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Clinical presentation of anti-N-methyl-D-aspartate receptor and anti-voltage-gated potassium channel complex antibodies in children: A series of 24 cases

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ABSTRACT

Objective: The symptomatology and paraclinical findings of antibody-mediated encephalitis, a relatively novel disorder, are still being characterized in adults and children. A high index of suspicion is needed in order to identify these cases among children presenting with various neurological symptoms. The aim of this study is to examine the clinical, demographic and laboratory findings and outcome of children with anti-NMDAR and anti-VGKC encephalitis for any typical or distinctive features.

Methods: Cases diagnosed with anti-N-Methyl D-aspartate receptor (NMDAR) and anti-voltage gated potassium channel (VGKC) antibody-mediated encephalopathy in four major child neurology centers are described.

Results: In four years, 16 children with NMDAR and 8 children with VGKC antibody-associated disease were identified in the participating centers. The most frequent initial manifestation consisted of generalized seizures and cognitive symptoms in both groups. Movement abnormalities were frequent in anti-NMDAR patients and autonomic symptoms, in anti-VGKC patients. Cerebrospinal fluid (CSF) protein, cell count and IgG index were normal in 9/15 anti-NMDAR and 5/8 anti-VGKC patients tested. EEG and MRI findings were usually nonspecific and non-contributory. The rate and time of recovery was not related to age, sex, acute or subacute onset, antibody type, MRI, EEG or CSF results. Treatment within 3 months of onset was associated with normal neurological outcome.

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Conclusions: Our results suggest anti-NMDAR and VGKC encephalopathies mostly present with non-focal neurological symptoms longer than 3 weeks. In contrast with adult cases, routine CSF testing, MRI and EEG did not contribute to the diagnosis in this series.

1. Introduction

Antibody (ab)-mediated encephalitis is being increasingly recognized with the accumulation of clinical knowledge and availability of diagnostic tests. Many cases are evaluated based on a high index of suspicion, but only a minority turn out to be ab-positive. The main ab groups associated with encephalitis in children are those against N-methyl-D-aspartate receptor (NMDAR), voltage-gated potassium channel complex (VGKC), and glutamic acid decarboxylase (GAD); in contrast with adult patients, anti-paraneoplastic abs are only rarely identified.[1] The reported incidences and manifestations of these disorders vary considerably among studies[2–4]; although psychiatric presentation in adults and epileptic in children have been emphasized, a wide spectrum comprising cognitive, behavioral, autonomic and sleep disturbances has also been described in both age groups. We examined our series of children with anti-NMDAR and anti-VGKC encephalitis in order to identify any typical or distinctive characteristics of these autoimmune disorders in children.

2. Methods

All patients diagnosed in the participating centers between 2012 and 2016 were reviewed from medical records. The diagnosis was based on serum, and in one patient, cerebrospinalfluid (CSF) testing for NMDAR or VGKC antibodies by commercially available tests (Euroimmun, Germany) after clinical suspicion and exclusion of other causes. VGKC complex antibodies could be specifically tested for LG1 or CASPR2 in 6 cases and were defined as LGI1 antibodies. Symptoms and signs, CSF, MRI and EEG and outcome data were collected from medical records. Onset was defined as acute if symptom duration was $\leq$3 weeks and subacute if >3 weeks.

Symptoms were grouped as in Hacohen et al.: cognitive, including confusion, aphasia, behavioral alteration, amnesia; and psychiatric, including mood disturbances, hallucinations, agitation, and altered behaviors.[5]

EEG findings were classified as "disturbances in background rhythm" which included excessively slow or fast rhythms, and "epileptic activity" to comprise both focal and generalized discharges.

First-line immunotherapy included corticosteroids, intravenous immunoglobulin (IVIg), and plasma exchange, alone or in combination; second-line agents included rituximab, cyclophosphamide and azathioprine.

Patients were considered to have relapsed if new symptoms developed or pre-existing symptoms worsened after at least 3 months' stabilisation or improvement.

3. Results

There were total 24 patients, 13 girls and 11 boys, aged 6 months to 18 years (Table 1). In the anti-NMDAR group (n = 16) the youngest patients were two infants who had antecedent herpes simplex virus (HSV) encephalitis, and a 2 year-old with no antecedent. In the anti-VGKC (n = 8) group, the youngest was 1.5 year old. M/F was 8/8 in anti-NMDAR and 3/5 in anti-VGKC group. Age and sex did not differ significantly between groups. Three patients in the anti-NMDAR group had an underlying etiology: HSV encephalitis (cases 9, 16) and mediastinal teratoma (case 11). One patient (case 7) had a history of post-measles vaccine encephalitis at age 9 months, was being followed-up for post-encephalitic disability and epilepsy, and developed involuntary movements at age 9 years, when anti-NMDAR Abs were demonstrated in serum. The majority of patients had subacute onset of symptoms. Four anti-NMDAR patients had acute onset included two with underlying HSV and one with teratoma. The most frequent initial manifestation consisted of seizures and cognitive symptoms in both groups. The type of seizure was either generalized or focal followed by secondary generalization. Movement abnormalities, described as dyskinesia, tremor or chorea were relatively more frequent in anti-NMDAR patients (7/16) compared to anti-VGKC patients (1/8). Autonomic symptoms and signs were more common among anti-VGKC patients (Table 2).

Serology was tested mean 30 days (5–45 days) and lumbar puncture, mean 14 days (5–23 days) after the onset of symptoms. Routine CSF analysis was normal in 9/15 anti-NMDAR and 5/8 anti-VGKC patients. Abnormal findings consisted of mild proteinorrhachia, pleocytosis or oligoclonal bands.

Initial EEG, performed 4–60 days (median 30 days) after the onset of symptoms, was abnormal in the majority of cases. Normal EEGs were observed in 2 patients with anti-NMDAR (including one with teratoma) and one with anti-VGKC encephalitis. Significant findings on the initial EEG were disturbances in background rhythm and epileptic activities. Focal or diffuse slowing, fast activity, rhythmic delta frequency activity and focal epileptic discharges were observed at similar incidence in both groups. Multifocal epileptic activity was only observed in two anti-VGKC cases.

Brain MRI was done in all patients at mean 4.9 weeks (range 1–10 weeks) after onset and were abnormal in 9 (37.5%)

Table 1 – Demographic, clinical and laboratory features, imaging and Accessory tests, treatment and outcome of 24 children with antibody-mediated encephalitis.

Case	Age at Diagnosis (years)	Sex	Diagnostic Ab	Onset Acute/ Subacute	Seizure Type	Associated Features	CSF Findings	MRI Findings	Initial EEG Findings	Immunotherapy/ Time to Initial Treatment (month)	Outcome/ Follow up Time (year)
1	4,5	M	NMDAR	Subacute	Generalized tonic-clonic and dyscognitive	Sleepiness, chorea, dyskinesia, aphasia, fever, headache	Pleocytosis (60/mm^3)	Normal	Moderate diffuse slowing, focal epileptic activity	IVIG, PMP, Plasmapheresis/3 months	Cognitive and motor impairment/>4 years
2	14	M	NMDAR	Subacute	Focal and secondary generalized tonic-clonic	Sleepiness, agitation, irritability, ataxia	Mildly elevated protein (54 mg/dl) OCB+	Possible increased hippocampal T2 signal	Asymmetric focal slowing, excess frontocentral beta frequency activity	IVIG, PMP/1 month	Recovery/>4 years
3	14	M	NMDAR	Acute	Focal, secondary generalized tonic-clonic and dyscognitive	Sleepiness, agitation, fever, vertigo	Normal	Normal	Excess frontal beta frequency activity, photic entrainment	Not given	Cognitive and psychiatric impairment/>4 years
4	2,5	F	NMDAR	Subacute	Focal and tonic	Lethargy, behavioral alteration, agitation, aphasia, hallucination	Not documented	Increased bilateral anteromesial temporal T2 signal	Mild diffuse slowing, occipital intermittent rhythmic delta activity, focal epileptic activity, extreme delta brushes, attenuation period	IVIG, PMP, Azathioprine/2 months	Relapse + Normal in between/>4 years
5	6	M	NMDAR	Subacute	Focal, secondary generalized tonic-clonic	Sleepiness, fever	Normal	Cerebral and cerebellar atrophy, bilateral hippocampal sclerosis	Modarate diffuse slowing, focal epileptic activity, brief rhythmic discharges	IVIG/3,5 months	Cognitive and motor impairment/>4 years
6	9,5	F	NMDAR	Subacute	Generalized and dyscognitive	Sleepiness, dyskinesia, hallucination	Normal	Normal	Bilateral occipital slowing, excess frontocentral beta frequency activity, focal epileptic activity	IVIG, Oral steroid/1,5 months	Recovery />4 years
7	9	M	NMDAR	Subacute	Generalized tonic-clonic and dyscognitive	Lethargy, chorea, irritability	Normal	Bilateral cerebral volume loss (left > right)	Severe diffuse slowing, bilateral focal epileptic activity, occipital intermittent rhythmic delta activity, attenuation period	IVIG, PMP, Rituximab/2 months	Cognitive and motor impairment/3,5 years

(*continued on next page*)

Table 1 – (*continued*)

Case	Age at Diagnosis (years)	Sex	Diagnostic Ab	Onset Acute/ Subacute	Seizure Type	Associated Features	CSF Findings	MRI Findings	Initial EEG Findings	Immunotherapy/ Time to Initial Treatment (month)	Outcome/ Follow up Time (year)
8	2	F	NMDAR	Subacute	No seizure	Ataxia	Normal	Normal	Normal	IVIG, Oral steroid/4 months	Recovery/> 4 years
9	0,5	F	NMDAR+HSV encephalitis	Acute	Generalized	Sleepiness	Increased protein (99 mg/dl), HSV PCR+	Bilateral necrosis in temporal lobes	Generalized rhythmic delta frequency activity, extreme delta brushes, focal epileptic activity	IVIG, ACTH/3,5 months	Cognitive and motor impairment/2,5 years
10	5,5	M	NMDAR	Subacute	Generalized	Sleepiness, dyskinesia, emotional lability, aphasia	Normal	Bilateral white matter signal intensity changes	Diffuse moderate slowing, diffuse moderate slowing superposed with beta activity, infrequent L occipital paroxysmal activity	IVIG, PMP, Oral steroid, ACTH, Rituximab, Azathioprine/1 month	Cognitive, psychiatric and motor impairment/3 years
11	12	F	NMDAR+ Teratoma	Acute	Generalized	Sleepiness, dyskinesia	Normal	Normal	Normal	IVIG, Oral steroid, Azathioprine/3 months	Recovery/>4 years
12	5	M	NMDAR	Subacute	Focal clonic and generalized	Lethargy, agitation, aphasia	OCB+, normal protein and glucose	Normal	Severe diffuse slowing, generalized rhythmic delta frequency activity, diffuse excess beta frequency activity	IVIG, PMP, Cyclophosphamide/ 1,5 months	Recovery/>4 years
13	6.5	F	NMDAR	Subacute	No seizure	Agitation, emotional lability	Normal	Normal	Asymmetric focal slowing	IVIG, Oral steroid/2 months	Recovery/3 years
14	13	F	NMDAR	Subacute	Generalized	Behavioral alteration, agitation	Normal	1.Hippocampal and amigdalar cytotoxic edema. 2. (15 months later) Hippocampal sclerosis	Modarate diffuse slowing, extreme delta brushes, periodic lateralized epileptiform discharges	IVIG, PMP, Plasmapheresis, Azathioprine/2,5 months	Recovery/3,5 years
15	7	F	NMDAR	Subacute	Generalized	Irritability, dystonia	Mildly elevated protein (50.5 mg/dl)	Normal	Severe diffuse slowing, focal epileptic activity	IVIG, PMP, Plasmapheresis, Rituximab, Cyclophosphamide, Azathioprine/2 months	Cognitive and psychiatric impairment Intractable seizures/2,5 years

16	0,5	M	NMDAR+HSV encephalitis	Acute	Generalized	Sleepiness, orolingual dyskinesia, chorea	Elevated protein (92 mg/dl) HSV PCR+Pleocytosis (14 lymph, 48 RBC/mm^3)	1. Contrast enhancement in bilateral occipital and R frontal pachymeninges. 2. (1 month later) Bilateral occipital encephalomalacia, cerebral atrophy	Severe diffuse slowing	IVIG, PMP/1,5 months	Cognitive and motor impairment, swallowing disorder/1 year
17	14	M	VGKC (low titer of NMDA)– unknown subtype	Subacute	No seizure	Fever, vomiting, ataxia, tremor	Pleocytosis (10/mm^3)	Normal	Mild diffuse slowing, excess frontal beta frequency activity	Not given	Ataxia, cognitive impairment/>4 years
18	11	M	VGKC– unknown subtype	Subacute	No seizure	Sleepiness, hemiparesis, headache, aphasia	Normal	T2 hyperintensity in pons white matter	Not documented	PMP, Oral Streoid/1 month	Recovery/>4 years
19	18	F	VGKC- LGI1	Acute	Generalized	Sleepiness, aphasia, hypertension	Normal	Normal	Focal epileptic activity	PMP, Oral steroid /1 month	Recovery/>4 years
20	16	F	VGKC - LGI1	Subacute	Focal and generalized	Sleepiness, hallucination, behavioral alteration, agitation, aura (smell), hypertension, tachycardia, fever	Normal	Restricted diffusion in bilateral medial temporal lobes, left insula, left cingulate gyrus	Normal	IVIG, Oral steroid/2 months	Cognitive impairment/>4 years
21	10	F	VGKC - LGI1	Subacute	Generalized	Seizures (status epilepticus)	OCB+	Normal	Multifocal epileptic activity	IVIG/2 months	Seizure (not intractable), cognitive impairment/3,5 years
22	1,5	F	VGKC - LGI1	Acute	Generalized tonic	Sleepiness,irritability, fever, aphasia, dyskinesia, tachycardia, hypertension	Mildly increased protein (52 mg/dl)	Normal	Generalized rhythmic delta frequency activity	IVIG, PMP, Oral steroid, Rituximab/ 0.5 month	Recovery/>4 years
23	5,5	M	VGKC - LGI1	Subacute	No seizure	Sleepiness, sleep disturbance, behavioral alteration, agitation, hypertension	Normal	Normal	Generalized rhythmic delta frequency activity	IVIG/2 months	Recovery/>4 years
24	4.5	F	VGKC - LGI1	Subacute	Generalized	Sleepiness, aphasia, ataxia	Normal	Normal	Multifocal epileptic activity	IVIG, PMP/1 month	Recovery/>4 years

Table 2 – Clinical and demographic characteristics, imaging and EEG features of 24 children with antibody-mediated encephalitis.

		NMDAR Ab (+) Group n = 16 (%)	VGKC Ab (+) Group n = 8 (%)
	Median age, (range, mean ± SD) in years	6,25 (0.5–14, 7.0 ± 4.6)	10,5 (1.5–18, 10.1 ± 5.9)
	M/F	8/8	3/5
Initial symptom/sign n (%)	Seizure	13 (81)	5 (62)
	Cognitive (sleepiness, lethargy, aphasia)	13 (75)	6 (75)
	Psychiatric (agitation,mood, hallucination)	10 (62)	3 (37)
	Movement (chorea, dyskinesia, dystonia)	7 (43)	1 (12)
	Fever	3 (18)	3 (37)
	Ataxia	2 (12)	2 (25)
	Headache	1 (6)	1 (12)
	Autonomic*	0 (0)	5 (62)
MRI normal (%)		8 (50)	6 (75)
EEG	Normal	2/16	1/7
	Abnormal background rhythm	14/16	5/7
	Epileptic activity	9/16	4/7

*p = 0.001.

patients. Findings consisted in volume and signal intensity changes. One patient in each group had lesions consistent with cytotoxic edema. Post-HSV anti-NMDAR patients' MRI demonstrated encephalomalacia and atrophy. The anti-VGKC group had MRI within median 4 weeks after onset, and frequently had a normal MRI (75% vs.50% in the NMDAR group, p = n.s). Abnormal MRI results were observed mean 5.4 weeks and normal results, 4.5 weeks after onset.

Time to treatment was from 2 weeks to maximum 4 months. Immunotherapy was given to 22 patients while two cases received no treatment because of stabilised symptoms before diagnosis. First-line immunotherapy consisted of IVIg (n = 9), intravenous pulse methylprednisolone (PMP) (n = 2), IVIg + PMP (n = 8), and IVIg + PMP + plasmapheresis (n = 3), in combination with oral steroids (n = 9) and ACTH (n = 2) in some cases (Table 1). Second-line immunotherapy consisted in azathioprine (n = 3), rituximab (n = 2), cyclophosphamide (n = 1), rituximab + azathioprine (n = 1), rituximab + azathioprine + cyclophosphamide (n = 1). The rate and time of response varied, and other immunotherapeutic agents: plasmapheresis, azathioprine, rituximab, or cyclophosphamide were administered if no response was observed 2–4 weeks after the first dose of IVIg and PMP. In the NMDAR group 1/16 (6%) patient had no immunotherapy, 15/16 (94%) patients received first-line immunotherapy and 7/16 (44%) second-line immunotherapy while these figures were 1/8, 6/8 and 1/8 (12.5, 87.5 and 12.5%) in the VGKC group respectively (Table 1).

The majority of the patients were followed-up for longer than 4 years (Table 1), the shortest for one year (case 16). Recovery was not significantly related to age, sex, acute or subacute onset, Ab type, MRI, EEG or CSF findings. Among anti-NMDAR cases, those post-encephalitis (two post-HSV and one following vaccination) developed neurological deficit although treatment was started within the first 3 months. Of all cases who were treated within the first 3 months, 6/9 recovered completely. In general, complete recovery was reached in 8/16 patients in the anti-NMDAR group including one relapsing case, and in 5/8 patients in the anti-VGKC group. The remaining patients had various degrees of cognitive or psychomotor disturbances.

4. Discussion

According to epidemiological research and results of large multicentric studies from California and England, anti-NMDAR encephalitis constitutes up to %21 of encephalitis cases.[6,7] VGKC antibodies appear to be less frequent: 2.2% in a series of 46 children with severe encephalitis,[8] 20% in encephalopathies, but also 7.6% in other inflammatory neurological and non-neurological conditions.[9,10] Our series is among the few childhood series where the two antibody groups are comparable. Our anti-NMDAR patients outnumbered the anti-VGKC group. Sex and age distribution of anti-NMDAR and anti-VGKC groups showed no difference, although the former tended to be younger.

The clinical presentation mostly consisted of seizures and abnormal movements. Certains report movement abnormalities and hallucinations being more frequent in anti-NMDAR cases and limbic encephalopathy, prolonged seizures, psychiatric symptoms predominating in anti-VGKC.[5] In adults, psychiatric presentation predominates in up to 70% of anti-NMDAR encephalitis.[11,12] However in a report of 36 children with anti-NMDAR encephalitis diagnosed over 5 years, seizures were the most common presenting symptom (50%), followed by psychiatric symptoms (30%).[13] Likewise, seizures were most frequent in our anti-NMDAR group. Interestingly, seizures tended to be generalized, even those with focal beginning showing secondary generalization. This may reflect the diffuse cerebral involvement of Ab-mediated encephalopathy. Anti-VGKC-positive cases can also manifest with epilepsy: Suleiman et al. found this ab in 4/10 patients presenting with status epilepticus.[10] In addition to seizures, all had cognitive or behavioral changes; however the reliability of such observations can be questioned in a child with active seizures. Our case 20 presented with status epilepticus; his cognitive impairment observed after seizure control could

have been due to prolonged status or to anti-VGKC encephalitis *per se*. Our anti-VGKC groups consists mainly of LGI1 patients (except two cases who could not be tested due to availability of the test at that time). This was expected, as CASPR2 antibodies are rare in children.[14]

Although cognitive symptoms were slightly more frequent in our anti-VGKC group, the main difference between two groups consisted of the absence of autonomic symptoms in anti-NMDAR cases in contrast with anti-VGKC patients who had hypertension (n = 2), hypertension and tachycardia (n = 2) and vomiting in the absence of meningeal irritation or seizures (case 17). Autistic regression has been reported as a symptom of NMDAR Ab-mediated encephalitis.[15] Our series did not include this symptom; however, in another study we found no NMDAR antibodies but only four cases of anti-glutamic acid decarboxylase antibodies in sera of 30 children with autistic regression (unpublished data).

As expected, antecedent or underlying conditions existed in the anti-NMDAR group only. We had only one patient with a thoracic teratoma: malignancy does not appear as a frequent etiology in the age spectrum of our pediatric clinic, i.e., early childhood and adolescence.

Among paraclinical findings, MRI obtained within 4 weeks of symptoms showed atrophy in 4 patients including 2 with HSV encephalitis, and hyperintense lesions mainly in temporal or hippocampal areas in 3 of our anti-NMDAR cases. Interestingly, anti-VGKC cases showed fewer abnormalities and no atrophy on MRI. The only brainstem involvement on MRI was in this group: Case 18, whose symptoms and signs also are compatible with brainstem encephalitis. Anti-VGKC Abs have been described in brainstem encephalitis.[16] Atrophy or various signal intensity changes on MRI were reported in 10–30% of anti-NMDAR encephalitis series.[13] Some of the atrophy, especially when reversible, might be due to steroid treatment, but one anti-NMDAR (case 5) had atrophy on initial MRI.

On EEG, encephalopathic slow background, diffuse and focal slowing are described in the majority of anti-NMDAR patients.[13] In our series, anti-VGKC and anti-NMDAR groups did not differ in terms of EEG findings. All had abnormal EEGs except two patients in the anti-NMDAR and one in the anti-VGKC group. The most frequent finding was in the background rhythm, consisting in slow or excessively fast rhythms.

Cerebrospinal fluid analysis has to be included in the work-up of all encephalopathies, but was often non-contributory, showing normal findings or increased protein, and rarely, OCB. Likewise, OCB were positive in only 20% of another childhood anti-NMDAR series.[13]

Regarding outcome, we did not observe any predictors although our sample size does not allow statistical correlation. Underlying HSV appeared as a negative factor in our series, mainly due to HSV encephalitis *per se* and also to the young age of these cases. In tumor-associated cases, early resection of tumor was associated with normal neurological outcome. Age >12 years may be a factor for good outcome: Zekeridou et al. in their series of 36 anti-NMDAR patients observed age as a predictor.[13] MRI is not related to outcome, as our patients with normal brain MRI (n = 8) could end up with complete recovery (n = 5) or sequelae (n = 3). Two patients with mesiotemporal lobe signal changes, hippocampal and amygdalar cytotoxic edematous lesions recovered completely, one after a relapse, while 2 with cerebral and cerebellar atrophy developed clinical sequelae.

Complete recovery was seen in 42% of Hacohen et al.'s series although no uniform assessment was done.[5] We did not include systematic assessment in our study either; however the absence of complaints from family and school implies these children did not have any deficits affecting their daily life significantly.

Time to treatment is likely to affect outcome. Time elapsed before immunomodulatory treatment varies in all series due to diagnostic delays: this precludes comparison of treatment efficacy. However recovery without treatment is possible.[5] In our series, 8 NMDAR and 6 VGKC patients responded to first line immunotherapy; 7 children in the NMDAR group and 1 in VGKC group required second-line immunotherapy. Second-line immunotherapy was administered to 44% of children in NMDAR group, like Sartori et al.'s case series (45%).[17] The rate and extent of recovery did not differ among treatment groups: however the need for a second-line treatment signifies more resistant or delayed cases and not necessarily lack of efficacy of first-line agents. With increased awareness, very late diagnosis (months to years) is becoming rare and prognosis is likely to be affected positively. Immunomodulatory treatment can be started without waiting for Ab results or even if they are negative, based on the observations on early treatment and recovery.[3,17] On the other hand, second-line agents do not appear mandatory especially in resource-limited areas, first line immunotherapy resulting in comparable outcome.[18]

The relapse rate of anti-NMDAR encephalitis is approximately 30% in adults but lower in children.[13,18,19] Among our patients only one experienced a neurologic relapse although all have been free from immunotherapy for at least 12 months. In our series, the relapse rate was 6% in the NMDAR group compared to around 15% in other pediatric series.[17] Most relapses have been reported in the first 2 years of the disease: because the duration of follow-up in our series is longer in most cases, we do not think the rate of relapse would increase significantly in longer follow-up, and is likely to diminish further in the future due to earlier and more efficient first-line treatment.

This study contributes to the recognition of ab-associated encephalitis in children presenting with subacute cognitive symptoms or with subacute-onset seizures. Its limitations lie in its retrospective nature. For instance, evaluation of personal and family history for autoimmune disorders, or assessment of outcome and treatment measures were not uniform. Specific testing for VGKC subtypes was available in only 6 patients, and CSF was tested for antibodies in only one patient because autoimmune encephalitis, not well known several years ago, was not suspected when lumbar puncture was performed in the work-up of encephalopathy. This limitation does not question the validity of the current series, but possibly signifies a few cases being left out. Another group of interest for future studies would consist of cases who receive immunomodulatory treatment based on clinical suspicion, but whose serology comes out negative. Their evaluation could be important in defining the group likely to benefit from such treatment. Presently, this series, larger than most

published single-center series in children, adds to the experience on antibody-mediated encephalities, particularly on the anti-VGKC group where data is relatively scarce. A prospective study is being planned including a registry system where all data would be recorded in standard fashion, as done in other large studies.[3,17] Expanding the pool of knowledge can facilitate the diagnosis and prompt immunomodulatory treatment, reducing sequelae and cost.

Conflict of interest

The authors declare that they have no conflict of interest.

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