

NMDA receptor antibodies associated with distinct white matter syndromes

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ABSTRACT

Objective: To report the clinical and radiologic findings of children with NMDA receptor (NMDAR) antibodies and white matter disorders.

Method: Ten children with significant white matter involvement, with or without anti-NMDAR encephalitis, were identified from 46 consecutive NMDAR antibody-positive pediatric patients. Clinical and neuroimaging features were reviewed and the treatment and outcomes of the neurologic syndromes evaluated.

Results: Three distinct clinicoradiologic phenotypes were recognized: brainstem encephalitis (n = 3), leukoencephalopathy following herpes simplex virus encephalitis (HSVE) (n = 2), and acquired demyelination syndromes (ADS) (n = 5); 3 of the 5 with ADS had myelin oligodendrocyte glycoprotein as well as NMDAR antibodies. Typical NMDAR antibody encephalitis was seen in 3 patients remote from the first neurologic syndrome (2 brainstem, 1 post-HSVE). Six of the 7 patients (85%) who were treated acutely, during the original presentation with white matter involvement, improved following immunotherapy with steroids, IV immunoglobulin, and plasma exchange, either individually or in combination. Two patients had escalation of immunotherapy at relapse resulting in clinical improvement. The time course of clinical features, treatments, and recoveries correlated broadly with available serum antibody titers.

Conclusion: Clinicoradiologic evidence of white matter involvement, often distinct, was identified in 22% of children with NMDAR antibodies and appears immunotherapy responsive, particularly when treated in the acute phase of neurologic presentation. When observed, this clinical improvement is often mirrored by reduction in NMDAR antibody levels, suggesting that these antibodies may mediate the white matter disease. *Neurol Neuroimmunol Neuroinflammation* 2014;1:e2; doi: 10.1212/NXI.000000000000002

GLOSSARY

Ab = antibody; **ADEM** = acute disseminated encephalomyelitis; **ADS** = acquired demyelination syndromes; **AQP4** = aquaporin-4; **HSV** = herpes simplex virus; **HSVE** = HSV encephalitis; **IVIg** = IV immunoglobulin; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **NMDAR** = NMDA receptor; **PLEX** = plasma exchange.

NMDA receptor antibody (NMDAR-Ab) encephalitis is characterized by seizures, movement disorders, and psychiatric symptoms.¹ It is now recognized that NMDAR-Ab-mediated neurologic syndromes can range from monosymptomatic and partial phenotypes to the full-blown “anti-NMDAR encephalitis.”¹ Despite the severity of the disease in many patients, conventional MRI of the brain is frequently normal, often referred to as the clinical-radiologic paradox.¹ When abnormal, MRI usually reveals discrete lesions that are predominantly subtle and nonenhancing, often reverse spontaneously, and are not usually restricted to the white matter¹; thus, they appear clinically and radiologically different from demyelinating syndromes such as multiple sclerosis (MS).

See editorial

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Recently, we observed that 1 patient, initially reported in the UK cohort of NMDAR-Ab encephalitis,² developed MS, and a further patient with MS subsequently developed NMDAR-Ab encephalitis. In addition, in a systematic evaluation of glial, myelin, and neuronal-directed antibodies in children with a range of demyelination syndromes, we identified 2 patients with NMDAR-Ab.³ These observations, together with existing case reports of NMDAR-Ab in patients with neuromyelitis optica spectrum disorder,⁴ acute demyelinating encephalomyelitis (ADEM),⁵ or MS,⁶ raise questions regarding the clinical relevance, potential pathogenic effect, and direct contribution of NMDAR-Abs to neurologic syndromes that involve the white matter.

Here, we report a group of children with NMDAR-Abs and clinical and/or radiologic evidence of a white matter disorder, identified from a larger cohort of children with NMDAR-Abs, and describe their clinical course in relation to (or independent of) features of NMDAR-Ab encephalitis.

METHODS Ten children with a clinical and/or radiologic evidence of white matter involvement were identified from a cohort of 46 pediatric patients, 18 years of age and younger, with a range of NMDAR-Abs–associated neurologic syndromes. Between 2009 and 2013, patients were referred, based on clinician decision, from 6 pediatric neurology centers to the Clinical Neuroimmunology Service at the Oxford Radcliffe Hospital Trust for serum and/or CSF NMDAR antibody testing and/or advice on further antibody testing. As antibodies to myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (AQP4) have been associated with demyelinating disorders,⁷ sera from all 10 cases and the other 36 NMDAR-Ab–positive patients were tested for both these antibodies. NMDAR, AQP4, and MOG antibodies were measured using cell-based assays in routine clinical use (sera at 1:20 dilution for NMDAR and AQP4 and 1:160 for MOG; CSF at 1:2 dilution for NMDAR) as previously described.^{2,8,9} For these cell-based assays, the binding of serum immunoglobulin G to the surface of human embryonic kidney cells, transfected with complementary DNA encoding the auto-antigens (MOG courtesy of M. Reindl, Innsbruck), was visualized using a fluorescence-labeled Alexafluor 568 secondary antibody (Molecular Probes, Eugene, OR), and the results were assessed by at least 2 independent observers (Y.H., L.J., P.W.). Clinical information and neuroimaging were reviewed (Y.H., M.A., A.S., M.L.). The outcomes, as measured by the range of difficulties the patients were experiencing, were retrieved from the patient's medical records or, if unavailable, were obtained directly from the patient's primary pediatric neurologist. Full recovery was defined by the absence of medical, educational, and social concerns reported from parents, school, and the patient's primary clinician.

Standard protocol approvals, registrations, and patient consents. Ethical approval for this study was from the Oxfordshire Regional Ethical Committee A (07/Q1604/28).

RESULTS Out of a total of 46 patients identified consecutively from 6 centers, 10 patients (cases 1–10; 5 male; age range 1.3–18 years, median 8.5 years; see table 1) were identified with a significant white matter involvement. They were classified as having 3 neurologic syndromes: brainstem encephalitis (n = 3), herpes simplex virus encephalitis (HSVE) relapsing with a distinct leukoencephalopathy (n = 2), and acquired demyelination syndromes (ADS) (n = 5). Their clinical features, imaging, and treatment responses are described below and summarized in table 1 and figures 1 and 2. The remaining 36 NMDAR-Ab–positive patients had minimal or absent white matter involvement; 28 of these had typical NMDAR-Ab encephalitis (cases 11–38; 8 male; age range 2–17 years, median 11 years; see table 2). Of the remaining 8 patients, 1 presented with a neurologic relapse following HSVE, and 7 had a partial phenotype (cases 39–46; 2 male; age range 1–18 years, median 11 years; see table 3). Only 1 patient, a 15-year-old girl with classical NMDAR-Ab encephalitis, had an ovarian teratoma. NMDAR-Abs were positive in the CSF in 10 of 11 patients tested with typical NMDAR-Ab encephalitis, in 2 of 3 tested with the partial phenotype, and in all 3 tested with white matter syndromes; serum levels were higher than CSF in all paired samples. All patients were empirically investigated by their physicians to exclude a range of infective, alternative inflammatory, and neurometabolic etiologies, of which none were identified. Cases 11–23,¹⁰ case 39,¹¹ and cases 40–42¹² have been previously described.

Brainstem encephalitis. Three patients had encephalopathy, predominant brainstem signs (cranial neuropathies and ataxia), and neuroimaging findings of brainstem abnormalities, or a clinical syndrome unequivocally localized to the brainstem.¹³ Case 1 (M, age 18) had brainstem changes at presentation (figure 1A) but evolved to a polysymptomatic encephalopathy, with resolution of the brainstem changes (figure 1B). NMDAR-Abs were only detected a year later after a relapse but fell with immunotherapies with a good clinical response (figure 2A). Case 2 (F, age 10) presented 3 weeks after first symptoms when her encephalopathy worsened with intractable seizures, movement disorder, and hyperpyrexia. She had recurrent periods of encephalopathy (figure 2B) associated with radiologic features of a leukoencephalopathy (figure 1D) that progressed over the following 5 years (figure 2B), when serum and CSF NMDAR-Abs were first identified. She was not given immunotherapies and is substantially impaired (table 1). Case 3 (M, age 5), the most recent patient, presented with brainstem signs and cranial nerve enhancement; NMDAR-Abs were identified within a few weeks of onset. He made a

Table 1 Clinical and paraclinical features of 10 NMDAR antibody-positive patients with distinct clinicoradiologic white matter syndrome

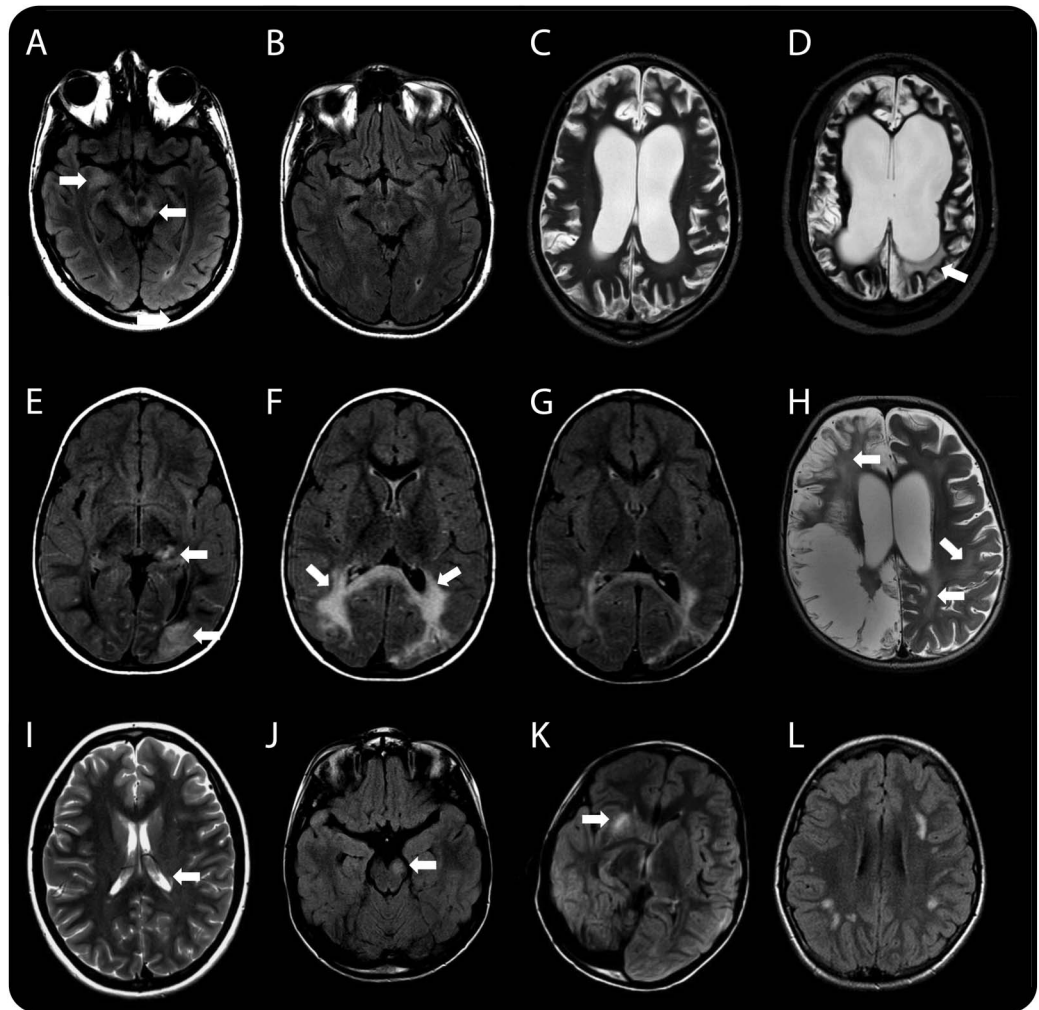
Case	Demo-graphics	Neurologic syndrome at onset	NMDAR antibody ^a	Subsequent neurologic event	Brain MRI	OCB	Treatment	Outcome/follow-up, ^b mo
1	M, 18 y, Caucasian	Brainstem encephalitis	Onset: ND, R1: ND, R2: S (1:500); CSF: ND	R1 (day 60): encephalopathy, psychiatric, movement disorder, dysautonomia, R2 (1 y): encephalopathy, psychiatric, movement disorder, dysautonomia	Onset: brainstem signal change, R1: resolution of brainstem changes, R2: new midbrain, mesial temporal lobe, and posterior periventricular diffuse white matter changes	ND	Onset: PLEX, OP, R1: PLEX, IVIg, R3: PLEX, MMF	Relapse free (oT), cognitive and behavioral problems, antibody negative, 30
2	F, 10 y, African Caribbean	Brainstem encephalitis	Onset: ND, R1: ND, R2: S (1:1,000); CSF (1:20)	R1 (day 21): encephalopathy, seizures, movement disorder, hyperpyrexia, R2 (5 y): encephalopathy, worsening seizures	Onset: no imaging, R1: widespread cortical signal change, R2: diffuse posterior white matter changes	ND	Onset: NT, 6 mo: IVIg, R1: NT	Quadriparesis, visual failure, seizures, 29
3	M, 5 y, Caucasian	Brainstem encephalitis	Onset: S (1:1,000); CSF (1:20)	Monophasic	Multiple cranial nerve enhancement	Negative	PLEX	Full recovery, antibody negative, 8
4	M, 2 y, African Caribbean	HSV encephalitis	Onset: S (-); CSF (-), R1: S (1:500); CSF (1:20)	R1 (day 60): cognitive, behavioral, and motor regression	Onset: focal parenchymal changes, R1: diffuse posterior bilateral white matter changes	Onset: negative, R1: positive	R1: IVIg (long term)	Full recovery, reduction in antibody titers, 11
5	F, 16 mo, Asian	HSV encephalitis	Onset: ND, R1: S (1:1,000); CSF (1:50)	R1 (day 60): encephalopathy, movement disorder	Onset: changes consistent with HSV, R1: posterior bilateral white matter changes	ND	R1: PLEX	Resolution of encephalopathy, residual motor deficit, reduction in antibody titers, 6
6	F, 6 y, African Caribbean	Bilateral ON (right > left)	Onset: S (1:150); CSF ND, additional MOG S (1:1,620)	Monophasic	Normal	ND	IVMP, OP	Incomplete visual recovery, 10
7	M, 9 y, Caucasian	Bilateral ON	Onset: S (1:150); CSF ND, additional MOG S (1:1,620)	Monophasic	Normal	ND	IVMP, OP	Full visual recovery, 30
8	F, 11 y, Caucasian	Right ON	Onset: ND, interval: S (1:150), R1: S (1:200); CSF ND	R1 (3 y): left ON	Onset: normal, R1: periventricular white matter lesions	ND	Onset: NT, OP (1 y from onset), R1: OP, IVIg	Poor visual recovery, antibody negative, 42
9	M, 8 y, Asian	ADEM	Onset: ND, R1: ND, interval: S (1:150), R2: S (1:500); CSF ND, additional MOG S (1:400)	R1 (day 30): ADEM, R2 (1 y): right ON, R3 (13 mo): left ON	Onset: bilateral deep gray and white matter lesions, R1: similar to onset, R2: new brainstem lesions	ND	Onset: IVMP, OP, R1: IVMP, OP, R2: MMF	Full recovery (NoT), antibody negative, 30
10	F, 11 y, Caucasian	Recurrent episodes of hyperventilation, dizziness, and double vision	Onset: S (1:100); CSF ND; serum levels increasing to 1:1,000	Recurrent episodes of initial presenting syndrome, one episode with loss of mobility for 2 weeks	Onset: numerous lesions in subcortical white matter and body of the corpus callosum, no significant change on repeat imaging	Negative	NT	Unchanged, 24

Abbreviations: ADEM = acute disseminated encephalomyelitis; HSV = herpes simplex virus; IVIg = IV immunoglobulin; IVMP = IV methylprednisolone; MOG = myelin oligodendrocyte glycoprotein; MMF = mycophenolate mofetil; ND = not done; NMDAR = NMDA receptor; NoT = not on treatment; NT = no treatment; OCB = oligoclonal bands; ON = optic neuritis; OP = oral prednisolone; oT = on treatment; PLEX = plasma exchange; R = relapse; S = serum.

Brainstem encephalitis was defined by encephalopathy with predominant brainstem signs (cranial neuropathies and ataxia). Neuroimaging findings of brainstem abnormalities during the admission were also required unless the clinical syndrome was unequivocally localized to the brainstem.¹² Herpes simplex virus encephalitis (HSVE) was defined by clinical, laboratory, and radiologic findings consistent with HSVE and a significant clinical improvement with IV acyclovir. Acquired demyelinating syndromes were classified based on the International Pediatric MS Study Group criteria into acute disseminated encephalomyelitis, clinically isolated syndrome, and optic neuritis.¹⁵

^a Serial antibody titers are shown in figure 2.

^b Median follow-up time of 30 months (range 8–54).



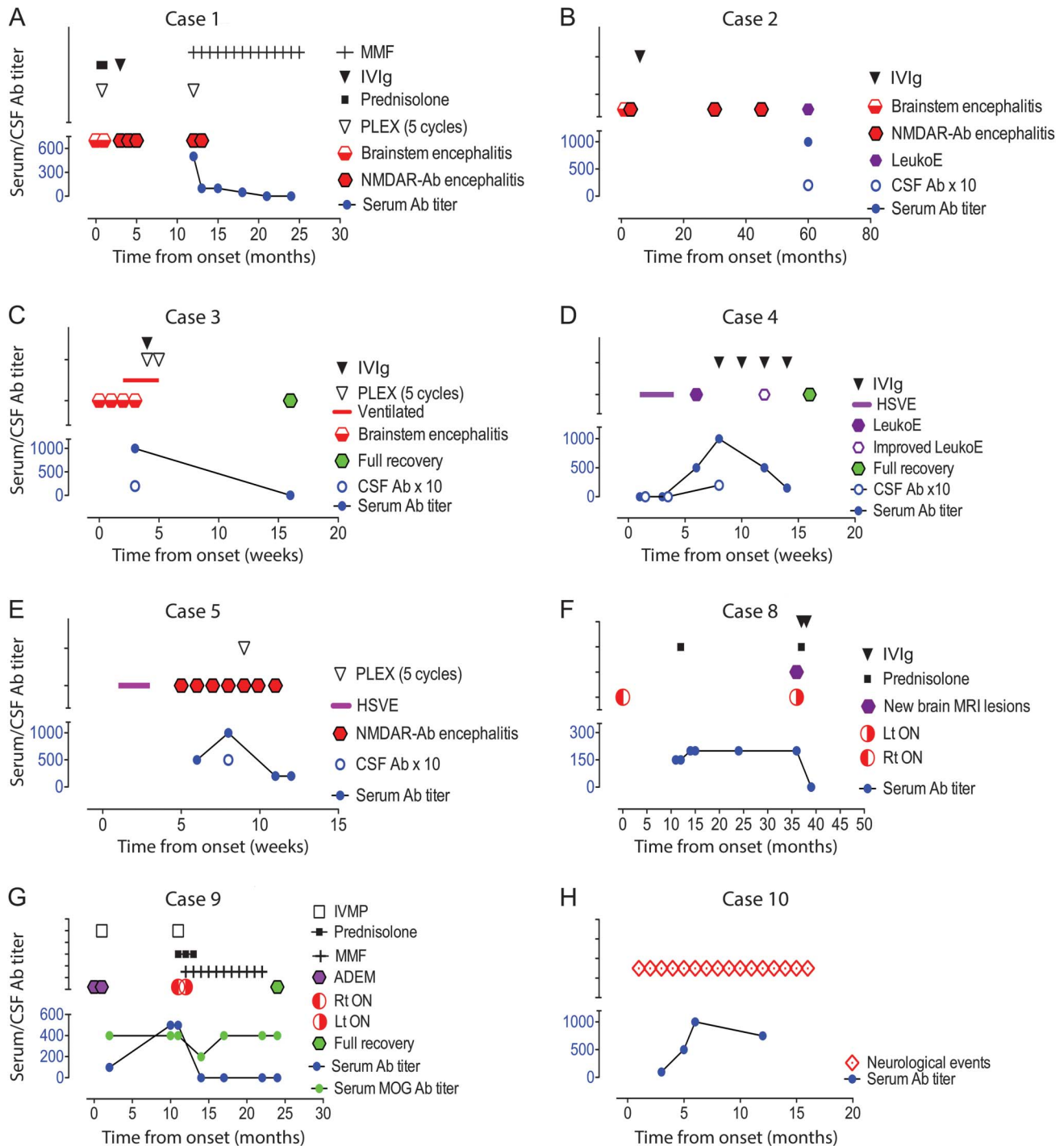
(A, B) Case 1, who presented with a brainstem syndrome. Axial T2 fluid-attenuated inversion recovery (FLAIR) images showing hyperintensity in the midbrain and mesial temporal lobe (arrows in A), which subsequently resolved on follow-up imaging performed at 2 months when the patient had relapsed with a polysymptomatic encephalopathy (B). (C, D) Case 2, who presented initially with a brainstem syndrome followed by periods of recurrent encephalopathy. Axial T2-weighted images 6 months after her initial brainstem syndrome revealed diffuse global cortical atrophy (C). Imaging during an encephalopathic episode 5 years later revealed new white matter changes (arrow in D) and further atrophy. This radiologic feature of leukoencephalopathy progressed on subsequent imaging (not shown). (E–H) Two patients with neurologic syndromes following herpes simplex virus encephalitis (HSVE). Serial axial T2 FLAIR images of case 4 (E–G) showing localized cortical changes in the left thalamus and occipital lobe (arrows in E) on initial imaging that progressed, demonstrating significant bilateral white matter signal changes in the parieto-occipital region 2 months later (arrows in F) when the patient presented with significant worsening of cognitive, behavioral, and motor regression. Following treatment and improvement of symptoms, follow-up neuroimaging 2 months later demonstrated a significant resolution of this white matter change (G). Axial T2-weighted image of case 5 at relapse 2 months after HSVE showing extensive bilateral but asymmetrical cystic encephalomalacia centered on the temporo-insular regions (only parietal changes shown) characteristic of HSVE, but in addition demonstrating the characteristic leukoencephalopathic changes seen globally (arrows in H). (I–L) Patients presenting with acquired demyelinating syndrome (ADS). At time of relapse with left optic neuritis, brain imaging in case 8 showed subtle periventricular white matter signal change on a T2-weighted image (arrow demonstrating one periventricular lesion in I). Imaging of case 9 showing midbrain (arrow in J), capsular (arrow in K), and thalamic changes (not shown) on axial T2 FLAIR. Axial T2 FLAIR image of case 10 demonstrating patchy subcortical white matter changes (L).

full recovery with steroids and plasma exchange (PLEX) (figure 2C). All 3 patients were negative for GQ1b antibodies.

HSVE relapse. Since we and others recognized a relationship between HSVE relapses and NMDAR-Abs,^{11,14–16} we have identified 2 additional patients, cases 4 and 5

(M, age 2; F, age 16 months), with NMDAR-Abs in serum and CSF (table 1) during neurologic relapses with substantial leukoencephalopathy on imaging (figure 1, E–H) occurring within 2 months of HSVE (headache, fever, seizures, typical imaging, and CSF herpes simplex virus [HSV] PCR positivity). Case 4 presented with cognitive, behavioral, and motor

Figure 2 NMDAR-Ab levels, clinical syndromes, and therapy in 8 informative patients with white matter syndromes in association with NMDAR-Ab



(A–C) Cases 1–3 presented initially with brainstem encephalitis; Cases 1 and 2 relapsed with encephalopathy, psychiatric features, movement disorder, and dysautonomia. Case 2 had additional seizures. In both, the diagnosis of NMDAR-Ab encephalitis was made at the time of relapse. Case 3 had a monophasic illness and did not have any of the clinical characteristics of NMDAR-Ab encephalitis. (D, E) Cases 4 and 5 presented with herpes simplex virus encephalitis (HSVE) and then had a neurologic relapse, which correlated with raised NMDAR-Ab in both serum and CSF and demonstrated a clinical response to immunotherapy with reduction of antibody levels. (F) Case 8 presented with optic neuritis and poor visual recovery, which prompted a neuroinflammatory screen and the identification of the antibody positivity. She only received a course of steroids 1 year into her illness and 3 years later had a neurologic relapse. (G) Case 9 presented initially with 2 episodes of acute disseminated encephalomyelitis (ADEM) and relapsed at 1 year with optic neuritis. He was also MOG-Ab positive, which remain detectable even when NMDAR-Ab are no longer detectable and when the patient had clinically recovered. (H) Case 10 had recurrent episodes of hyperventilation, dizziness, and double vision; did not receive any treatment; and both her clinical and radiologic features remained unchanged. Ab = antibody; CSF Ab $\times 10$ = NMDAR antibody titers in CSF (all between 1:20 and 1:50) multiplied by 10 to provide visibility in comparison to serum levels; IVIg = IV immunoglobulin; IVMP = IV methylprednisolone; LeukoE = radiologic leukoencephalopathy; Lt = left; MMF = mycophenolate mofetil; NMDAR = NMDA receptor; ON = optic neuritis; PLEX = plasma exchange; Rt = right; Serum Ab titer = titer measured by endpoint dilution.

Table 2 Clinical and paraclinical features in patients with NMDAR-Ab encephalitis

Case	Demographics	Presentation	Relapse	OCB	NMDAR-Ab	Conventional brain MRI abnormalities	Immunotherapy	Outcome/follow-up, mo
11	F, 14 y, Asian	Cog, Psych ^a	No	ND	S 1:1,000	Normal	Steroids, IVIg, PLEX	Full recovery, 54
12	F, 2 y, Asian	Cog, S, M	No	Positive	S 1:1,000	Normal	Steroids, IVIg, PLEX, RTX	Cog, 58
13	F, 13 y, Caucasian	Cog, Psych, S, M, A	No	Positive	S 1:1,000	Normal	Steroids, IVIg, MMF	B, 46
14	F, 11 y, Caucasian	Cog, Psych, A	No	Positive	S 1:100	Normal	Steroids, IVIg	Cog, B, 52
15	F, 4 y, Black	Cog, Psych, S, M	No	Negative	S 1:500	Normal	Steroids	Cog, B, 20
16	M, 8 y, Black	Cog, Psych, S, M	No	Negative	S 1:500	Normal	Steroids, IVIg	Cog, B, 54
17	F, 2 y, Black	Cog, Psych, S, M	No	Negative	S 1:1,000, C 1:10	Normal	Steroids	Cog, S, 38
18	F, 5 y, Asian	Cog, Psych, S, M	No	Positive	S 1:1,000, C 1:50	Normal	Steroids, IVIg, RTX	Cog, B, 50
19	F, 3 y, Caucasian	Cog, Psych, S	No	Positive	S 1:500	Normal	Steroids	Full recovery, 48
20	M, 6 y, Middle Eastern	Psych, S	No	Positive	S 1:100	Normal	Steroids, IVIg	S, 48
21	F, 15 y, Asian	Cog, Psych	No	Positive	S 1:200	Normal	NT	Cog, Psych, 43
22	M, 16 y, Caucasian	Cog, Psych, S, A	No	ND	S 1:500	Transient cortical	Steroids, IVIg, PLEX	Full recovery, 54
23	F, 17 y, Chinese	Psych, M, A	No	Positive	S 1:500, C 1:10	Transient cortical and subcortical	Steroids, IVIg, PLEX	Full recovery, 53
24	F, 2 y, Caucasian	S, Psych, M	No	Positive	S 1:2,000, C 1:10	Normal	Steroids, IVIg	Cog, B, 28
25	F, 5 y, Black	S, Psych, M	No	ND	S 1:1,000	Normal	Steroids	S, 36
26	M, 3 y, Black	Cog, Psych, S	No	ND	S 1:2,000	Normal	Steroids	Full recovery, 8
27	F, 14 y, Caucasian	Cog, Psych, M	No	ND	S 1:1,000, C 1:10	Left cortical and cerebellar	Steroids, IVIg	Cog, B, 54
28	F, 5 y, Black	Cog, S, M	No	Positive	S 1:1,000, C 1:10	Hippocampus and medial temporal gyrus	Steroids	Full recovery, 20
29	M, 16 y, Caucasian	Cog, Psych	Yes	ND	S 1:500	Transient hippocampus and insular	Steroids, IVIg, MMF	Full recovery, 44
30	F, 17 y, Caucasian	Cog, Psych, S, M	Yes	Negative	S 1:100, C negative	Long-standing PVL	Steroids	Full recovery, 22
31	F, 7 y, Middle Eastern	Psych, S	Yes	ND	S 1:2,000, C 1:10	Mild signal change hippocampus	Steroids, IVIg	Cog, S, 24
32	F, 16 y, Caucasian	Cog, S	Yes	ND	S 1:500	Normal	Steroids, IVIg, PLEX, AZA	S, 56
33	M, 4 y, Caucasian	Cog, Psych, S, M, A	Yes	ND	S 1:2,000	Normal	Steroids, IVIg, PLEX, RTX, MMF	Cog, B, S, 18
34	F, 13 y, Black	Cog, Psych, S, M, A	Yes	Positive	S 1:500	Normal	Steroids, IVIg, PLEX, MMF	Full recovery, 38
35	F, 11 y, Caucasian	Psych, S, M, A	No	Positive	S 1:1,000, C 1:50	Normal	Steroids, IVIg, PLEX, MMF	Full recovery, 19
36	M, 13 y, Middle Eastern	Psych, S, M	No	Negative	S 1:500	Normal	Steroids, PLEX	Full recovery, 18
37	F, 14 y, Caucasian	Cog, Psych, S, M, A	No	ND	S 1:1,000, C 1:10	Normal	Steroids, IVIg, PLEX, CYC, RTX	Cog, B, S, 60
38	F, 16 y, Caucasian	Cog, Psych, S, M	No	ND	S 1:1,000, C 1:50	Normal	Steroids, PLEX, CYC, RTX	Cog, Psych, S, 32

Abbreviations: Ab = antibody; AZA = azathioprine; C = CSF; CYC = cyclophosphamide; IVIg = IV immunoglobulin; MMF = mycophenolate mofetil; ND = not done; NMDAR = NMDA receptor; NT = not treated; OCB = oligoclonal bands; PLEX = plasma exchange; PVL = periventricular leukomalacia; RTX = rituximab; S = serum.

Symptoms at presentation in addition to encephalopathy and at final follow-up were classified as A = autonomic; B = behavioral; Cog = cognitive; M = movement disorder; Psych = psychiatric; S = seizures.

^aDenotes patient with ovarian teratoma.

Table 3 Clinical and paraclinical features of 8 patients with atypical NMDAR-Ab-mediated CNS disorder

Case	Demographics	Presentation	Relapsing neurologic events	OCB	NMDAR-Ab	Conventional brain MRI abnormalities	Immunotherapy	Outcome/follow-up, mo
39	F, 1 y, Caucasian	E, S, M	Yes	Positive	S 1:1,000	HSVE changes	IVIg	Cog, B, S, 18
40	M, 12 y, Caucasian	M, Psych	No	ND	S 1:100	Normal	Steroids	Psych, 48
41	F, 10 y, Caucasian/Black	M, Cog	Yes	Negative	S 1:500	Normal	Steroids, IVIg	Full recovery, 28
42	F, 5 y, Black	M, Cog, S	No	Negative	S 1:2,000, C 1:50	Normal	Steroids, IVIg	Full recovery, 30
43	M, 18 y, Caucasian	M, Cog, Psych	No	ND	S 1:500	Normal	Steroids	Psych, 20
44	F, 11 y, Caucasian	S	Yes	Negative	S 1:100, C negative	Normal	NT	S, 20
45	F, 8 y, Caucasian	S, Cog	Yes	ND	S 1:500	Right mesial temporal	NT	S, B, 22
46	F, 15 y, Asian	Cog	No	ND	S 1:1,000, C 1:50	Normal	NT	Cog, 8

Abbreviations: Ab = antibody; C = CSF; HSVE = herpes simplex virus encephalitis; IVIg = IV immunoglobulin; ND = not done; NMDAR = NMDA receptor; NT = not treated; OCB = oligoclonal bands; S = serum.

Patient 39 had typical NMDAR encephalitis 1 month following HSVE. Patients 40–46 presented with the nonencephalopathic partial phenotype, with predominantly movement disorder (40–43), seizures (44–45), and cognitive decline (46). Clinical symptoms at presentation and at outcome were classified as B = behavioral; Cog = cognitive; E = encephalopathy; M = movement disorder; Psych = psychiatric; S = seizures.

decline, and case 5 presented with a further encephalopathic illness with new-onset movement disorder. Both patients had negative HSV PCRs in the CSF at relapse. Both were treated with IV immunoglobulin (IVIg) or PLEX, which resulted in clinical improvement and reduction of NMDAR-Ab titers (figure 2, D and E). A significant radiologic improvement was observed in case 4 (figure 1G). Other potential causes of leukoencephalopathies, such as neurometabolic conditions, were excluded.

Acquired demyelination syndromes. Five patients presented with ADS classified according to the International Pediatric MS Study Group criteria.¹⁷ Three initially had optic neuritis. Case 6 (F, age 6) and case 7 (M, age 9), with bilateral optic neuritis, were treated with IV methylprednisolone followed by a weaning course of oral prednisolone. Case 8 (F, age 11) presented with right optic neuritis and poor visual recovery; she only received a course of oral steroids 1 year later and relapsed 3 years later with left optic neuritis and new brain lesions (figures 1I and 2F). Case 9 (M, age 8) presented with ADEM, relapsed at 1 month with a second encephalopathic illness and imaging evidence of new brainstem lesions (figure 1J), and developed right and left optic neuritis at 12 and 13 months, respectively. At this stage, he was treated with mycophenolate mofetil with good visual recovery, no further relapse, and a reduction in NMDAR-Ab levels (figure 2G). Case 10 (F, age 10) had an unusual presentation of recurrent episodes of hyperventilation, dizziness, and double vision lasting from 2 days to more

than 2 weeks (figure 2H). Her brain imaging revealed periventricular and subcortical white matter changes (figure 1L). She has not been treated as the relevance of the NMDAR-Ab in her clinical and radiologic syndrome remains unclear.

General features of cases 1–10 and differences from the remaining 36 patients with NMDAR-Abs. The mean follow-up time in the cohort was 34 months (median 30, range 8–60), and this was not significantly different between the patients with white matter syndromes (mean 27, median 30, range 8–54) and the other patients with NMDAR-Abs (mean 36, median 37, range 8–60). Overall in the white matter patients, 6 of the 7 patients (85%) who were treated acutely improved following immunotherapy with steroids, IVIg, and PLEX, either individually or in combination. At relapse, 2 patients had escalation of immunotherapy resulting in improvement of clinical syndrome. Patients who were treated late (n = 2) or untreated (n = 1) had either a poorer outcome or persistence of symptoms. In 6 of the 7 patients with serial samples available, there were relationships between NMDAR-Ab titers and severity of clinical syndrome (figure 2, A–H). Of interest, MOG antibodies did not disappear after treatment in case 9, even when NMDAR-Abs became undetectable and after clinical recovery (figure 2G).

Serum levels of NMDAR-Abs ranged from 1:100 to 1:1,000 at the earliest sample available, with CSF levels (cases 2–5) from 1:20 to 1:50. It is important that both

serum and CSF NMDAR-Ab titers were negative during the HSVE that preceded NMDAR-Ab relapse in case 4 (figure 2D); the relevant samples were not available for case 5. After immunotherapies, antibody levels fell in all patients and became undetectable in cases 1, 3, 8, and 9. Follow-up CSFs were not available. MOG antibodies were found in only 3 of the 5 patients with ADS (cases 6, 7, and 9) (table 1). All patients were negative for AQP4 antibodies.

Cases 1–10 presented with distinct white matter changes, either radiologic changes compatible with the respective clinical syndromes (brainstem encephalitis and ADS group) or a leukoencephalopathy in addition to the radiologic changes commonly observed within the relevant phenotype (brainstem encephalitis and HSVE). These patients were radiologically distinct from the NMDAR-Ab encephalitis cases (table 1), where only 6 of 28 (21%) had abnormal neuroimaging, all sparing the white matter ($p < 0.0001$, Fisher exact test). Cases 1–10 were also distinct clinically. Although 3 patients had classical NMDAR encephalitis, in cases 1 and 2, these episodes were remote from the first neurologic syndrome (brainstem encephalitis), and in case 5, the NMDAR-Ab encephalitis occurred following HSVE. In addition, 7 of the 10 cases (70%) had recurrent neurologic episodes, compared to only 6 of 28 patients (21%) with typical NMDAR-Ab encephalitis or 10 of 36 cases (28%) without white matter involvement ($p = 0.003$ and 0.02 , respectively; Fisher exact test). Oligoclonal bands were positive in the CSF in 1 of 3 patients tested with white matter disorder compared to 14 of 18 with typical NMDAR-Ab encephalitis, although this was not statistically significant ($p = 0.18$, Fisher exact test). Finally, those patients with white matter disorders were more likely to have MOG antibodies (30% vs 0%; $p = 0.008$, Fisher exact test) than those without white matter involvement.

DISCUSSION Three distinct white matter clinicoradiologic syndromes—brainstem encephalitis, leukoencephalopathy following HSVE, and CNS demyelination—were identified in 10 of 46 (22%; 95% confidence interval 11%–36%) consecutive children from 6 centers in the UK in whom NMDAR-Abs were detected. The antibodies were present at high titers (up to 1:1,000), and all available CSFs were positive (up to 1:50). Collectively, relapses were seen in 63% (5/8) of our cohort (excluding the 2 HSVE cases), a rate higher than that seen in our classical NMDAR encephalitis patients (28%; 6/28) or than previously reported.^{1,2,18} This included 2 of the 3 patients with brainstem encephalitis, usually a monophasic disease,^{13,19} and 3 of the 5 patients (60%) in the ADS group, in which relapses are seen in 25% of patients.²⁰

Nevertheless, there was a good response to immunotherapies once the antibodies were detected, and improvement broadly paralleled serum NMDAR-Ab levels over the following months.

The brainstem parenchyma could be particularly susceptible to systemic autoantibodies. It is well known that antibodies can diffuse into the area postrema, as in neuromyelitis optica,²¹ and other brainstem regions may also be permeable, as inferred recently from rodent studies.²² However, although brainstem encephalitis is assumed to be due to autoimmune and inflammatory etiologies,¹³ no disease-defining autoantibodies have been defined to date. Brainstem encephalitis does share clinical features with NMDAR-Ab encephalitis, and it was suggested that one of the original reported cases of Bickerstaff brainstem encephalitis had features of NMDAR-Ab encephalitis.²³ Hypoventilation, probably due to disruption of the medullary-pontine respiratory network^{1,2} and leading to ventilator dependency despite the improvement of the encephalopathy, was seen in case 3. Typically, however, brainstem involvement in NMDAR-Ab encephalitis manifests as autonomic symptoms such as hyperthermia, blood pressure lability, arrhythmias, hypersalivation, and urinary incontinence,^{1,2} and is usually seen more frequently in adults than in children.¹

Distinct episodes of classical NMDAR-Ab encephalitis were observed in 2 of the 3 patients with brainstem encephalitis. Although the NMDAR-Ab positivity in both cases (cases 1 and 2) could only be determined in sera taken during relapses, when they were polysymptomatic, the identification of NMDAR-Abs (serum and CSF) in case 3 during the acute phase of brainstem encephalitis suggests that the initial brainstem event in all 3 patients could represent a localized form of NMDAR-Ab-mediated brainstem inflammation. Early and optimal treatment, as in case 3, may prevent the subsequent evolution to a more generalized NMDAR-Ab encephalitis.

There have been recent reports that NMDAR-Abs, often with choreoathetosis, can be identified before² and/or during neurologic relapses following HSVE.^{11,14–16,24} An infective etiology causing brainstem encephalitis may trigger similar brain autoimmunity. The distinct white matter changes seen in both the HSVE relapse patients (figure 1, E–H) are atypical for NMDAR encephalitis, although we have previously described this radiologic feature in 1 child who relapsed following HSVE,¹¹ and these striking leukoencephalopathic changes were also evident in a patient in the brainstem encephalitis group (case 2, figure 1, C and D). Following immunotherapy, both patients with HSVE improved clinically, and, in the 1 patient imaged after treatment, significant radiologic improvement was demonstrated. The relevance of

leukoencephalopathy in these syndromes requires further evaluation; its detection by MRI could be a useful biomarker for patients at risk of relapses after HSVE or brainstem encephalitis, with obvious treatment implications.

There is a growing interest in the role of CNS antibodies in demyelination, stemming from the discovery of AQP4 antibodies in neuromyelitis optica²⁵ and detection of MOG antibodies in a range of ADS,^{26–28} although the clinical use of MOG antibodies as a marker of disease activity and prognosis is still being evaluated.²⁶ Of interest, 3 of the 5 patients in the ADS group, 2 with bilateral optic neuritis (cases 6 and 7) and 1 (case 9) who presented with ADEM followed by recurrent optic neuritis, had antibodies to MOG as well as NMDAR. Both these demyelinating phenotypes are recognized in children with MOG antibodies,^{27,28} suggesting that these antibodies may have contributed to the clinical picture in addition to the NMDAR-Abs.

An association between NMDAR antibodies and CNS demyelination has been recognized in individual cases with both monophasic^{3,5} and relapsing syndromes,^{4,6} but it is unknown whether these antibodies are causative or secondary to the demyelination. As NMDARs are activated on oligodendrocytes following ischemia,²⁹ the white matter may be a target for antibodies following prior or recurrent neurologic insults; this could be the case in our patients who had either a distinct previous neurologic syndrome (HSVE and brainstem encephalitis) or frequent relapses of demyelination. Furthermore, upregulation of NMDA receptor subunits, in particular highly calcium permeable NR2B-containing and magnesium-insensitive NR3A NMDARs, appears to increase the vulnerability of the white matter to injuries in the developing brain,³⁰ and such age-specific NMDAR subunit composition³¹ could also predispose children with an actively myelinating CNS to developing leukoencephalopathies, thus explaining the high rate of white matter involvement in this pediatric NMDAR-Ab-positive cohort. Experimental studies looking at the role of NMDARs in white matter suggest their importance in remyelination³² and the regenerating optic nerve,³³ which could possibly explain the slow visual recovery seen in cases 6 and 8; if they are induced secondary to the demyelination, the NMDAR-Abs may cause a loss of function and reduce this beneficial response to nerve injury.

It was the leukoencephalopathy, and the less severe but distinct white matter changes, that drew our attention to these patients. In fact, advanced neuroimaging techniques are starting to identify white matter abnormalities in patients with anti-NMDAR encephalitis with no apparent abnormality on conventional imaging,³⁴ suggesting that perturbations

in white matter tracts are more widespread than previously thought. These could be mediated by direct antibody binding to NMDAR on oligodendrocytes, as discussed above, and/or secondary to neuronal glutamate-mediated excitotoxicity.³¹ Although the improvement following immunotherapy in our patients with white matter disorders could simply reflect the natural history of these conditions, the poorer outcomes of those untreated or treated later and the parallel reduction or resolution of antibody levels provide evidence that whatever the origins and roles of the NMDAR-Abs, their removal can be helpful.

Only 3 of 10 patients with white matter syndromes had CSF available for testing. However, in each of the patients reported here, including the 11 with typical NMDAR-Ab encephalitis, serum levels were higher than those in the paired CSFs. Although the added sensitivity of CSF NMDAR-Ab evaluation has recently been reported,³⁵ whether serum analysis without an available paired CSF can result in a “false-positive” result was not evaluated in that study. The definition of a false-positive requires a gold standard clinical diagnosis, which, in the context of an expanding phenotype such as that described here, cannot be established. Moreover, since NMDAR-Abs can remain detected in both serum and CSF³⁵ after the patient has recovered, a positive result does not necessarily reflect “false positivity” but merely that the antibodies are not causing a detectable neurologic syndrome. Our suggestion would be that CSF testing, if unavailable initially, should be performed if the serum is negative with a strongly suggestive clinical phenotype or, conversely, can be used to provide further support for the “clinical relevance” of the serum antibodies in patients in whom the clinical features are less typical.

Other limitations of this study include the retrospective nature of the cohort collection and the small sample size that is further confounded by the heterogeneous clinical phenotypes. Further studies are now required to confirm our observation that children and adults with NMDAR-Abs can present with these distinct clinicoradiologic white matter syndromes and to determine whether, and if so how, NMDAR-Abs bind to white matter, in which patients and clinical syndromes it could be relevant, and the treatment implications.

AUTHOR CONTRIBUTIONS

Yael Hacoen: acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, study concept or design. Michael Absoud: drafting/ revising the manuscript, acquisition of data. Cheryl Hemingway: acquisition of data, drafting/ revising the manuscript. Leslie Jacobson: acquisition of data, drafting/ revising the manuscript. Jean-Pierre Lin: acquisition of data, drafting/ revising the manuscript. Michael G. Pike: acquisition of data, drafting/ revising the manuscript. Sunil Pullaperuma: acquisition of data, drafting/ revising the manuscript. Ata Siddiqui: acquisition of data, drafting/ revising the manuscript. Evangeline Wassmer: acquisition of data, drafting/ revising the manuscript. Patrick

Waters: acquisition of data, drafting/revising the manuscript. Sarosh Irani: drafting/revising the manuscript, study concept or design. Camilla Buckley: acquisition of data, drafting/revising the manuscript, study concept or design. Angela Vincent: analysis or interpretation of data, drafting/revising the manuscript, study concept or design, study supervision. Ming Lim: analysis or interpretation of data, drafting/revising the manuscript, study concept or design, study supervision.

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