Neuronal antibody prevalence in children with seizures < 3 years: a prospective national cohort

Joseph D. Symonds, MRCPCH, PhD[1,2], Teresa C. Moloney, PhD[3], Bethan Lang, PhD [3], Ailsa McLellan, FRCPCH [4], Mary E. O'Regan, FRCPCH, FRCPI[1], Stewart MacLeod, MRCP[1], Alice Jollands, MMPaed[5], Angela Vincent, FRCPath, FRS[3], Martin Kirkpatrick, FRCPCH[5], Andreas Brunklaus, MRCPCH, MD[1,2], Jayakara Shetty, FRCPCH[4], Liam Dorris, DClinPsych [1,2], Kirsten Forbes, FRCR[6], Ishaq Abu-Arafeh, DM, FRCPCH[7], Jamie Andrew, MRCPCH[8], Philip Brink, MMPaed[5], Mary Callaghan, FRCPCH[8], Jamie Cruden, MRCPCH[9], Christine Findlay, FRCPCH[10], Rosemary Grattan, MRCPCH[7], Jane MacDonnell, FRCPCH[11], Jean McKnight, MRCPI[12], Calum A. Morrison, FRCPCH[10], Lesley Nairn, MRCPCH[13], Elizabeth Pilley, MRCPCH, PhD[5], Elma Stephen, FRCPCH, MD[14], Selina Thomsen, HND[3], Alan Webb, MRCP[15], Margaret Wilson, BA, MSc[1], and Sameer M. Zuberi FRCPCH, MD[1,2]ǂ

1. Paediatric Neurosciences Research Group, Royal Hospital for Children, Glasgow, UK, G51 4TF
2. College of Medical, Veterinary & Life Sciences, University of Glasgow, UK, G12 8QQ
3. Nuffield Department of Clinical Neurosciences, Level5/6 West Wing, John Radcliffe Hospital, Oxford, UK, OX3 9DU
4. Department of Paediatric Neurosciences, Royal Hospital for Sick Children, Sciennes Road, Edinburgh, UK, EH9 1LF
5. Paediatric Neurology, Tayside Children's Hospital, Dundee, UK, DD1 9SY
6. Neuroradiology, Queen Elizabeth University Hospitals, Glasgow, UK, G51 4TF
7. Department of Paediatrics, Forth Valley Royal Hospital, Larbert, UK, FK5 4WR
8. Department of Paediatrics, University Hospital Wishaw, Netherton Street, Wishaw, UK, ML2 0DP
9. Department of Paediatrics, Victoria Hospital, Kirkcaldy, UK, KY2 5AH
10. Department of Paediatrics, University Hospital Crosshouse, Kilmarnock, UK, KA2 0BE
11. Department of Paediatrics, Borders General Hospital, Melrose, UK, TD6 9BS
12. Department of Paediatrics, Dumfries and Galloway Royal Infirmary, Dumfries, UK, DG2 8RX

13. Department of Paediatrics, Royal Alexandra Hospital, Paisley, UK, PA2 9PN
14. Paediatric Neurology, Royal Aberdeen Children's Hospital, Aberdeen, UK, AB25 2ZG
15. Department of Paediatrics, Raigmore Hospital, Inverness, UK, IV2 3UJ

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Corresponding author
Professor Sameer M Zuberi
Royal Hospital for Children, Glasgow, UK, G66 7AB
tel: 0044 141 452 6685
email: sameerzuberi@nhs.net

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Abstract

Objective:

To report the prevalence of anti-neuronal antibodies in a prospectively whole nation cohort of children presenting with seizures before their third birthday.

Methods:

This was a prospective population-based national cohort study involving all children presenting with new onset epilepsy or complex febrile seizures before their 3rd birthday over a three-year period. Patients with previously identified structural, metabolic or infectious cause for seizures were excluded. Serum samples were obtained at first presentation and tested for seven neuronal antibodies using live cell-based assays. Clinical data were collected using structured proformas at recruitment, and 24 months after presentation. In addition, patients with seizures and clinically suspected autoimmune encephalitis were independently identified by reviewing the case records of all children < 3 years in Scotland who had undergone electroencephalography (EEG).

Results: 298 patients were identified, recruited and underwent autoantibody testing. Antibody positivity was identified in 18/298 (6.0%). The antibodies identified were: GABABR (n = 8, 2.7%), CASPR2 (n = 4, 1.3%), GlyR (n = 3, 1.0%), LGI1 (n = 2, 0.7%), NMDAR (n = 1, 0.3%), and GABAAR (n = 1, 0.3%). None of these patients had a clinical picture of autoimmune encephalitis. Seizure classification and clinical phenotype did not correlate with antibody positivity.

Conclusions: Autoimmune encephalitis is very rare in early childhood. However serum neuronal antibodies are identified in 6.4% of children presenting with seizures < 3 years. Antibody testing should not be a routine clinical test in early childhood-onset epilepsy as in the absence of other features of autoimmune encephalitis antibody-positivity is of doubtful clinical significance. Antibody testing should be reserved for patients with additional features of encephalitis.

Introduction

Autoimmune encephalitis encompasses a constellation of acquired immune mediated conditions in which acute or subacute central nervous system dysfunction is associated with a proven or suspected autoimmune process. The ability to identify circulating antibodies directed against synaptic epitopes is a major aid to clinical diagnosis. Recent advances in the identification and detection of antibodies have allowed the characterisation of a number of autoimmune neurological syndromes in adults, about half of which are most commonly paraneoplastic in nature[1]. Some neuronal antibody encephalitides are associated with distinct phenotypic features, such as the faciobrachial dystonic seizures in LGI1-antibody disease[2], but for the majority of antibody-associated encephalitides overlapping phenotypic spectra are observed. The most common clinical features are seizures, working memory deficits, psychiatric symptoms, and encephalopathy, with movement disorders frequent in NMDAR-antibody encephalitis. Typical limbic encephalitis is associated with bilateral signal changes within the temporal lobes on MRI T2-weighted FLAIR and CSF pleocytosis, though both can be normal in a substantial minority of patients[3].

Autoimmune encephalitis is well described in the paediatric population[4]. 40% of patients with NMDAR-antibody encephalitis are < 18 years old[5], with the incidence of this specific autoimmune encephalitis estimated at 0.85 per million children per year in the UK[6]. There have been reports of children as young as eight months presenting with NMDAR encephalitis[7] and reports of children as young as 20 months benefiting from immunomodulating therapy[8]. Good quality paediatric epidemiological data for encephalitis associated with other neuronal antibodies is lacking, and antibody-defined causes appear very rare.

Rapid identification of antibodies may facilitate early initiation of specific therapy, which may in turn improve outcomes. De Bruijn et al. studied a cohort of 110 adult patients with seizures associated with autoimmune encephalitis. 14% achieved seizure-freedom whilst receiving only antiepileptic drugs (AEDs) yet 53% achieved seizure-freedom shortly after commencing immunotherapy[9].

Epileptic seizures are an early clinical feature for the majority of children presenting with antibody-associated encephalitis[10]. Since children presenting for the first time with epileptic seizures are likely to present to hospital, screening of such children for neuronal antibodies presents a good opportunity to identify autoimmune encephalitis early.

Methods

Participants were recruited from all 20 regional paediatric departments and four tertiary children's hospitals in Scotland, from May 8th 2014 to May 7th 2017. Only children who met the inclusion criteria during this time period, and who were under 36 months of age, were included. The same cohort underwent genetic testing using a gene panel of 104 genes[11].

***Inclusion criteria*:** any of: i) child receiving a new diagnosis of epilepsy (recurrent unprovoked seizures); ii) child presenting with an episode of febrile or afebrile status epilepticus (seizure >30 minutes); iii) child presenting with two or more febrile or afebrile epileptic seizures within a 24-hour period; iv) child presenting with a second prolonged (>10 minutes) febrile seizure.

***Exclusion criteria*:** Patients were excluded if an aetiology that would fully explain seizures was already established prior to or at first presentation with seizures. Patients were not

excluded if an aetiology was subsequently identified, for example through imaging or genetic testing.

Maximum case ascertainment was ensured by weekly email reminders throughout the study period to the eight paediatric neurophysiology departments, a link clinician in each of the 24 centres and all 17 epilepsy specialist nurses in Scotland. Research nurses throughout Scotland reviewed admissions to intensive care and high dependency units. A national continuing education program maintained the profile of the study.

Autoantibody testing

Serum samples were tested at the University of Oxford using live cell-based assays for antibodies to leucine rich glioma inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2), gamma-amino butyric acid receptors A and B (GABAAR, GABABR), N-Methyl-D-aspartic acid receptor (NMDAR), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and glycine receptor (GlyR). Cut-off values for considering positive were a clear signal at the following dilutions: LGI1 (1:100), CASPR2 (1:100), GABAAR (1:100), GABABR (1:50), NMDAR (1:50), AMPAR (1:50), GlyR (1:100). Methods for these antibody tests have been reported previously[12].

Clinical information

At the time of case recruitment, clinicians completed a structured proforma detailing clinical features and investigation findings (Supplement A). All proformas were reviewed by a panel of three paediatric neurologists (SMZ, AM, MK) to ensure that eligibility criteria had been met. The clinician recruiting each participant was contacted 24 months after recruitment for a diagnostic update. This update specifically enquired as to whether the patient had a diagnosis of epilepsy; how the epilepsy diagnosis was classified according to the

recommendations of the 2017 position paper of the International League Against Epilepsy (ILAE)[13]; whether a diagnosis of drug-resistant epilepsy (DRE) had been made; and whether the child satisfied a diagnosis of global developmental delay (GDD). DRE was defined as a child continuing to have seizures (at least one pre six months) despite two adequately trialled and tolerated anti-epileptic drug (AED) regimens. GDD was defined as a developmental attainment at least two standard deviations below the mean for age in at least two different domains of development (gross motor, fine motor, speech and language, or social).

As a separate study the same cohort of patients underwent genetic testing, involving a 104 gene panel[11]. Gene panel testing identified a causative genetic variant in 24% of patients, with the most commonly-implicated genes being *PRRT2*, *SCN1A*, *KCNQ2*, and *SCL2A1*. Genetic diagnosis was significantly associated with early age of onset, presentation with afebrile focal seizures, and with development of both drug-resistance and developmental impairment at 2-year follow-up.

Further biochemical, genetic and neuroradiological investigations, including lumbar puncture, chromosomal microarray, directed single gene sequencing, whole genome sequencing, and MRI neuroimaging were requested at the discretion of the recruiting clinician and these results were available to them as per usual clinical practice. The recruiting clinician was blinded to the results of antibody testing, unless they had also requested antibody testing on a clinical basis.

Clinical case identification

To determine if there were any children with clinically diagnosed with autoimmune encephalitis presenting during the study period who were not recruited to the prospective

study we reviewed the case records of all children who had undergone EEG investigation across the eight paediatric EEG departments in Scotland. The case records of all children who underwent EEG between January 1st 2014 and December 31st 2017 and who were under 48 months of age were reviewed (total number = 2,396). Children who were over 36 months of age at presentation and children who presented before May 8th 2014 or after May 7th 2017 were excluded.

Blinded neuroimaging review

Additional review of MRI neuroimaging was undertaken by a neuroradiologist (KF) who was blinded to the antibody findings in each case. MRI scans of all patients with antibody positivity who had undergone MRI, and an equal number of closely age-matched patients from this cohort without positive neuronal antibodies were reviewed systematically. Images were scored according to the presence or absence of features suggestive of autoimmune encephalitis (Supplement B).

Population data

Denominator data for the <3 years population in Scotland during the study period were taken from National Records of Scotland birth records[14]. The figures were as follows: 2014 – 172,570; 2015 – 170,492; 2016 – 169,265. The sum of these figures comes to 512,237 person-years.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the United Kingdom NHS National Research Ethics Service. Signed parental consent for immunological testing, and for questionnaire-based follow-up, was obtained for each participant in the prospective study.

Role of the Funding Sources

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data Availability

Following publication of this manuscript all anonymised data upon which this study is based will be deposited and freely available on the University of Glasgow Enlighten Research Data Repository, available at http://researchdata.gla.ac.uk/

Results

298 participants were recruited, underwent testing for seven neuronal antibodies, and were followed up for 24 months.

At 24 months post-presentation, 228 (76.5%) of participants had a diagnosis of epilepsy, 87 (29.2%) had a diagnosis of GDD, and 63 (21.1%) had DRE. Epilepsy classification for all participants, 24 months after presentation, is shown in Table 1. The full spectrum of early childhood epilepsies is represented in this cohort. For the majority, a precise epilepsy syndrome classification could not be achieved.

None of the patients recruited to the prospective study was deemed to have encephalitis clinically. Nevertheless, neuronal antibodies were identified in serum of 18 (6.0%) of patients (Figure 1), including one who was positive for both NMDAR- and GABABR-antibodies. Age-related control data using these live assays are not available, and the only systematic study of asymptomatic adults used the commercially-available fixed assays[15].

GABABR-antibodies were more common in this cohort (8/228, 2.7%) than in that study (0.2%).

The epilepsy syndromes diagnosed in each of the 18 individuals with positive antibodies are shown in Table 2. The antibodies were not associated with any of the clinical presentations (Supplement C). The ages at presentation of the antibody positive patients were evenly distributed throughout the three years (Supplement D).

Nine (47%) of the 18 antibody-positive patients also have genetic diagnoses. One patient, with a paternally inherited duplication of the *KCNQ2* gene (44kb duplication at 20q13.33) also had LGI1 antibodies. This patient came from a family with a dominant family history of self-limited infantile seizures. Benign familial neonatal seizures is a typical phenotype in this duplication syndrome[16], though in this family seizure onset was later at between three and six months of age. The patient began having seizures at four months of age. Unlike in the other affected family members, seizures were drug-resistant and were associated with severe global developmental delay and cerebral visual impairment. At 34 months of age the patient was functioning at six month level for gross motor, fine motor, visual and social skills, and at eight month level for speech and language.

242 patients had neuroimaging, of whom 218 had MRI and 24 had CT only. Out of the 242 patients who had MRI (n=218) or CT (n=24), 17 patients had a structural aetiology identified. Of these, none was antibody-positive. On blinded review of the MRI brain scans of all 11 antibody-positive patients who had had MRI and 11 age-matched antibody-negative patients, none showed radiological features of encephalitis. Seven of the antibody-positive patients underwent diagnostic lumbar puncture at the time of their initial presentation. In all seven cases the CSF cell count, protein, and glucose were in the normal range for age.

From the retrospective EEG/case note review only one patient with autoimmune encephalitis was identified, and this was secondary to viral encephalitis. This individual presented at 21 months of age with focal seizures and encephalopathy. Herpes Simplex Virus (HSV) was isolated from his cerebrospinal fluid (CSF). This patient was not recruited to the prospective study since an aetiology had been identified. Herpes simplex encephalitis was associated with a destructive brain lesion with bilateral perisylvian cortical and subcortical abnormalities on MRI and subsequent cortical atrophy. At first presentation NMDAR antibodies were tested and were negative. Four weeks later the patient developed a hyperkinetic movement disorder. Both serum and CSF tested positive for NMDAR antibodies. Secondary NMDAR encephalitis following HSV encephalitis is a recognised association[17,18].

Discussion:

Autoimmune encephalitides are rare conditions[3]. In this prospective population-based cohort study we have shown that in children < 3 years of age, these are extremely rare. Nevertheless, 6% of the patients had positive serum neuronal antibodies which did not associate with any of the clinical features studied. Additionally blinded review of the MRI brain scans of 11 antibody-positive patients and 11 age-matched antibody-negative patients showed no radiological features of encephalitis.

Only one patient <3 years presented in Scotland with clinically suspected autoimmune encephalitis over the three-year period of this study, and this was secondary to Herpes simplex encephalitis[17,18]. This equates to an incidence of autoimmune encephalitis in this age group of 0.19 per 100,000 person-years. Given the wide confidence intervals from a small study population, this figure is not very different from the 0.085 per 100,000 person-

years for all paediatric NMDAR encephalitis, estimated from a UK prospective surveillance study which included patients aged 0-17 years[6].

There is a well-established link between autoimmune disease (AD) and epilepsy. One in five people with epilepsy has a co-morbid AD. This link appears to be stronger with paediatric-onset disease. In a study evaluating insurance records of >2.5 million individuals in the United States, the odds ratio for a diagnosis of epilepsy was 3.8 (95% CI, 3.6-4.0) in patients who had one or more of the following autoimmune diseases: type 1 diabetes mellitus, psoriasis, rheumatoid arthritis, Graves disease, Hashimoto thyroiditis, Crohn disease, ulcerative colitis, systemic lupus erythematosus, antiphospholipid syndrome, Sjogren syndrome, myasthenia gravis, coeliac disease. In the < 18 years age group the odds ratio was 5.2 (95% CI, 4.1-6.5). A temporal association between AD and epilepsy has also been observed, with most patients experiencing seizure onset within the first two years of AD diagnosis. This observation lends support to the hypothesis that seizures in these patients may be a direct result of an autoimmune process, as opposed to reflecting a shared genetic predisposition[19].

When adults presenting with seizures are tested for neuronal antibodies in serum, the presence of these antibodies is usually associated with features of autoimmune encephalitis, including history of viral prodrome, neuropsychiatric changes, autonomic instability, and medial temporal sclerosis on MRI[20]. Antibody-positive adults with epilepsy are less likely to respond to conventional anti-epileptic medication, and more likely to respond to immunomodulating treatments[20,21].

Unlike in adults, when cohorts of children with epilepsy are tested for serum neuronal antibodies, associations with clinical features of encephalitis and with drug-resistance are

less clear. Earlier studies, several before the discovery of neuronal surface antibodies as we examined here, measured VGKC-complex antibodies, which can target intracellular epitopes, and GAD antibodies which always target the intracellular enzyme[22]; both of these are relatively common in epilepsy patients but are unlikely to be directly pathogenic. Wright et al. retrospectively analysed the serum of 178 patients recruited to the Dutch Study of Epilepsy in Childhood (DESC). They tested for antibodies to NMDAR, CASPR2 and contactin-2. Overall 14 patients (7.7%) were antibody positive. The antibody positive patients did not differ from the antibody negative patients in terms of seizure types, age of onset, seizure frequency or AED response. Wright and colleagues also noted that, despite not receiving specific treatment, the majority of patients with antibody positivity became antibody negative over time, whilst others developed antibodies at a later stage[23]. Borusiak et al. screened for serum GAD65, VGKC, LGI1 and CASPR2 antibodies in 124 children who were seen in a single epilepsy centre and diagnosed with focal epilepsy. 5/124 (5%) were antibody positive, and none of these were thought to have features characteristic of autoimmune encephalitis[24].

Thus the findings from our prospective population-based study support the conclusion that antibody positivity in children presenting with seizures is usually non-specific, and is rarely associated with a clinical picture of encephalitis. There are several specific strengths to this cohort. First, it includes more children than previous paediatric cohorts. Second, there was minimal selection bias since all children presenting with seizures in Scotland over a three-year period were eligible. Third, we tested a wider array of antibodies than previous paediatric cohorts. Finally, this cohort was extensively investigated for other aetiologies, most notably though genetic testing, with 281/298 (94.3%) being tested on a 104 gene epilepsy panel. Comprehensive investigation for alternative aetiologies allowed us to

compare differences in antibody positivity between those with and without confirmed aetiologies. There were no significant differences observed. Antibody positivity was found in 5/69 (7.2%) patients with a genetic cause, and in 14/229 (6.1%) patients without a genetic cause. Whilst this clearly supports the notion that neuronal antibodies are unlikely to be sufficient to cause epilepsy in this age group on their own, it does not exclude the possibility that they may be part of a more complex multi-factorial picture. Indeed in the case of one patient with both genetic *KCNQ2* duplication and LGI1 positivity, it is possible that a genetic potassium channel disease had somehow initiated an antibody response to LGI1, which is part of a potassium channel complex; alternatively, the spontaneous presence of LGI1 antibodies may have modified expression of the genetic disorder.

The only antibody that was more prevalent in this cohort than in healthy adult control populations was GABABR. This antibody is associated with adult-onset limbic encephalitis, a condition characterised by behavioural and cognitive changes and prominent seizures which are often prolonged. Two thirds of adult patients affected by GABABR encephalitis have a tumour, most commonly non-small cell lung cancer[25]. The significance of GABABR antibodies in this <3 years paediatric epilepsy group is unclear, but is worthy of further investigation, particularly since all of those with GABABR positivity presented in the first 18 months of life. However, as with the other patients with antibody positivity, those with GABABR positivity presented with a variety of clinical phenotypes not suggestive of encephalitis and included patients with a confirmed genetic cause for their epilepsy (1 Wolf-Hirschhorn, 1 *PRRT2*, 1 *ALG3*). We identified four patients with CASPR2 antibodies and two with LGI antibodies. Autoimmune syndromes associated with these potassium channel antibodies have previously been reported in children as young as two years, but in these cases seizures are typically associated with encephalopathy, behavioural changes, and/or

dyskinesia[26]. Three patients in our cohort had GlyR antibodies. GlyR associated disease also been reported to affect children as young as one year, albeit very rarely. These patients more often show typical features of progressive encephalomyelitis with rigidity and myoclonus (PERM)[27].

Limitations:

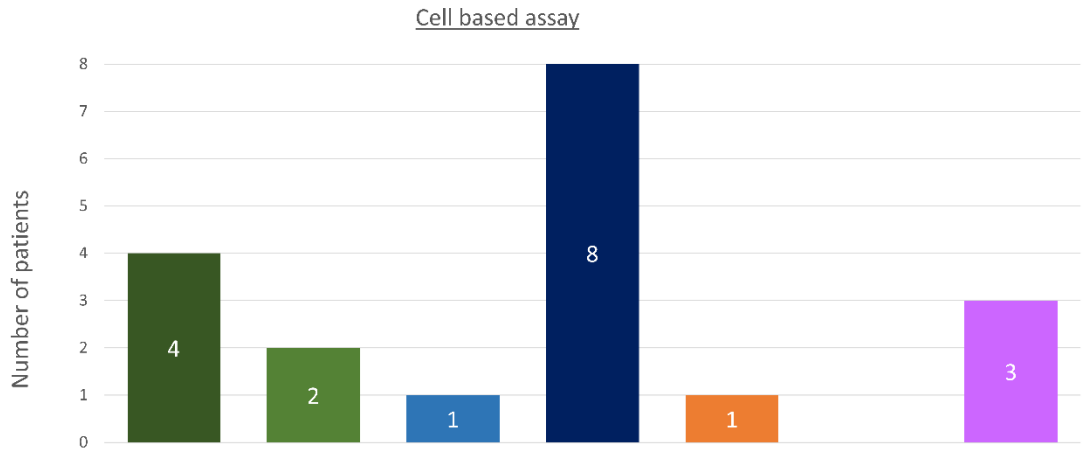
- The prevalence of positive neuronal antibodies in healthy young children without epilepsy is not known. We relied on published data from adult healthy controls.
- In the majority of patients only serum samples were tested. Testing for antibodies in the CSF may only be appropriate if lumbar puncture is clinically indicated.
- Samples were only tested at initial presentation with seizures. Repeat testing over a period of time may determine the natural course of antibody positivity.
- This study only included children under three years of age, an age group not typically thought to be high risk for autoimmune encephalitis.
- In young infants IgG antibodies may be transplacentally transmitted from the mother. We did not test mothers in this cohort for antibodies.
- The current study was limited to the common neuronal antibodies and did not test for other rarer encephalitis-associated neuronal antibodies
- Future follow up studies of these patients is needed to establish the natural course and the relationship between antibody-positivity and later development of autoimmune neurological syndromes

Conclusions:

A small proportion of children presenting with seizures in the first 36 months of life have circulating neuronal antibodies. In only a very small fraction of cases are these associated with a clinical picture of autoimmune encephalitis. The significance of antibody positivity in those without encephalitis is unclear but these are unlikely to provide an aetiological explanation for the epilepsy. We do not recommend routine testing for neuronal antibodies in patients presenting with early childhood onset epilepsy.

Figure Legend

Figure 1: 19 positive cell-based assays in 18 patients. Dilution is that used in the assays; only samples giving a clear signal on the surface of the live cells were designated as positive.



Number positive	4	2	1	8	1	0	3
Percentage	1.3%	0.7%	0.3%	2.7%	0.3%	0.0%	1.0%
Population %[15]	1.4%	1.2%	1.3%	0.2%	1.1%	0.1%	1.3%
Antibody	CASPR2	LGI1	GABAAR	GABABR	NMDAR	AMPAR	GlyR
Dilution	1:100	1:100	1:100	1:50	1:50	1:50	1:100

Table 1 – Epilepsy syndrome classification 24 months after initial presentation

Epilepsy syndrome	Number
Developmental and epileptic encephalopathies (DEE), n = 41	
West syndrome	22
Dravet Syndrome	10
Early infantile-onset* DEE, including Ohtahara syndrome, Early Myoclonic Encephalopathy (EME), and Epilepsy of Infancy with Migrating Focal Seizures (EIMFS) *onset at < 4 months of age	9
Self-limited epilepsies, n = 24	
Self-limited familial neonatal epilepsy	4
Self-limited non-familial neonatal epilepsy	3
Self-limited familial infantile epilepsy	3
Self-limited non-familial infantile epilepsy	10
Myoclonic epilepsy of infancy	4
Other specific syndromes, n = 35	
Febrile seizures plus	13
Epilepsy with myoclonic atonic seizures	10
Early onset absence epilepsy	7
Epilepsy with myoclonic absences	1
Absences with eyelid myoclonia	1
Glut1-deficiency syndrome	1
Infantile spasms without hypsarrhythmia	1
Panayioutopoulos syndrome	1
Unclassified epilepsies, n = 128	
Unclassified focal epilepsy	52
Unclassified generalised epilepsy	13
Unclassified focal and generalised epilepsy	10
Unclassified myoclonic epilepsy	5
Unclassified epilepsy	48
Not epilepsy, n = 70	
Single episode of afebrile status epilepticus (>30 mins)	5
Single cluster of afebrile seizures (2 or more in 24 hours)	7
Febrile status epilepticus (>30 mins)	33
Cluster(s) of febrile seizures (2 or more in 24 hours)	16
Recurrent prolonged (> 10 mins) febrile seizures	9

Table 2 – epilepsy syndromes diagnosed in patients with positive antibody findings

Antibody			
CASPR 2	**Total number**	**4**	
	Syndrome classification		
	Unclassified focal epilepsy	2	
	Unclassified epilepsy	1	
	West syndrome	1	
LGI1	**Total number**	**2**	
	Syndrome classification		
	Other early infantile-onset DEE	1†	† Had causative *KCNQ2* gene variant
	Unclassified epilepsy	1	
GABAAR	**Total number**	**1**	
	Syndrome classification		
	Single cluster of febrile seizures	1	
GABABR	**Total number**	**8**	
	Syndrome classification		
	Unclassified epilepsy	2Ψ	Ψ 1 Also positive for NMDAR and had Wolf-Hirschhorn syndrome
	Self-limited familial infantile epilepsy	1	† Had a causative *PRRT2* gene variant
	Febrile seizures plus	2	
	West syndrome	1	
	Other early infantile-onset DEE	1†	† Had causative *ALG3* gene variants
	Febrile status	1	
NMDAR	**Total number**	**2**	
	Syndrome classification		
	Unclassified epilepsy	1*	* Also positive for GABABR
AMPAR	**Total number**	0	
GlyR	**Total number**	**3**	
	Syndrome classification		
	Myoclonic epilepsy of infancy	1	
	Unclassified myoclonic epilepsy	1†	† Had causative *SLC2A1* variant
	Unclassified epilepsy	1	

Table 3 – Associations between antibody-positivity and clinical features of the seizure disorder

	N (%) autoantibody positive	Odd's ratio for antibody positivity [95% confidence intervals], using Fisher's exact test*	Statistical significance
Total cohort	18/298 (6.0%)		
Age of first seizure			
< 6 months	4/70 (5.7%)	0.93 [0.29-2.9]	n.s.
6-12 months	5/75 (6.7%)	1.2 [0.40-3.4]	n.s.
12-18 months	7/63 (11.1%)	2.6 [0.98-7.2]	n.s.
18-24 months	1/40 (2.5%)	0.36 [0.047-2.8]	n.s.
24-30 months	0/21 (0.0%)	Not calculable	n.s.
30-36 months	1/29 (3.4%)	0.53 [0.068-4.1]	n.s.
Type of first seizure			
Febrile generalised (not including status)	2/37 (5.4%)	0.88 [0.19-4.0]	n.s.
Febrile focal (not including status)	0/7 (0.0%)	Not calculable	n.s.
Febrile status (generalised or focal)	3/44 (6.8%)	1.2 [0.32-4.2]	n.s.
Afebrile focal (not including status)	6/73 (8.2%)	1.6 [0.57-4.4]	n.s.
Afebrile status (generalised or focal)	1/20 (5.0%)	0.81 [0.10-6.4]	n.s.
Afebrile unclassified	0/3 (0.0%)	Not calculable	n.s.
Infantile spasms	2/21 (9.5%)	1.7 [0.37-8.0]	n.s.
Afebrile generalised (not including status) ¥	4/93 (4.3%)	0.61 [0.20-1.9]	n.s.
Afebrile generalised tonic-clonic	1/47 (2.1%)	0.30 [0.039-2.3]	n.s.
Afebrile generalised myoclonic	2/21 (9.5%)	1.7 [0.37-8.0]	n.s.
Afebrile generalised tonic	1/9 (11.1%)	2.0 [0.24-17]	n.s.
Afebrile generalised atonic	0/3 (0.0%)	Not calculable	n.s.
Afebrile generalised absence	0/12 (0.0%)	Not calculable	n.s.
Findings at 24 month follow-up			
Genetic aetiology identified	5/69 (7.2%)	1.3 [0.45-3.8]	n.s.
Structural aetiology identified	0/15 (0.0%)	Not calculable	n.s.
Epilepsy diagnosed	16/228 (7.0%)	2.6 [0.58-11]	n.s.
Global developmental delay	8/87 (9.2%)	2.0 [0.78-5.3]	n.s.
Drug-resistant epilepsy	4/63 (6.3%)	1.1 [0.34-3.4]	n.s.

¥ Composite group including all generalised seizure types, with subgroups listed in the subsequent five rows

* Numbers rounded to two significant figures

n.s.: not significant

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