Paediatric brainstem encephalitis associated with glial and neuronal autoantibodies

YAEL HACOHEN[1] | YUKIHIRO NISHIMOTO[2] | YUKI FUKAMI[3] | BETHAN LANG[1] | PATRICK WATERS[1] | MING J LIM[1,4] | NOBUHIRO YUKI[3,5] | ANGELA VINCENT[1]

1 Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, UK. **2** Department of Pediatrics, Wakayama National Hospital, Wakayama, Japan. **3** Department of Medicine, Yong Loo Ling School of Medicine, National University of Singapore, Singapore, Singapore. **4** Children's Neurosciences, Evelina London Children's Hospital, at Guy's and St Thomas' NHS Foundation Trust, King's Health Partners Academic Health Science Centre, London, UK. **5** Department of Physiology, Yong Loo Ling School of Medicine, National University of Singapore, Singapore, Singapore.

Correspondence to Angela Vincent at Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Level 6, West Wing, Oxford OX3 9DU, UK.
E-mail: angela.vincent@ndcn.ox.ac.uk

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ABBREVIATIONS

ADEM	Acute disseminated encephalomyelitis
BBE	Bickerstaff's brainstem encephalitis
AQP4	Aquaporin-4
CIS	Clinically isolated syndrome
GlyR	Glycine receptor
MOG	Myelin oligodendrocyte glycoprotein
NMDAR	*N*-methyl-D-aspartate receptor
VGKC	Voltage gated potassium channel

AIM Central nervous system (CNS) autoantibodies have been reported in a range of neuroimmune diseases, but there has not been a systematic evaluation of autoantibodies in paediatric patients with brainstem encephalitis.
METHOD Serum samples from 57 children (40 male, 17 female, median age 12y, range 0.6–18y) with a diagnosis of brainstem encephalitis were tested retrospectively for antibodies to GQ1b, aquaporin-4 (AQP4), myelin oligodendrocyte glycoprotein (MOG), *N*-methyl-D-aspartate receptor, LGI1, CASPR2, glycine receptor (GlyR), DPPX, and the voltage gated potassium channel (VGKC)-complex.
RESULTS Disease localized to the brainstem was seen in 19 patients: Bickerstaff's brainstem encephalitis (n=14) and clinically isolated syndrome (n=5). Polyfocal presentation was seen in 38 children, with predominantly white matter disease in 18 patients and grey matter in 20 patients. CNS surface antibodies were found in 22/57 patients (two patients with double positivity): GQ1b (n=6), NMDAR (n=7), GlyR (n=5), MOG (n=5), and one AQP4. Three patients were positive for VGKC-complex antibodies. All patients were negative for antibodies to DPPX and the VGKC-complex antigens LGI1, CASPR2, and contactin-2. Although there were some partial differences in the presentations, the clinical features and outcomes did not relate clearly to the presence or absence of specific antibodies.
INTERPRETATION As determined retrospectively, 39% of patients had cell surface antibodies. The results did not suggest any relationship with treatment or outcomes obtained but it is possible that specific antibody detection could be a helpful guide to more intensive immunotherapies in some cases.

Brainstem encephalitis is an uncommon condition, and little is known about the aetiologies. Several entities including infectious, autoinflammatory, and paraneoplastic syndromes have been reported. A cross-sectional study at a single hospital in the USA identified inflammatory/autoimmune aetiology in 54 (67%) of 81 adult patients with brainstem encephalitis, but these patients were not tested for any specific antibodies (Ab).[1] However, it is clear that antibodies can diffuse into the area postrema, which lacks a blood brain barrier, as in neuromyelitis optica,[2] and other brainstem regions may also be permeable, as inferred recently from rodent studies.[3] Moreover, brainstem involvement is not uncommon in antibody-mediated central nervous system (CNS) disorders. This includes autonomic symptoms such as hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, and erectile dysfunction in patients with *N*-methyl-D-aspartate receptor (NMDAR)-Ab encephalitis;[4] vomiting, hiccups, oculomotor dysfunction in patients with aquaporin-4 (AQP4)-Ab positive neuromylitis optica;[5] a predominant brainstem disease in patients with glycine receptor (GlyR)-Ab and progressive encephalomyelitis with rigidity and myoclonus;[6] diplopia, dysphagia, and respiratory failure in patients with dipeptidyl-peptidase-like protein-6-Ab;[7] and, most closely linked, GQ1b antibodies in Bickerstaff's brainstem encephalitis (BBE).

The aims of this study were to: (1) evaluate retrospectively a cohort of paediatric patients with signs of brainstem encephalitis for the presence of both neuronal and glial antibodies; and (2) by studying the clinical features at presentation, the response to treatment and the long-term outcomes, infer on the clinical relevance of CNS antibodies in brainstem encephalitis.

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METHOD

Patients

Since the identification of GQ1b ganglioside antibodies in patients with BBE, sera from Japanese patients, who were suspected of having BBE and a range of brainstem syndromes, were referred to the neuroimmunology laboratory in Dokkyo Medical University from 1996 to 2013. Demographic and clinical data for each patient at presentation and at 1-year follow-up, including sex, age at onset, and results of laboratory, electrophysiological, and neuroimaging testing were reviewed. Brainstem encephalitis was diagnosed for patients with encephalopathy (depressed or altered level of consciousness, lasting more than 24 hours, lethargy, or change in personality or behaviour[8]) and (1) predominant brainstem signs (cranial neuropathies or ataxia) and neuroimaging findings of brainstem abnormalities, or (2) a clinical syndrome unequivocally localized to the brainstem. All patients were managed according to their primary diagnosis, and not antibody results which were mostly obtained retrospectively.

As patients with encephalopathy and brainstem features may fulfil a number of clinical diagnoses, these were re-reviewed by an expert panel (YN, YF, YH, ML). Brainstem syndromes were characterized, by the neurological features at presentation, to those that localize to the brainstem (clinically monofocal) or additionally involve multiple CNS regions (polyfocal) (Fig. 1). As the encephalopathy in some of the cases was thought to be part of the brainstem syndrome, these cases were reclassified according to the International Pediatric Multiple Sclerosis Study Group criteria to clinically isolated syndrome (CIS).[9] Patients with polyfocal encephalopathy were divided into conditions that clinically appear to primarily affect the white matter or the grey matter (encephalitis). Figure 1 shows the patients and their subclassifications. The modified Rankin Scale (mRS) for children, as previously used by Bigi et al.,[10] was used to assess the degree of disability at 1-year follow-up.

Autoantibody testing

Serum samples (no CSFs) taken within 3 months of symptom onset had been tested for IgG anti-GQ1b antibodies by an enzyme-linked immunosorbent assay and stored at −80°C. Samples were sent to Oxford and screened for antibodies to NMDAR, LGI1, CASPR2, Contactin-2, GlyR, and dipeptidyl-peptidase-like protein-6 using immunofluorescence cell-based assays in routine clinical use (sera at 1:20 dilution except for CASPR2 and Contactin-2, 1:100, and MOG, 1:160) as previously described, where healthy and disease controls were used to optimise the assays.[6,11–14] For these cell-based assays, the binding of serum IgG to the surface of human embryonic kidney cells, transfected with cDNA encoding the auto-antigens, was visualised using a fluorescence-labelled secondary antibody. All assays were assessed by two independent observers (YH, PW). Positive serum samples were further diluted to determine their end-point titres. VGKC-complex antibodies were measured by immunoprecipitation of rabbit brain VGKC-complexes labelled with radioactive dendrotoxin.[12]

What this paper adds

- 39% of children with brainstem encephalitis had antibodies to central nervous system surface antibodies.
- Antibody-positive patients had phenotypes broadly associated with the specific antibody.
- Results did not suggest any relationship with immunotherapies or outcomes.
- Nevertheless, detection of antibodies at onset could be a guide to intensive immunotherapies.

Statistical analysis

Non-parametric statistical tests (Kruskal–Wallis tests) were used for continuous distributions as appropriate given normality, and χ^2 or Fisher's exact tests were used for nominal data.

Ethical approval

Written informed parental consent was obtained from each patient, and the ethics committee at Dokkyo Medical University approved the study.

RESULTS

Antibodies detected

Sera from 57 children were tested (40 male, 17 female, median age 12y, range 0.6–18y). Although patients were referred with a suspected diagnosis of BBE, only 14 patients (25%) fulfilled the diagnostic criteria[15] of external ophthalmoplegia and ataxia, with disturbance of consciousness or hyperreflexia. In five children, the encephalopathy was thought to be secondary to a symptomatic brain lesion and they were reclassified to CIS. Thirty-eight children had a polyfocal encephalopathy; 18 with predominant white matter disease (hereafter called acute disseminated encephalomyelitis [ADEM]), and 20 with predominant grey matter encephalitis.

Six patients had GQ1b-Abs. CNS surface antibodies (end point titres) were identified in 16: seven NMDAR (1:200–1:1600, median 1:800), five MOG (1:800–1:1600, median 1:1600), five GlyR 1:100–1:400, median 1:400), and one AQP4 (1:800). Two patients were positive for two antibodies (NMDAR/GlyR and MOG/GlyR). All patients were negative for LGI1, CASPR2, and contactin-2. Fifteen patients were positive on the VGKC-complex mmunoprecipitation assay (111–527pM, median 231pM) but only three had antibody titres >400 pm, a cut-off previously shown to be useful in identifying children with inflammatory diseases.[16] Of these three, one had both NMDAR and GlyR Abs and one had AQP4-Abs. Thus, overall, 17 individuals had antibodies detected.

Clinical associations

Antibodies to GQ1b were found in six of the 13 (46%) patients with BBE and were specific to that syndrome. The one patient with AQP4-Ab presented with somnolence, ataxia, nystagmus, sensory abnormalities, and hyperreflexia. All patients with NMDAR-Ab were diag-

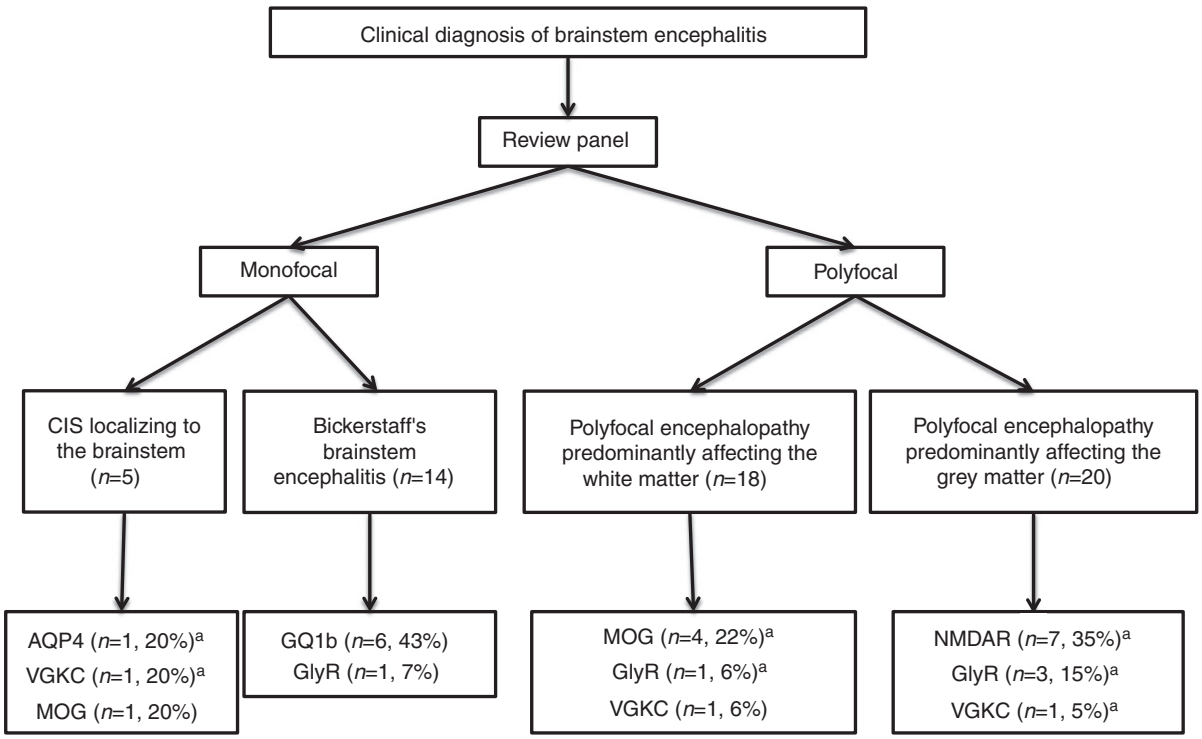

Figure 1: Flow chart of samples and results. Brainstem syndromes were characterized by the neurological features at presentation to those that localized to the brainstem (clinically monofocal) or additionally involved multiple central nervous system regions (polyfocal). As the encephalopathy in some of the cases was thought to be part of the brainstem syndrome, these cases were reclassified as CIS. Patients with polyfocal encephalopathy were divided into conditions that clinically appeared to primarily affect the white matter (ADEM) or the grey matter (encephalitis). [a]Three patients were positive for more than one antibody: NMDAR/GlyR/VGKC, MOG/GlyR, and VGKC/AQP4. CIS, clinically isolated syndrome.

nosed with encephalitis and had at least one of psychiatric features, movement disorder, or seizures. MOG-Ab were only seen in patients with acquired demyelinating syndromes (ADEM 4, CIS 1) presenting with T2 hyperintensities on MRI and reactive CSF. GlyR-Ab were seen in three patients with grey matter encephalitis (one fulfilling criteria for BBE) and in a patient with ADEM also positive for MOG-Ab. Further demographic, clinical and paraclinical features of all patients are summarised in Tables I and II.

The treatments and outcomes, where available, are also detailed in Table I. Most patients were given acyclovir and prednisolone, and around 60% also received intravenous immunoglobulins. The outcomes were generally good with a median mRS score of 1. There was no difference in outcomes between the antibody-positive and antibody-negative groups (range 1–3, median 1 vs range 1–5, median 1). However, two of the children with NMDAR-Abs were left with severe learning difficulties.

DISCUSSION

Autoantibodies to glial and neuronal antigens have been reported in a range of well-defined neurological syndromes and a growing range of disorders in which the clinical relevance of the antibodies is less clear.[17] In this first study to focus on a range of brainstem inflammation in a large paediatric cohort, we identified surface antibodies against GQ1b, neuronal and glial antibodies in 39% of patients with brainstem encephalitis. Although all patients had brainstem involvement, the clinical features were often partly those associated with the specific antibodies identified.

In 1951, Bickerstaff and Cloake reported three cases of reversible brainstem encephalitis with benign outcome.[18] The concept of autoantibody-associated encephalitis had not been proposed at the time when they astutely recognized the importance of disease pattern recognition and postulated an autoimmune mechanism. The syndrome defined by Bickerstaff of acute progressive, external ophthalmoplegia and ataxia, with hypersomnolence, has subsequently been associated with IgG anti-GQ1b antibodies.[19] Some investigators argued that one of the three original participants, a 24-year-old female with severe encephalopathy and an ovarian cyst, had features more consistent with anti-NMDAR encephalitis.[20] This patient had a movement disorder, psychiatric features, and seizures; features not typically seen in patients with brainstem encephalitis. None of the patients in the current study with BBE had NMDAR-Abs, but one patient who fulfilled the clinical criteria for BBE had GlyR-Abs rather than GQ1b-Abs.

Table I: Clinical and paraclinical features of children with brainstem encephalitis

	BBE, *n*=14	CIS, *n*=5	ADEM, *n*=18	Encephalitis, *n*=20	*p* value[a]
Age in y, median (IQR)	13.3 (9.3–13.3)	14 (6.5–14.5)	5.5 (2.75–12.5)	11 (5.5–12)	0.076
Sex, male:female	10:4	2:3	15:3	13:7	0.269
Autoantibodies (%)					
GQ1b	6 (43)	0 (0)	0 (0)	0 (0)	0.001
NMDAR	0 (0)	0 (0)	0 (0)	7 (35)	0.002
MOG	0 (0)	1 (20)	4 (22)	0 (0)	0.0435
GlyR	1 (7)	0 (0)	1 (6)	3 (15)	0.630
AQP4	0 (0)	1 (20)	0 (0)	0 (0)	0.014
VGKC	0 (0)	1 (20)	1 (6)	1 (5)	0.398
Seronegative	7 (50)	3 (60)	13 (72)	10 (50)	0.495
Clinical features, *n*=57 (%)					
Opthalmoplegia, *n*=35 (61)	14 (100)	4 (80)	10 (55)	7 (35)	0.001
Ataxia, *n*=41 (72)	14 (100)	4 (80)	18 (100)	5 (25)	<0.001
Bulbar/facial weakness, *n*=34 (60)	11 (79)	2 (40)	9 (50)	11 (60)	0.303
Respiratory support, *n*=14 (25)	1 (7)	0 (0)	9 (50)	4 (20)	0.015
Seizures, *n*=13 (23)	0 (0)	0 (0)	5 (28)	8 (40)	0.032
Movement disorder, *n*=14 (25)	1 (7)	0 (0)	3 (17)	8 (40)	
Dyskinesia	0 (0)	0 (0)	2 (11)	7 (35)	0.028
Myoclonus	1 (7)	0 (0)	1 (6)	1 (5)	0.944
Psychiatric features, *n*=11 (19%)	0 (0)	0 (0)	3 (17)	8 (40)	0.018
Investigations (%)					
Abnormal brain MRI, *n*=32	2 (14) 2 oedema	5 (36) >2 T2 hyperintense lesions	18 (100) >2 T2 hyperintense lesions	7 (35) 6 oedema, 1 atrophy	<0.001
CSF pleocytosis, *n*=30	4 (29)	2 (40)	11 (61)	13 (65)	0.018
Elevated CSF protein	2 (14)	2 (40)	4 (22)	8 (40)	0.336
Outcome					
mRS, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1.75)	1 (0.5–3)	0.728

[a]4 way χ^2. BBE, Bickerstaff's brainstem encephalitis; CIS, clinically isolated syndrome; ADEM, acute disseminated encephalomyelitis; IQR, interquartile range; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; mRS, modified Rankin Scale.

Table II: Clinical and paraclinical features of antibody-positive children

	NMDAR, *n*=7	GlyR, *n*=5	MOG, *n*=5	GQ1B, *n*=6	*p* value[a]
Age in y, median (IQR)	6 (6–16)	12 (3.5–16.5)	8 (2.5–13)	14 (11–17)	0.092
Sex, male:female (%)	2:5 (71)	4:1 (20)	3:2 (40)	5:1 (16)	0.164
Diagnosis (%)					
BBE, *n*=14	0 (0)	1 (20)	0 (0)	6 (100)	0.002
ADEM[b], *n*=18	0 (0)	1 (20)	4 (80)	0 (0)	0.004
CIS[c], *n*=5	0 (0)	0 (0)	1 (20)	0 (0)	0.288
Encephalitis, *n*=20	7 (100)	3 (60)	0 (0)	0 (0)	0.004
Clinical features (%)					
Opthalmoplegia	1 (14)	3 (60)	1 (20)	6 (100)	0.009
Ataxia	0 (0)	3 (30)	3 (60)	6 (100)	0.004
Bulbar/facial weakness	4 (57)	4 (80)	2 (40)	6 (100)	0.141
Respiratory support	1 (14)	0 (0)	2 (40)	0 (0)	0.182
Seizures	3 (43)	1 (20)	1 (20)	0 (0)	0.318
Movement disorder	5 (71)	1 (20)	1 (20)	1 (17)	0.112
Psychiatric features	4 (57)	0 (0)	0 (0)	0 (0)	0.011
Investigations (%)					
Abnormal brain MRI	3 (43) 2 oedema, 1 atrophy	3 (60)	5 (100) 5>2 T2 hyperintense lesions	0 (0)	0.010
CSF pleocytosis	5 (71)	3 (60)	4 (80)	1 (17)	0.129
Outcome					
Median mRS	1	1	1	1	0.306

[a]4 way χ^2. [b]A 7-year-old male with ADEM and VGKC-complex antibodies titres of 527pM was not included in the table's subcategories. [c]A patient with CIS and AQP4-Abs was not included in the table's subcategories. IQR, interquartile range; BBE, Bickerstaff's brainstem encephalitis; ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; mRS, modified Rankin Scale.

The incidence of NMDAR-Ab in this cohort of patients with brainstem encephalitis (12%) was lower than we previously reported in a UK cohort of paediatric autoimmune encephalitis (27%),[21] but higher than an unselected cohort of children with encephalitis from Australia and a UK cohort of children presenting with acquired demyelinating syndromes[22] in whom NMDAR-Ab were identified in only 6% and 3% respectively. Patients presented with disease involving the grey matter but also the white matter, which highlighted that brain stem inflammation (or a brain stem

syndrome per se) may sometimes be a clinical marker of anti-NMDAR encephalitis, as previously suggested.[23,24] Similarly, in this cohort, where patients with acquired demyelinating syndromes also had either clinical or radiological evidence of brainstem involvement, we identified a higher incidence of neuronal and glial antibodies (58%) compared with a previous study of antibody prevalence in a range of childhood demyelination syndromes, where 4 of 14 (29%) ADEM patients had glial (MOG) and neuronal (anti-VGKC-complex and anti-NMDAR) antibodies.[22] On the other hand, only 22% of patients with ADEM had MOG antibodies, lower than reported in a recent cohort of children with ADEM (4/18 vs 19/33, p=0.02).[25] Identification of a patient with AQP4 antibodies presenting with a brainstem syndrome supports recent diagnostic criteria of neuromyelitis optica[26] and highlights that, although rare, patients with brainstem symptoms should be tested for this antibody even in the absence of optic neuritis and transverse myelitis. These results illustrate the growing awareness that antibodies to highly specific antigens can be associated with a variety of clinical presentations.[17]

It should be noted that all the patients studied here were ethnically Japanese and other populations should be studied. Furthermore, as the serum samples were initially sent for GQ1b testing, it is likely that there is a selection bias with higher representation of patients with BBE phenotype. Another limitation of our study is the retrospective nature of the cohort identification, often from samples collected over a decade ago, the lack of CSFs for comparison, and the incomplete outcome data. Nevertheless, the results do not infer a need to look for specific antibodies in most patients with clear evidence of brainstem inflammation, as even those who were antibody-negative had similar clinical features, and treatments and outcomes were not clearly different. Importantly, this study demonstrates that brainstem encephalitis associated with antibody positivity does not comprise a new clinical phenotype, but rather a previously unrecognized or 'undiagnosed' one. It is possible that, if the antibodies had been identified at the time, treatment of patients with specific antibodies, particularly NMDAR-Abs, could have been more aggressive and outcomes might have been better for the two who, while improving in most respects, were left with severe learning difficulties. Thus in patients who remain symptomatic or follow a more protracted course of illness, antibody testing might provide guidance on more intensive and optimal immune therapy.

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REFERENCES

1. Tan IL, Mowry EM, Steele SU, et al. Brainstem encephalitis: etiologies, treatment, and predictors of outcome. *J Neurol* 2013; **260**: 2312–19.
2. Ratelade J, Bennett JL, Verkman AS. Intravenous neuromyelitis optica autoantibody in mice targets aquaporin-4 in peripheral organs and area postrema. *PLoS ONE* 2011; **6**: e27412.
3. Chang T, Alexopoulos H, Pettingill P, et al. Correction: immunization against GAD induces antibody binding to GAD-independent antigens and brainstem GABAergic neuronal loss. *PLoS ONE* 2013; **8**: e72921.
4. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; **10**: 63–74.
5. Kremer L, Mealy M, Jacob A, et al. Brainstem manifestations in neuromyelitis optica: a multicenter study of 258 patients. *Mult Scler* 2014; **20**: 843–47.
6. Carvajal-Gonzalez A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. *Brain* 2014; **137**: 2178–92.
7. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. *Neurology* 2014; **83**: 1797–803.
8. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* 2010; **10**: 835–44.
9. Krupp LB, Banwell B, Tenembaum S. International pediatric MSSG. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. *Neurology* 2007; **68**: S7–12.
10. Bigi S, Fischer U, Wehrli E, et al. Acute ischemic stroke in children versus young adults. *Ann Neurol* 2011; **70**: 245–54.
11. Irani SR, Bera K, Waters P, et al. *N*-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010; **133**: 1655–67.
12. Irani SR, Alexander S, Waters P, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis. Morvan's syndrome and acquired neuromyotonia. *Brain* 2010; **133**: 2734–48.
13. Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. *Neurology* 2012; **78**: 665–71; discussion 669.
14. Hacohen Y, Absoud M, Deiva K, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. *Neurol Neuroimmunol Neuroinflamm* 2015; **2**: e81.
15. Odaka M, Yuki N, Yamada M, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barré syndrome. *Brain* 2003; **126**: 2279–90.
16. Hacohen Y, Singh R, Rossi M, et al. Clinical relevance of voltage-gated potassium channel-complex antibodies in children. *Neurology* 2015; **85**: 967–75.
17. Irani SR, Gelfand JM, Al-Diwani A, Vincent A. Cell-surface central nervous system autoantibodies: clinical relevance and emerging paradigms. *Ann Neurol* 2014; **76**: 168–84.
18. Bickerstaff ER, Cloake PC. Mesencephalitis and rhombencephalitis. *Br Med J* 1951; **2**: 77–81.
19. Yuki N, Sato S, Tsuji S, Hozumi I, Miyatake T. An immunologic abnormality common to Bickerstaff's brain stem encephalitis and Fisher's syndrome. *J Neurol Sci* 1993; **118**: 83–87.
20. Merwick A, Dalmau J, Delanty N. Bickerstaff encephalitis and atypical features – Bickerstaff's papers revisited. *J Neurolog Sci* 2014; **341**: 173.
21. 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; **84**: 748–55.

22. Hacohen Y, Absoud M, Woodhall M, et al. Autoantibody biomarkers in childhood-acquired demyelinating syndromes: results from a national surveillance cohort. *J Neurol Neurosurg Psychiatry* 2014; **85**: 456–61.
23. Hacohen Y, Absoud M, Hemingway C, et al. NMDA receptor antibodies associated with distinct white matter syndromes. *Neurol Neuroimmunol Neuroinflamm* 2014; **1**: e2.
24. Titulaer MJ, Hoftberger R, Iizuka T, et al. Overlapping demyelinating syndromes and anti-*N*-methyl-D-aspartate receptor encephalitis. *Ann Neurol* 2014; **75**: 411–28.
25. Baumann M, Sahin K, Lechner C, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. *J Neurol Neurosurg Psychiatry* 2015; **86**: 265–72.
26. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015; **85**: 177–89.