune encephalitis

Recognition and diagnosis

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Abstract

Objective

The aims of this study were (1) to describe the incidence of autoimmune encephalitis (AIE) and acute disseminated encephalomyelitis (ADEM) in children, (2) to validate the currently used clinical criteria to diagnose AIE, and (3) to describe pitfalls in the diagnosis of pediatric autoimmune (AI) and inflammatory neurologic disorders.

Methods

This study cohort consists of 3 patient categories: (1) children with antibody-mediated AIE (n = 21), (2) children with ADEM (n = 32), and (3) children with suspicion of an AI etiology of their neurologic symptoms (n = 60). Baseline and follow-up clinical data were used to validate the current guideline to diagnose AIE. In addition, patient files and final diagnoses were reviewed.

Results

One-hundred three of the 113 included patients fulfilled the criteria of possible AIE. Twenty-one children had antibody-mediated AIE, of whom 19 had anti-N-methyl-D-aspartate receptor (NMDAR), 1 had anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, and 1 had anti-leucine-rich glioma-inactivated protein 1 encephalitis. Finally, 34 children had ADEM, and 2 children had Hashimoto encephalopathy. Mean incidence rates were 1.54 children/million (95% CI 0.95–2.35) for antibody-mediated AIE and 2.49 children/million (95% CI 1.73–3.48) for ADEM. Of the other 48 children, treating physicians' diagnoses were reviewed. In 22% (n = 6) of children initially diagnosed as having an AI/inflammatory etiology (n = 27), no support for AI/inflammation was found.

Conclusion

Besides anti-NMDAR encephalitis and ADEM, other AIEs are rare in children. The current guideline to diagnose AIE is also useful in children. However, in children with nonspecific symptoms, it is important to review data critically, to perform complete workup, and to consult specialized neuroinflammatory centers.

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Glossary

ADEM = acute disseminated encephalomyelitis; **AE** = autoimmune etiology; **AI** = autoimmune; **AIE** = autoimmune encephalitis; **AMPA** = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **CBA** = cell-based assay; **CHANCE** = Children's Autoimmunity Related to Neuropsychiatric symptoms, Chorea and Epilepsy; **FBDS** = faciobrachial dystonic seizures; **GAD65** = glutamic acid decarboxylase 65; **HSVE** = herpes simplex virus encephalitis; **IPMSSG** = International Pediatric Multiple Sclerosis Study Group; **ivMP** = IV methylprednisolone; **LGII** = leucine-rich glioma-inactivated protein 1; **MOG** = myelin oligodendrocyte glycoprotein; **NMDA receptor** = N-methyl-D-aspartate receptor; **TPO** = thyroid autoantibodies.

Autoimmune encephalitis (AIE) has expanded the already comprehensive list of pediatric neuroinflammatory disorders of the CNS. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis and acute disseminated encephalomyelitis (ADEM) are the most frequently described cause of AIE in children,¹⁻⁴ and disease courses have been studied in detail, including treatment responses, functional recovery,^{1,4} and long-term neuropsychological outcome.⁵

Next to anti-NMDAR, other neuronal antibodies have been described only sporadically in children,⁶⁻⁸ whereas in adults, reported incidence of these antibodies has increased dramatically.^{9,10} This could indicate that besides anti-NMDAR encephalitis, neuronal antibodies occur less frequent in children or that these syndromes are unrecognized.

In 2016, Graus et al.¹¹ have described criteria to diagnose antibody-mediated AIE, ADEM, and other related autoimmune (AI) encephalitis, including Bickerstaff brainstem encephalitis, Hashimoto encephalopathy, and autoantibody-negative (seronegative) AIE, in adults and in children. These criteria allow physicians to start first-line immunotherapy in patients with typical limbic encephalitis or probable anti-NMDAR encephalitis before definite antibody diagnosis. As already stated by the authors, the criteria should be used with caution in children because the differential diagnosis is more widespread.

This prospective, observational, cohort study describes the incidence of pediatric antibody-mediated AIE and ADEM in the Netherlands since 2015. In addition, the diagnostic criteria of Graus et al.¹¹ are validated using data of prospectively collected cohorts of children with AIE, ADEM, and children with neurologic symptoms and suspicion of an autoimmune etiology (AE). Finally, we describe pitfalls in the diagnosis of pediatric AI and inflammatory neurologic disorders.

Methods

Patients

This study cohort contains data of 3 patient groups, included between January 2015 and December 2018 in the Netherlands. The first group consists of all Dutch children, aged 0–18 years, diagnosed with antibody-mediated (definite) AIE. Antibodies were detected in serum and CSF, using commercial cell-based assays (CBAs; Euroimmun, Lübeck,

Germany). Antibodies were confirmed with immunohistochemistry. All children were included after diagnosis and are being followed prospectively since. The second group consists of all Dutch children with ADEM diagnosed according to the International Pediatric Multiple Sclerosis Study Group (IPMSSG) criteria,¹² who were prospectively included in the nationwide, multicenter PROUD kids study.¹³ The third group consists of children with a suspected AE of their neurologic symptoms. These children were prospectively included in the observational, multicenter, “Children's Autoimmunity Related to Neuropsychiatric symptoms, Chorea and Epilepsy” (CHANCE) study. The CHANCE study was a multicenter study, with national accrual, but no means to be complete. Inclusion criteria were age below 18 years at symptom onset and one of the following clinical phenotypes: (1) limbic encephalitis, (2) new-onset status epilepticus, (3) acute encephalopathy, or (4) neuropsychiatric symptoms combined with symptoms of basal ganglia dysfunction. All serum samples, and if available CSF samples, were screened for neuronal antibodies using immunohistochemistry¹⁴ and CBAs (Euroimmun, Lübeck, Germany). Questionable or positive samples were tested with conformational laboratory techniques, including live hippocampal neurons,¹⁵ in-house CBAs, and ELISA. Antithyroid autoantibodies (TPO) were detected by fluorescence enzyme immunoassay on the Phadia 250 system using EliA according to the manufacturer's instructions (Thermo Fisher Scientific, Freiburg, Germany).

Data about medical history, disease course, treatment responses, and final diagnoses were collected. Data were collected from interviews with patients, from treating physicians, or were retrieved from patient files.

Definitions

The criteria of Graus et al.¹¹ were used to define possible AIE, definite AI limbic encephalitis, probable anti-NMDAR encephalitis, Bickerstaff brainstem encephalitis, Hashimoto encephalopathy, and seronegative but probable AIE. The IPMSSG criteria¹² were used to define ADEM.

Final etiology was classified as (1) Definite AIE, including children with antibody-mediated AIE and ADEM. (2) Probable AIE, according to the diagnostic criteria.¹¹ This category consisted of children with ADEM without follow-up MRI and of children with Hashimoto encephalopathy. (3) Possible

AE/inflammatory, included children not fulfilling any of the diagnostic criteria panels, but with support for autoimmunity or inflammation. This category consisted partially of children with clinically defined acquired AE/inflammatory disorders, such as Rasmussen encephalitis or Sydenham chorea, and partially of children with MRI or CSF abnormalities pointing toward an AE/inflammatory etiology (pleocytosis, elevated protein, or oligoclonal bands in CSF, and MRI lesions in the temporal lobe), with exclusion of other causes, and not fulfilling the criteria of seronegative AIE.¹¹ (4) Unknown etiology and no support for AE/inflammatory, including children without MRI or CSF abnormalities pointing toward and AE/inflammatory etiology. (5) Other diagnosis and no support for AE/inflammatory. R.F.N., M.J.T., and M.A.A.M.d.B. reviewed follow-up etiologies. Definite diagnoses were determined by consensus.

Standard protocol approvals, registrations, and patient consents

The Institutional Review Board of the Erasmus MC University Medical Center approved the study protocol (MEC-2014-048; MEC-2005-247). Informed consent was obtained from all parents and additionally from children aged 12–17 years at inclusion.

Statistics

The annual incidence rate (from 2015 to 2018) was calculated with 95% CIs, assuming a Poisson distribution. Available data of the Dutch pediatric population were used (StatLine; statline.cbs.nl/statweb/). Comparisons were performed using the χ^2 test or the Kruskal-Wallis test.

Data availability

Any data not published in this article are available at the Erasmus MC University Medical Center. Patient-related data will be shared on request from any qualified investigator, maintaining anonymization of the individual patients.

Results

Patient characteristics

We included 113 patients. Twenty-one patients had definite AIE (19%), including 19 (90%) children with anti-NMDAR encephalitis. Among them, 12 had an idiopathic etiology (63%), 6 children recently had herpes simplex virus encephalitis (HSVE; 32%), and 1 girl had an ovarian teratoma (5%) detected shortly after disease onset. The other 2 children with neuronal antibodies had anti-leucine-rich glioma-inactivated protein 1 (LGII) encephalitis ($n = 1$; 5%) and anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) encephalitis ($n = 1$; 5%). Thirty-two children diagnosed with ADEM (28%) were included from the PROUD kids cohort. The other 60 patients (53%) were included from the CHANCE study.

Incidence

The annual incidence rates of antibody-mediated AIE and ADEM of 4 consecutive years (2015–2018) are shown in table 1. Mean incidence rates were 1.54 children/million

Table 1 Annual incidence of pediatric AIE and ADEM

Year	AIE—incidence children/million (95%-CI)	ADEM—incidence children/million (95% CI)	No. of Dutch pediatric inhabitants
2015	1.46 (0.47–3.40)	2.62 (1.20–4.98)	3,429,193
2016	1.76 (0.64–3.82)	2.05 (0.82–4.22)	3,416,581
2017	1.76 (0.65–3.84)	3.23 (1.16–5.78)	3,404,098
2018	1.18 (0.32–3.02)	2.07 (0.83–4.26)	3,386,096
2015–2018	1.54 (0.95–2.35)	2.35 (1.61–3.31)	3,408,992

Abbreviations: AIE = autoimmune encephalitis, ADEM = acute disseminated encephalomyelitis.

(95% CI 0.95–2.35) and 2.49 children/million (95% CI 1.73–3.48) for AIE and ADEM, respectively.

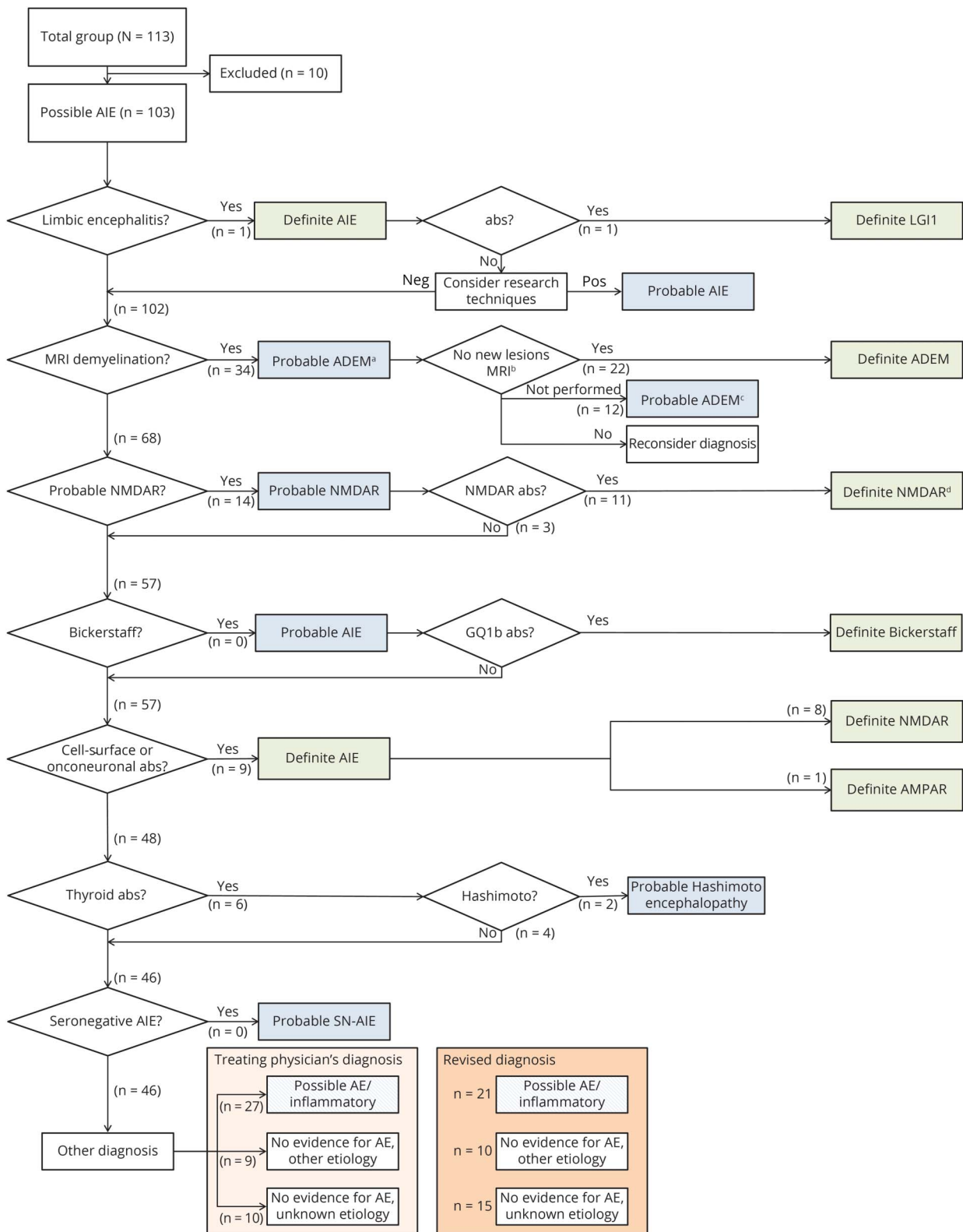
Validation of AIE criteria

Of all 113 patients included, 103 (89%) fulfilled the criteria of possible AIE (figure 1). Demographical data are described in table 2. Children with AIE were more often female ($p = 0.023$), and children with ADEM were younger ($p < 0.0001$). Ten patients included in the CHANCE cohort did not fulfill the criteria and were excluded because of the absence of working memory deficits or psychiatric symptoms ($n = 6$) or because of the longer duration of symptoms ($n = 4$). These 10 children had epilepsy without additional symptoms ($n = 4$), psychiatric disorders ($n = 3$), mild encephalopathy with reversible lesion in the splenium ($n = 1$), Niemann-Pick disease type C ($n = 1$), or Rasmussen encephalitis without epilepsy ($n = 1$).

Of the 103 children shown in the flowchart, 1 child had definite limbic encephalitis according to the criteria (figure e-1, links.lww.com/NXI/A197). This was a 9-year old boy who presented with tonic-clonic seizures originating in the left temporal lobe, followed by refractory status epilepticus. He was treated with valproic acid, midazolam, and phenytoin. After status epilepticus, he developed faciobrachial dystonic seizures (FBDS)¹⁶ and hyperactive behavior. He was considered to have anti-LGI1 encephalitis, later confirmed in his serum and CSF. He was treated with IV methylprednisolone (ivMP). Because of ongoing FBDS, he was treated again with ivMP and additionally with mycophenolate mofetil, which led to seizure freedom and complete recovery.

The brain MRI showed demyelinating features in 34 children (33%). In all these children, encephalopathy and other symptoms appeared reversible. In 22/34 children, the brain MRI was repeated, and in none of them, new lesions were visible. These children were diagnosed as having definite ADEM (22/103; 21%). In 31/34, myelin oligodendrocyte glycoprotein (MOG) antibodies were tested. Twelve of 31 (39%) ADEM children were MOG positive, 4 children had

Figure 1 Flowchart showing the validation of the diagnostic criteria of AIE



^aAccording to the International Pediatric Multiple Sclerosis Study Group criteria. ^bIn 21 of the 22 patients without new lesions on the second MRI anti-myelin oligodendrocyte glycoprotein (MOG) was tested; in 8/21, antibodies were present (38%). ^cIn 10 of the 12 patients who had no follow-up MRI, anti-MOG was tested, of them 40% (n = 4) tested positive. ^dOf whom, 8 had an idiopathic etiology, and 3 recently had herpes simplex virus encephalitis. In blue: probable diagnosis, first-line immunotherapy can be started. In green: definite diagnosis. ADEM = acute disseminated encephalomyelitis; AE = autoimmune etiology; AIE = autoimmune encephalitis; AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; GQ1b = Ganglioside Q1b; LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = NMDA receptor; SN-AIE = seronegative autoimmune encephalitis.

a relapsing disease course (ADEM-optic neuritis [N = 3], and multiphasic demyelinating encephalomyelitis [n = 1]).

Fourteen of the 68 remaining patients fulfilled the criteria of probable anti-NMDAR encephalitis, of whom 11 had NMDAR antibodies, whereas the other 3 had no NMDAR antibodies (table 3). Of the children with anti-NMDAR encephalitis, 8 children had an idiopathic etiology and 3 children recently had HSVE.

Nine additional patients had neuronal antibodies, without fulfilling the criteria of probable anti-NMDAR encephalitis. Eight turned out to have definite anti-NMDAR encephalitis, of which 4 with an idiopathic etiology (50%) but with less symptoms, 3 post-HSVE (38%), and 1 girl had an ovarian teratoma triggering the antibody production (13%). The other patient was a 17-year-old girl with anti-acetylcholine receptor-positive bulbar myasthenia gravis and a thymoma, which was surgically removed. She developed severe memory problems and mood changes within days, accompanied by clinical signs of polyneuropathy. Laboratory results showed AMPAR antibodies in her serum and CSF and an elevated anti-CV2 titer in serum (>12,800). She was treated with ivMP and IV immunoglobulins resolving both the encephalitis and polyneuropathy.

No patient had Bickerstaff brainstem encephalitis. All remaining 48 children with possible AIE were tested for TPO antibodies. Six of 48 children had an increased anti-TPO titer, of whom 2 met the criteria for Hashimoto encephalopathy. One of the other 4 patients (table 4) had diabetes mellitus type 1 and co-occurrence of low-titer anti-glutamic acid decarboxylase 65 (anti-GAD65), considered clinically irrelevant.

Follow-up etiology of patients with possible AIE

Nine of the 46 children (20%) were diagnosed by their treating physician with seronegative or probable AIE, whereas none of these children fulfilled the criteria of seronegative AIE. Four of these 9 children had a pleocytosis in CSF, but no MRI abnormalities in the mesial temporal lobe. In the other 5 children, brain MRI and white blood cell count in CSF were normal. However, complete CSF analysis, including immunoglobulin G (IgG) index and oligoclonal bands, was not performed.

Concerning follow-up etiology based on treating physicians' diagnosis, these 46 children had (1) a possible AE/inflammatory etiology (n = 27), (2) no support for AE/inflammatory and another etiology (n = 9), and (3) no support for AIE/inflammatory and unknown etiology (n = 10). After revising the data, in 6 children (22%) initially considered as possible AE/inflammatory, no support for an AI/inflammatory etiology was found.

Differential diagnosis of possible AIE

In table 5, exemplary cases of the included patients with AIE and with other diagnoses are shown. These cases show

overlapping features, which may suggest AIE, but also signs and symptoms pointing toward another diagnosis.

Discussion

This prospective observational cohort study shows that besides anti-NMDAR encephalitis and ADEM, the prevalence of other AI encephalitides is very low in children. Furthermore, we describe that these AI disorders show a stable incidence over the past 4 years. In addition, this study validates the criteria currently used to diagnose AIE and shows their usefulness to detect pediatric antibody-mediated AIE, ADEM, and Hashimoto encephalopathy in an early stage. In our cohort, a substantial number of children were diagnosed and treated as having an AI/inflammatory etiology of their neurologic symptoms, whereas in more than 20% of them, the support for autoimmunity or inflammation was lacking.

The vast majority of children with definite AIE described in this cohort had anti-NMDAR encephalitis, whereas only 2 children had other neuronal antibodies (anti-LGII and anti-AMPA). These antibodies have been described only sporadically in pediatric cases,¹⁷ next to other neuronal antibodies, including anti-gamma-aminobutyric acid B receptor,⁷ anti-gamma-aminobutyric acid A receptor,⁶ anti-glycine receptor,¹⁸ and anti-GAD65.¹⁹ The high prevalence of anti-NMDAR encephalitis in children compared with the very low prevalence of other antibodies is largely explained by epidemiologic factors. In our cohort, in more than 40% of the children with anti-NMDAR encephalitis, antibody production was triggered by HSVE or an ovarian teratoma, both

Table 2 Demographic data and comparisons between groups

	AIE (n = 21)	ADEM (n = 32)	CHANCE (n = 60)	p Value
Sex, male (%)	5 (24)	19 (59)	22 (37)	0.023 ^a
Onset age (years), median (IQR; range)	14 (8–16; 3–18)	4 (2–6; 1–16)	9 (5–13; 0–17)	<0.0001 ^a
Prodromal symptoms	13 (62%)	24 (75%)	36 (60%)	0.16
Seizures	13 (62%)	2/31 (6%)	22 (37%)	<0.0001 ^a
Immunotherapy	21 (100%)	31 (97%)	32 (53%)	<0.0001 ^a
CSF				
Pleocytosis	14/19 (74%)	23/27 (85%)	9/49 (18%)	<0.0001 ^a
Protein	1/18 (6%)	3/24 (13%)	5/46 (11%)	0.76
OCB	2/3 (66%)	10/26 (38%)	2/24 (8%)	0.014

Abbreviations: AIE = autoimmune encephalitis; ADEM = acute disseminated encephalomyelitis; CHANCE = Children's Autoimmunity Related to Neuropsychiatric symptoms, Chorea and Epilepsy; IQR = interquartile range; OCB = oligoclonal bands.

^a p < 0.05.

Table 3 Patients without NMDA receptor antibodies fulfilling the criteria “probable anti-NMDA receptor encephalitis”

Sex, onset age (years)	Clinical presentation and ancillary testing	Criteria	Follow-up etiology after revision
M, 15	Flu, followed by confusion, hemiparesis and aphasia, somnolence, and tonic-clonic seizures.	Abnormal behavior	Probable AI (Hashimoto encephalopathy)
	Anti-TPO increased 1,920 IE/mL and subclinical hypothyroidism.	Speech dysfunction	
	FU: improvement after ivMP. Treated with levothyroxine. The disease relapsed 2 mo later (status epilepticus), again treated with ivMP.	Seizures	
		Decreased level of consciousness	
		EEG: diffuse slowing	
F, 5	Flu, followed by confusion, aphasia, focal seizures, decreased consciousness, memory impairment, and status epilepticus.	Abnormal behavior	Possible AI/ inflammatory
	FU: 2 mo seizure-free after ivMP and IVIg, followed by drug-resistant focal seizures.	Speech dysfunction	
		Seizures	
		Decreased level of consciousness	
		EEG: diffuse slowing	
F, 3	Flu, recurrent tonic posture of body and discomfort, developmental regression, dysarthria, ataxia, somnolence, and chorea.	Abnormal behavior	Possible AI/ inflammatory
	FU: stabilization after ivMP (repeated twice). improvement in months.	Speech dysfunction	
		Decreased level of consciousness	
		Movement disorder	
		EEG: diffuse slowing	
	CSF: pleocytosis		

Abbreviations: AI = autoimmune; FLAIR = fluid attenuation inversion recovery; FU = follow-up; IVIg = IV immunoglobulin; ivMP = IV methylprednisolone; TPO = thyroid autoantibodies.

occurring more in children and young adults.^{1,20} The other antibody-mediated AIE syndromes are not associated with these factors and are usually idiopathic or associated with malignancy, not occurring in childhood.¹¹

No additional neuronal antibodies were identified in our prospectively collected cohort of children with possible AIE (CHANCE cohort), whereas others identified neuronal antibodies in 4%–10% of children with selected neurologic symptoms or syndromes (i.e., epilepsy²¹ and demyelinating disorders²²). However, pathogenicity of most of the detected antibodies in these studies is unproven, including double-negative voltage-gated potassium channel antibodies (anti-voltage-gated potassium channel, without anti-LGI1 or anti-contactin-associated protein 2) and low-titer anti-GAD65.^{23–25}

We describe that the current guideline to diagnose AIE is of additional value to correctly diagnose AI-related neurologic conditions in children. One of the most important panels

in the current guideline is “probable anti-NMDAR encephalitis.” If children fulfill these criteria, immunotherapy can be started before definite antibody diagnosis. In our cohort, almost 70% of children with anti-NMDAR encephalitis with an idiopathic etiology could be identified by the use of these criteria, whereas 50% of post-HSVE anti-NMDAR encephalitis children fulfilled the criteria of “probable anti-NMDAR encephalitis.” As the criteria were meant to identify patients for initiation of treatment before antibody results are available, the identification of 70% of idiopathic patients is relevant and important. The criteria are less important in post-HSVE anti-NMDAR encephalitis. In most children with recent history of HSVE, deterioration of symptoms promptly leads to NMDAR antibodies testing because of increased knowledge of this syndrome.²⁰ One-third of children with idiopathic or paraneoplastic anti-NMDAR encephalitis did not fulfill the criteria of probable anti-NMDAR encephalitis; these children had less symptoms, and most of them had milder disease courses than the ones who did fulfill the criteria.

Table 4 Patients with increased anti-TPO not fulfilling the criteria of Hashimoto encephalopathy

Sex, onset age (years)	Clinical presentation	Laboratory results	Follow-up etiology after revision
F, 16	Malaise and fever, followed by nausea, dysarthria, and ataxia.	IHC: serum and CSF negative	Possible AI/ inflammatory
		Anti-NMDAR negative in CSF	
		Anti-VGKC 141, anti-LGI1, and Caspr2 negative	
		Anti-TPO 57	
M, 9	Somnolence, apathy, fever, progressive facial weakness and respiratory problems.	IHC: serum and CSF negative	Possible AI/ inflammatory
		Anti-GQ1B negative and anti-GlyR negative	
		Anti-TPO 50	
F, 5	Flu, followed by confusion, aphasia, focal seizures, decreased consciousness, memory impairment, and status epilepticus.	IHC: serum and CSF negative	Possible AI/ inflammatory
		Anti-NMDAR negative in CSF	
		Anti-TPO 35	
F, 5	History of DM 1. Malaise, followed by recurrent attacks of delayed response, sometimes accompanied by nonrhythmic upper limb movements.	IHC: serum and CSF negative	No support for AI, other etiology ^a
		Anti-NMDAR negative in serum and CSF	
		Anti-GAD65 364 IU/mL	
		Anti-TPO 454 IU/mL, but no thyroid dysfunction	

Abbreviations: AI = autoimmune; DM1 = diabetes mellitus type 1; GAD65 = glutamic acid decarboxylase 65; IHC = immunohistochemistry; LGI1 = leucine-rich glioma-inactivated protein 1; NMDAR = NMDA receptor; TPO = thyroid autoantibodies; VGKC = voltage-gated potassium channels.

^a Attacks related to DM1-associated hypoglycemia.

These findings emphasize the importance of also considering this disease in children with unexplained neuropsychiatric disorders without many additional signs.

An important difficulty broached in this study was that in one-fifth of the children diagnosed with an AI or inflammatory etiology, no support for autoimmunity or inflammation was found. In many of these children, improvement after immunotherapy was considered as a criterion favoring autoimmunity. An unjustified conclusion, because many diseases can (temporarily) respond to immunotherapy, or the observed response may even be the natural course of the disease.²⁶ However, there will always be a small level of uncertainty, which makes it even more important to perform complete workup in these children, MRI and CSF analysis, including IgG index and oligoclonal bands. In the diagnosis of these syndromes, it is important to look for signs and symptoms favoring autoimmunity or inflammation, but the differential diagnosis of possible AIE is broad, and other causes should also be considered, especially in children with aspecific signs.

This study was limited because of the number of patients included. However, it is the first nationwide study describing annual incidence of pediatric antibody-mediated AIE. In the CHANCE cohort, coverage was well, but there was no nationwide coverage, and children may have been selected toward an AE, as samples of patients with a higher suspicion for AE are often referred to our center for antibody testing. Another limitation is that in most patients, CSF analysis was incomplete, and oligoclonal bands and IgG index were often lacking. Occasionally, this resulted in difficulties to adequately revise diagnosis. In doubt, we preferred to be cautious by diagnosing children with an AI of inflammatory disorder because of the therapeutic and prognostic implications.

From this study, we can conclude that AIE seems to be recognized properly in children. The majority of children have anti-NMDAR encephalitis or ADEM whereas other AIE syndromes occur only sporadically in children. The current guideline to diagnose AIE syndromes seems to be a useful tool to detect children with an AE of neurologic symptoms. However, especially in children not fulfilling

Table 5 Mimics of autoimmune encephalitis in children²⁷

Sydenham chorea	Boy (aged 16 y) presented with <i>chorea</i> and <i>nocturnal agitation</i> two weeks after laryngitis . Ancillary testing was normal, whereas anti-DNase titer was increased (298 IE/mL). Cardiac ultrasound showed mitral valve regurgitation . He was treated with ivMP and penicillin.
Neuropsychiatric systemic lupus erythematosus	Girl (aged 16 y) with ANA, anti-ENA, anti-RNP, and anti-dsDNA-positive polyarthritis and neutropenia , had <i>memory problems and behavioral changes</i> , followed by hypersomnia and reduced awareness . She was suspected to have bacterial meningitis. CSF showed a <i>mild pleocytosis</i> . Because of negative cultures, she was treated with ivMP, oral steroids, and mycophenolate mofetil. She recovered after ivMP. The disease relapsed 2 y later.
Rasmussen encephalitis	Boy (aged 6 y) developed <i>daily focal seizures</i> with impaired awareness and behavior arrest. He had over 20 focal seizures a day, refractory to antiepileptic treatment, combined with <i>aggressive behavior</i> . His MRI showed lesions in the right hemisphere and atrophy . CSF analysis was normal. He was treated with ivMP and responded. He had a hemispherectomy 6 mo later because of recurrent seizures, and he is seizure-free since. Pathology examination showed infiltration of T lymphocytes and cavitation in the cortex .
PANDAS	Girl (aged 10 y) developed a <i>complex motor tic disorder</i> and <i>childish behavior</i> with overnight explosion 1 mo after laryngitis . Ancillary testing showed an increased AST (400 IE/mL) and positive throat culture for <i>Streptococcus</i> . She was treated with IVIg, which reduced the tics only moderately. She was treated with clonidine and with amoxicillin for 5 y. Her tics improved, but worsen during illnesses.
Klein Levine syndrome	Girl (aged 16 y) fell of a horse . Three days later, she developed <i>disinhibited behavior</i> and hypersomnolence . MRI and CSF analyses were normal. She recovered within 5 wk without treatment. Seven months later, she had a comparable episode after a cold; again, symptoms were reversible.
Narcolepsia	Girl (aged 9 y) developed excessive daytime sleepiness , <i>emotional behavior</i> , <i>irritability</i> , and collapses while being emotional , after scarlet fever. MRI and CSF analyses were normal. Hypocretin-1 was absent in CSF, and a multisleep latency test showed severe daytime sleepiness . She was treated with sodium oxybate and is doing well since.
Gilles de la Tourette	Boy (aged 10 y) developed <i>motor facial tics and vocal tics</i> , <i>hyperactive behavior</i> , and <i>irritability</i> . Brain MRI was normal. He was not treated and has a stable disease, but tics worsen during illness.
Hashimoto encephalopathy	Boy (aged 15 y), had <i>acute confusion</i> , aphasia , central facial palsy , and a right-sided sensory disorder . He was treated with thrombolysis because of suspicion of cerebral ischemia. MRI was normal and showed no abnormalities on DWI. He developed <i>focal seizures and status epilepticus</i> . EEG showed sharp activity parieto-temporo-occipital. He was treated with ivMP because of an increased anti-TPO titer (1,920 IE/mL) and subclinical hypothyroidism . He recovered completely, but disease relapsed 2 mo later.

Abbreviations: ANA = anti-nuclear antibody; AST = anti-streptolysin titer; dsDNA = double stranded DNA; DWI = diffusion-weighted imaging; ENA = extractable nuclear antigen; IVIg = IV immunoglobulin; ivMP = IV methylprednisolone; PANDAS = Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections; RNP = ribonucleoprotein; TPO = thyroid autoantibodies.

Italic: signs or symptoms that can point toward autoimmune encephalitis.

Bold: signs and symptoms contributing to another diagnosis.

any of the current guideline panels, it is important to be critical before diagnosing them as having an AI or inflammatory etiology of their neurologic symptoms. In addition, it is essential to perform complete diagnostic workup and to consult specialized AI/inflammatory tertiary centers if in doubt.

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Rogier Q. Hintzen: Deceased May 15, 2019.

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Disclosure

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Marienke A.A.M. de Bruijn, MD	Erasmus MC University Medical Center	Study design, acquisition of data, interpretation of data, and drafting of the manuscript
Arlette L. Bruijstens, MD	Erasmus MC University Medical Center	Acquisition of data and revision of the manuscript for content
Anna E.M. Bastiaansen, MD	Erasmus MC University Medical Center	Acquisition of data and revision of the manuscript for content
Agnes van Sonderen, MD, PhD	Erasmus MC University Medical Center	Acquisition of data and revision of the manuscript for content
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Peter A.E. Sillevs Smitt, MD, PhD	Erasmus MC University Medical Center	Acquisition of data and revision of the manuscript for content
Rogier Q. Hintzen, MD, PhD	Erasmus MC University Medical Center	Study design, interpretation of data, and revision of the first draft of the manuscript
Rinze F. Neuteboom, MD, PhD	Erasmus MC University Medical Center	Study design, interpretation of data, and revision of the manuscript for content
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Appendix 2 CHANCE study group

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Appendix 2 (continued)

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References

1. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurol* 2013;12:157–165.
2. Armangue T, Titulaer MJ, Malaga I, et al. Pediatric anti-N-methyl-D-aspartate receptor encephalitis-clinical analysis and novel findings in a series of 20 patients. *J Pediatr* 2013;162:850–856.e2.
3. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009;66:11–18.
4. de Mol CL, Wong YYM, van Pelt ED, et al. Incidence and outcome of acquired demyelinating syndromes in Dutch children: update of a nationwide and prospective study. *J Neurol* 2018;265:1310–1319.
5. de Bruijn M, van Sonderen A, van Coevorden-Hameete MH, et al. Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABABR encephalitis. *Neurology* 2019;92:e2185–e2196.
6. Petit-Pedrol M, Armangue T, Peng X, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol* 2014;13:276–286.
7. Krüer MC, Hoefberger R, Lim KY, et al. Aggressive course in encephalitis with opsoclonus, ataxia, chorea, and seizures: the first pediatric case of gamma-aminobutyric acid type B receptor autoimmunity. *JAMA Neurol* 2014;71:620–623.
8. Hacoen Y, Singh R, Rossi M, et al. Clinical relevance of voltage-gated potassium channel–complex antibodies in children. *Neurology* 2015;85:967–975.
9. van Sonderen A, Thijs RD, Coenders EC, et al. Anti-LGI1 encephalitis: clinical syndrome and long-term follow-up. *Neurology* 2016;87:1449–1456.
10. van Coevorden-Hameete MH, de Bruijn M, de Graaff E, et al. The expanded clinical spectrum of anti-GABABR encephalitis and added value of KCTD16 autoantibodies. *Brain* 2019;142:1631–1643.
11. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391–404.
12. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013;19:1261–1267.
13. Ketelslegers IA, Catsman-Berrevoets CE, Neuteboom RF, et al. Incidence of acquired demyelinating syndromes of the CNS in Dutch children: a nationwide study. *J Neurol* 2012;259:1929–1935.
14. Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain* 2005;128:1764–1777.
15. Gresa-Arribas N, Titulaer MJ, Torrents A, et al. Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study. *Lancet Neurol* 2014;13:167–177.

16. Irani SR, Michell AW, Lang B, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. *Ann Neurol* 2011;69:892–900.
17. Lopez-Chiriboga AS, Klein C, Zekeridou A, et al. LGI1 and CASPR2 neurological autoimmunity in children. *Ann Neurol* 2018;84:473–480.
18. Hacothen 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;84:748–755.
19. Mishra N, Rodan LH, Nita DA, Gresa-Arribas N, Kobayashi J, Benseler SM. Anti-glutamic acid decarboxylase antibody associated limbic encephalitis in a child: expanding the spectrum of pediatric inflammatory brain diseases. *J Child Neurol* 2014;29:677–683.
20. Armangue T, Spatola M, Vlasea A, et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol* 2018;17:760–772.
21. Borusiak P, Bettendorf U, Wiegand G, et al. Autoantibodies to neuronal antigens in children with focal epilepsy and no prima facie signs of encephalitis. *Eur J Paediatr Neurol* 2016;20:573–579.
22. Kiztanir H, Bektas G, Yildiz EP, et al. Coexisting neuronal autoantibodies among children with demyelinating syndromes. *Brain Dev* 2017;39:248–251.
23. Lang B, Makuch M, Moloney T, et al. Intracellular and non-neuronal targets of voltage-gated potassium channel complex antibodies. *J Neurol Neurosurg Psychiatry* 2017;88:353–361.
24. van Sonderen A, Schreurs MW, de Bruijn MA, et al. The relevance of VGKC positivity in the absence of LGI1 and Caspr2 antibodies. *Neurology* 2016;86:1692–1699.
25. Muñoz-Lopetegi A, de Bruijn M, Boukhrissi S, et al. Neurologic syndromes related to anti-GAD65: Clinical and serological response to treatment. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e696. doi: 10.1212/NXI.0000000000000696.
26. Bakker DP, Catsman-Berrevoets CE, Neuteboom RF. Effectiveness of a hybrid corticosteroid treatment regimen on refractory childhood seizures and a review of other corticosteroid treatments. *Eur J Paediatr Neurol* 2015;19:553–560.
27. Armangue T, Petit-Pedrol M, Dalmau J. Autoimmune encephalitis in children. *J Child Neurol* 2012;27:1460–1469.