Journal of Neuroimmunology 332 (2019) 1–7

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short Communication

Anti-NMDAR encephalitis preceded by non-herpetic central nervous system infection: Systematic literature review and first case of tick-borne encephalitis triggering anti-NMDAR encephalitis

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ARTICLE INFO

Keywords:
Anti-*N*-methyl-D-aspartate receptor encephalitis
Anti-NMDAR encephalitis
Tick-borne encephalitis
Children

ABSTRACT

After the recent description of biphasic disease with herpes simplex virus (HSV) encephalitis followed by anti-*N*-methyl-D-aspartate receptor encephalitis (anti-NMDARE), anti-NMDARE preceded by non-HSV central nervous system (CNS) infection has been more rarely reported. We report the first case of TBE followed by anti-NMDARE and carry out a systematic literature review on anti-NMDARE preceded by non-HSV CNS infection.

1. Introduction

Tick-borne encephalitis (TBE) is caused by an RNA virus of genus Flavivirirus, tick-borne encephalitis virus (TBEV), transmitted by infected ticks or, rarely, by unpasteurized dairy products. In endemic areas, TBEV accounts for about 10% of all pediatric encephalitis. About 15% of all TBEs in Europe involve subjects under 19 years of age, mainly school-age children (Taba et al., 2017; Rostasy, 2012). TBE is a milder illness in children than in adults, mostly asymptomatic or paucisymptomatic, with serious consequences (such as lethal outcome or severe neurological disabilities) in about 2% (Taba et al., 2017; Fritsch et al., 2008). After an incubation period of 7–14 days, the disease follows a biphasic course: the first phase appears as an acute non-specific febrile illness characterized by fever, headache, myalgia, malaise, nausea and vomiting lasting up to 5 days; the second phase, occurring in 5–30% of children, is characterized by recurrence of fever in addition to symptoms of meningitis or meningoencephalitis (Rostasy, 2012).

Anti-*N*-methyl-D-aspartate receptor encephalitis (anti-NMDARE) is the most common autoimmune encephalitis, increasingly recognised in childhood. After prodromal flu-like symptoms, the clinical presentation includes seizures, abnormal behaviour, psychiatric changes, speech dysfunction, movement disorder, decreased level of consciousness and dysautonomias (Favier et al., 2018; Ho et al., 2017). Detection of anti-NMDAR antibodies in the cerebrospinal fluid (CSF) in a patient with suggestive clinical picture leads to a definitive diagnosis (Ho et al., 2017; Graus et al., 2016). Although in most cases anti-NMDARE is 'idiopathic', a significant minority recognises a paraneoplastic etiology or an infection trigger (Scheer and John, 2016). Herpes simplex virus (HSV)-induced anti-NMDARE has been widely described, with the first 43 published cases recently reviewed in 2017 (Nosadini et al., 2017). Whereas, anti-NMDARE preceded by non-HSV central nervous system (CNS) infection has more rarely been reported.

We present the case of an 11-year-old girl who presented to our pediatric hospital in Padua (Italy) with anti-NMDARE following an episode of TBE; to our knowledge, this is the first reported case of TBEV-induced anti-NMDARE. A review of the literature on anti-NMDARE following a non-HSV CNS infection was also carried out.

Abbreviations: Anti-NMDARE, Anti-*N*-methyl-D-aspartate receptor encephalitis; CMV, Cytomegalovirus; CNS, Central nervous system; CSF, Cerebrospinal fluid; *CT, Computed tomography*; EBV, Epstein Barr virus; EEG, Electroencephalography; HHV6, Human herpesvirus 6; HHV7, Human herpesvirus 7; HIV, Human immunodeficiency virus; HSV, Herpes Simplex virus; *JE, Japanese encephalitis*; MRI, Magnetic resonance imaging; mRS, Modified Rankin scale; RNA, Ribonucleic acid; PCPC, Pediatric Cerebral Performance Category scale; *PCR, Polymerase chain reaction*; TBE, Tick-borne encephalitis; TBEV, Tick-borne encephalitis virus; VZV, Varicella zoster virus

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https://doi.org/10.1016/j.jneuroim.2019.03.011
Received 13 February 2019; Received in revised form 18 March 2019; Accepted 18 March 2019
0165-5728/

Table 1
Results of the systematic literature review on patients with biphasic disease with non-HSV CNS infection followed by anti-NMDAR encephalitis.

Author, year	Age at onset of anti-NMDARE (years), gender	Anti-NMDAR antibodies in serum/CSF	Infectious agent: serum and CSF data (timing of detection)	Clinical infectious illness prior to anti-NMDARE (days between infectious illness and anti-NMDARE)	CSF data during anti-NMDARE: WBC/mm3, proteins (mg/dL), OCB	Brain MRI during anti-NMDARE	EEG during anti-NMDARE	Immune therapy during anti-NMDARE	Treatment of infection	Tumour	Length of follow-up after anti-NMDARE (months)	Relapses of anti NMDARE	Neurological outcome at last follow-up (mRS, PCPC)
Present case	11, F	Positive/Positive	TBEV Serum: positive IgM CSF: not done at TBE (detected 30 days before anti-NMDARE)	TBE (30 days)	WBC: 11 Proteins: 51.8 OCB: +	Negative	Diffuse slow activity and temporoparietal epileptiform discharges	IVIG, CS, PE, RTX, MMF	Ceftriaxone, Acyclovir	No	12	No	Fine postural tremor (0,1)
Tian et al., 2019	7, M	Positive/Positive	JE virus Serum: positive IgM CSF: positive Ig (detected before anti-NMDARE)	JE (28 days)	WBC: 29 Proteins: 29.1	Hyperintensity in T2-weighted and FLAIR sequences in bilateral thalami, basal ganglia, and midbrain; more conspicuous and expanded lesions than at JE onset	Delta slow waves in occipital regions	IVIG, CS, CTX	Acyclovir supportive therapy	No	18	No	Learning disability, ADHD (2,3)
Shaik et al., 2018	10, F	Positive/Positive	JE virus Serum: positive CSF: positive (detected before anti-NMDARE)	JE (n.s.)	n.s.	T2 FLAIR hyperintensities in the midbrain, basal ganglia, and thalamus	Slow background activity with intermittent epileptiform discharges	CS	Supportive therapy	No	n.s.	n.s.	n.s.
Haneche et al., 2018	47, F	Negative/Positive	HIV Serum: positive PCR CSF: positive PCR (detected 22 days before anti-NMDARE)	HIV encephalitis (22 days)	WBC: 48 Proteins: 60 OCB: +	Increased signal on T2-weighted and FLAIR imaging in the supratentorial white substance	Slow background activity	IVIG	Foscarnet Maraviroc Emtricitabine/Tenofovir Dolutegravir	No	24	No	Complete recovery (0)
Ma et al., 2017	2.5, M	Positive/Positive	JE virus Serum: positive IgM CSF: positive IgM (detected 29 days before anti-NMDARE)	JE (29 days)	WBC: 6 Proteins: 102	More conspicuous and expanded lesions in bilateral thalamus than the onset of JE	n.s.	IVIG, CS	n.s.	No	2.4	No	Improvement of sleep disorder, choreoathetosis and peri-oral dyskinesia (3, 4)
Ma et al., 2017	14, M	Negative/Positive	JE virus Serum: positive IgM CSF: positive IgM (detected 25 days before anti-NMDARE)	JE (25 days)	WBC: 4 Proteins: 83	More conspicuous and expanded lesions in bilateral thalamus than the onset of JE	n.s.	IVIG, CS	n.s.	No	2	No	Simple verbal response, emotional instability (2,3)
Ma et al., 2017	6, F	Negative/Positive	JE virus Serum: positive IgM CSF: positive IgM (detected 27 days before anti-NMDARE)	JE (27 days)	WBC 3 Proteins: 78	More conspicuous lesions in bilateral thalamus than the onset of JE	n.s.	IVIG, CS	n.s.	No	2	No	Reduction of choreoathetosis, improvement of sleep (3, 4)

(*continued on next page*)

Table 1 (*continued*)

Author, year	Age at onset of anti-NMDARE (years), gender	Anti-NMDAR antibodies in serum/CSF	Infectious agent: serum and CSF data (timing of detection)	Clinical infectious illness prior to anti-NMDARE (days between infectious illness and anti-NMDARE)	CSF data during anti-NMDARE: WBC/mm3, proteins (mg/dL), OCB	Brain MRI during anti-NMDARE	EEG during anti-NMDARE	Immune therapy during anti-NMDARE	Treatment of infection	Tumour	Length of follow-up after anti-NMDARE (months)	Relapses of anti NMDARE	Neurological outcome at last follow-up (mRS, PCPC)
Pastel et al., 2017	7, M	Positive/Positive	JE virus Serum: positive IgM CSF: n.s. (detected during anti-NMDARE)	JE B (25 days)	n.s.	Symmetrical bilateral substantia nigra, caudate nucleus, putamen, and globus pallidus signal changes with asymmetric thalamic signal changes (left > right)	n.s.	IVIG, CS	n.s.	No	3	No	Complete recovery (0,0)
Peng et al., 2017	51, M	Positive/Positive	*Angiostrongylus cantonensis* Serum: positive IgG CSF: positive IgG (detected 1 month before anti-NMDARE)	Eosinophilic meningitis (30 days)	WBC > 125 Proteins: 210	T2-hyperintense lesions in cerebral white matters and right cerebellum	Mildly abnormal	IVIG	Albendazole	No	1	No	Complete recovery (0)
Goenka et al., 2017	0.5, M	Positive/Positive	Tuberculous meningitis Serum: not tested CSF: n.s. (detected 7 days before anti-NMDARE)	Tubercular meningitis (7 days)	Consistent with tubercular meningitis	Diffuse basal enhancement with enhancing exudate	Diffuse background slowing	IVIG, CS	n.s.	No	n.s.	No	Global development delay (3, 4)
Schumacher et al., 2016	11, F	n.s./Positive	EBV[a] Serum: n.s. CSF: n.s. (detected before anti-NMDARE)	Possible EBV encephalitis[a] (n.s.)	n.s.	n.s.	n.s.	CS, IVIG	n.s.	No	3	No	Complete recovery (0, 0)
Spatola et al., 2017	0.2, F	Positive/Positive	HHV6 Serum: positive PCR CSF: positive PCR (detected 35 days before anti-NMDARE)	HHV6 encephalitis[b] (35 days)	WBC: 40 Proteins 85	Extensive residual, post-viral, areas of encephalomalacia	Asymmetric slowing, bilateral epileptiform activity	CS, IVIG	n.s.	No	6	No	Partial recovery (4, 3)
Linnoila et al., 2016	46, F	Negative/Positive	EBV Serum: not tested CSF: positive PCR (n.s.)	Likely EBV systemic and EBV meningoencephalitis (n.s.)	WBC: 600 Proteins: 228	Leptomeningeal enhancement	n.s.	CS	n.s.	No	2	No	Death

(*continued on next page*)

Table 1 (*continued*)

Author, year	Age at onset of anti-NMDARE (years), gender	Anti-NMDAR antibodies in serum/CSF	Infectious agent: serum and CSF data (timing of detection)	Clinical infectious illness prior to anti-NMDARE (days between infectious illness and anti-NMDARE)	CSF data during anti-NMDARE: WBC/mm3, proteins (mg/dL), OCB	Brain MRI during anti-NMDARE	EEG during anti-NMDARE	Immune therapy during anti-NMDARE	Treatment of infection	Tumour	Length of follow-up after anti-NMDARE (months)	Relapses of anti NMDARE	Neurological outcome at last follow-up (mRS, PCPC)
Schäbitz et al., 2014	76, F	Positive/ Positive	VZV Serum: not tested CSF: positive PCR (detected during anti-NMDARE)	VZV brainstem encephalitis with polyneuritis cranialis (n.s.)	WBC: 138 Proteins: 701 OCB: +	Inflammatory lesions in left brainstem, enhanced cranial nerves	n.s.	CS, PE	Ceftriaxone, Acyclovir, Ampicillin	No	0.45	No	Complete recovery (3)

Legend: ADHD: attention deficit hyperactivity disorder; anti-NMDARE: anti-*N*-methyl-D-aspartate receptor encephalitis; CS: corticosteroids; CSF: cerebrospinal fluid; CTX: cyclophosphamide; EBV: Epstein-Barr Virus; ECT: electroconvulsive therapy; EEG: electroencephalography; F: female; FLAIR: fluid attenuation inversion recovery; HIV: Human Immunodeficiency Virus; HHV6: Human Herpesvirus 6; IVIG: intravenous immunoglobulin; JE: Japanese encephalitis; M: male; MMF: mycophenolate mofetil; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; n.d.: not done; n.s.: not specified; OCB: oligoclonal band; PCPC: Pediatric Cerebral Performance Category; PCR: polymerase chain reaction; PE: plasma exchange; WBC: white blood cell; RTX: rituximab; TBE: tick borne encephalitis; TBEV: tick borne encephalitis virus; VZV: Varicella Zoster Virus.

[a] The authors reported two prior admissions for possible EBV encephalitis complicated by seizures and cerebral edema.

[b] Anti-GABAA receptor antibodies (GABAAR) were also identified.

2. Methods

Our literature review was carried out in the English literature of Pubmed (uptodate to 27.01.2019) using the following terms: (anti–*N*-methyl-D-aspartate receptor encephalitis) OR (*N*-methyl-D-aspartate antibody encephalitis) OR (anti-NMDAR encephalitis) OR (anti-NMDA receptor encephalitis) OR (NMDA receptor encephalitis) OR (anti-*N*-methyl-D-aspartate receptor antibody encephalitis). The yielded articles were searched manually for non-HSV CNS infections preceding anti-NMDARE (HSV-induced anti-NMDAR encephalitis has been described elsewhere and was excluded from our analysis) (Nosadini et al., 2017).

Inclusion criteria was biphasic clinical disease with non-HSV CNS infection followed by anti-NMDARE; both adult and pediatric patients were included. Demographics, infectious agents, clinical, CSF and serum data, antibody status, brain magnetic resonance imaging (MRI), electroencephalography (EEG), treatment and outcome were recorded. Modified Rankin Scale (mRS) scale was retrospectively scored at the last follow-up by one of the main investigators (EC) (Van Swieten et al., 1988). For pediatric patients the Pediatric Cerebral Performance Category scale (PCPC) was also applied in addition to the mRS scoring (Armangue et al., 2013).

3. Results

3.1. Case report

A previously healthy 11-year-old girl presented with headache, vomit and insomnia. A tick bite was reported in her recent past medical history. Serum positive TBEV-specific IgM was firstly detected with TBEV-specific IgG titer of 294.1 VIEU/ml which increased to > 2900 VIEU/ml in a following sample; therefore the patient was diagnosed with TBE. Anti-NMDAR antibodies were not tested at this stage. She completely recovered although she had some residual symptoms such as fatigue and fine hand tremors after discharge.

One month after onset of TBE, she presented to the emergency room with confusion, amnesia, apathy, mutism, insomnia, worsening hands tremors and balance disturbances. Blood tests and contrast-enhanced brain MRI were unremarkable. EEG showed diffuse slow activity and temporo-parietal epileptiform discharges. Ten days after admission she developed orobuccal dyskinesias, ocular fluttering and gait instability due to tremors. CFS analysis revealed 11 leukocytes/uL (mononuclears), 60 mg/dL glucose, 51.8 mg/dL proteins, 1.6 mmol/L lactates and negative polymerase chain reaction (PCR) for TBEV, CMV, HSV 1–2, HHV6, VZV, parechovirus. Anti-NMDAR antibodies were detected both in serum and CSF. Therefore, the diagnosis of anti-NMDARE was formulated and the patient received 2 g/kg of intravenous immunoglobulin in 5 days on day 12 and 30 mg/kg/day of intravenous methylprednisolone for 5 days from day 13, and was transferred to our centre.

A second lumbar puncture on day 15 after anti-NMDARE onset showed 6 leukocytes/uL, 28 mg/dL proteins, increased IgG index, intrathecal synthesis of oligoclonal bands. On day 17, the patient deteriorated with worsening orofacial dyskinesias, hyperkinetic-dystonic movements and dysautonomias (fever, tachycardia and dysphagia), requiring mechanical ventilation. Intravenous broad-spectrum antibiotics (ceftazidime and teicoplanin) were administered for the occurrence of septic shock, and continuous infusion of midazolam (1 mg/kg/h) was started for sedation and movement disorder control. Seven plasma exchanges were carried out, with limited improvement (mRS 5, PCPC 5).

On day 20, a third CSF analysis showed mild lymphocytic pleocytosis (14 leucocytes/uL, mostly monocytes) and intrathecal synthesis of oligoclonal bands. CSF culture was negative. Serologic tests and serum PCR for CMV, EBV and Borrelia Burgdorferi were negative. Serum TBEV-IgG and IgM positivity was confirmed. Repeat anti-NMDAR antibodies were positive in CSF and negative in serum. Repeat brain MRI

one month after onset was unremarkable. Rituximab 375 mg/m^2 weekly for 4 weeks was subsequently administered (approximately one month after anti-NMDARE onset) obtaining a substantial recovery. She was discharged on oral mycophenolate mofetil (20 mg/kg/day). At 12-month follow-up after onset of anti-NMDARE, the patient reported only mild fatigue, but did well at school and had normal neurological examination (mRS 1, PCPC 0); mycophenolate mofetil was weaned.

3.2. Literature review

Our literature search identified 11 articles published between 2014 and 2018, reporting a total of 13 cases of biphasic disease with anti-NMDARE occurring after non-HSV CNS infection. With the addition of our case, 14 patients were analysed (8 were ≤18 years; 8 were female) (Table 1).

Regarding etiology, 12 of the 14 patients had viral encephalitis preceding anti-NMDARE: 6 had Japanese encephalitis (JE), 1 had HIV encephalitis, 2 EBV encephalitis, 1 had VZV encephalitis, 1 had HHV6 encephalitis, 1 TBE. The remaining 2 cases had eosinophilic meningitis (with detection of the parasite *Angiostrongylus cantonensis*) and tubercular meningitis, respectively. Six of the patients received treatment for the non-HSV CNS infection.

At the time of CNS infection, anti-NMDAR antibodies were searched in 2 cases resulting negative (Schäbitz et al., 2014; Pastel et al., 2017). Time between onset of non-HSV CNS infection and anti-NMDARE ranged between 7 and 35 days (median 27.5 days, mean 25.8; data available in 10 patients).

Clinical symptoms at anti-NMDARE are detailed in Supplementary Table 1. Encephalopathy was reported in 11 patients, psychiatric/behavioural disturbances in 10, movement disorder in 9, sleep disturbances in 7, speech disturbances in 3, cognitive deterioration in 2, seizures in 2, other in 2. All patients received first-line immune therapy (corticosteroids, intravenous immunoglobulin and/or plasma exchange) for *anti-NMDARE, while* second-line treatments (rituximab or cyclophosphamide) were used only in 2 cases. *No tumours were detected.* None of the patients experienced recurrence of infectious or autoimmune encephalitis. Four patients had complete or almost complete recovery with mRS ≤ 1 or PCPC = 1 at last follow-up. One patient died for unspecified reason.

4. Discussion

We report the first patient with anti-NMDARE preceded by TBE and carry out a systematic literature review of anti-NMDARE following non-HSV CNS infection.

Our patient presented re-emergence of neurological symptoms one month after TBE onset, following complete remission. At this time, the hypothesis of TBE recurrence was considered less likely, based on negative CSF PCR for TBEV, and clinical symptoms not typical for TBE; on the other hand, CSF and serum anti-NMDAR antibodies were positive, and the clinical syndrome was characteristic for anti-NMDARE (Ho et al., 2017; Graus et al., 2016). Moreover, brain MRI at TBE typically shows involvement of the thalami, while in our case MRI was negative at relapse (Rostasy, 2012). In addition, CSF neuropathologic changes with inflammatory reaction in TBEV meningitis or meningoencephalitis are reported (Růžek et al., 2010), differently to our case. TBE recurrence or reinfection are highly unlikely, since specific IgG antibodies persist for a lifetime and prevent reinfection; indeed, seroconversion was documented in our case (Růžek et al., 2010).

Since the first description of anti-NMDARE in women with ovarian teratoma in 2007 (Dalmau et al., 2007), the syndrome has increasingly been reported in childhood, and is now recognised as one of the most common non-viral encephalitides in children; approximately 37% of anti-NMDARE occurs in childhood (Titulaer et al., 2013; Goenka et al., 2017). While approximately 50% of the adult cases have a paraneoplastic etiology, the association with tumour (most often ovarian teratoma) is much lower in children (Titulaer et al., 2013). Emerging literature suggests that postinfectious immune-mediated etiology may be linked to non-paraneoplastic anti-NMDARE [16,17]. In particular, HSV-induced anti-NMDARE is now a well-recognised entity, and the first 43 published cases of anti-NMDARE preceded by HSE were recently reviewed (Nosadini et al., 2017; Armangue et al., 2018).

Several hypotheses on the pathogenesis of HSV encephalitis followed by anti-NMDARE have been put forward. Namely, molecular mimicry due to shared epitopes between HSV and the NMDAR may occur. This hypothesis also adapts well to paraneoplastic cases, since teratoma expresses epitopes mimicking the NMDAR. Although, our case report and the results of our literature review seem to challenge this hypothesis, since all the patients of our literature cohort had a non-HSV CNS infection, and none had tumour. It is still possible, though, that the infectious agents involved share some epitopes with the NMDAR, undergoing a molecular mimicry mechanism. A wide array of pathogens have been associated with anti-NMDARE in the literature, including EBV (Linnoila et al., 2016; Xu et al., 2011; Mirza et al., 2011; Schumacher et al., 2016), HHV-6 (Linnoila et al., 2016; Armangue et al., 2013; Spatola et al., 2017), HHV-7 (Venâncio et al., 2014), VZV (Solís et al., 2016; Gahr et al., 2015; Schäbitz et al., 2014), Influenza virus A e B (Pastel et al., 2017; Prüss et al., 2010; Baltagi et al., 2010), HIV (Arboleya et al., 2016; Patarata et al., 2016; Haneche et al., 2018), Measles virus (Ioannidis et al., 2015), Rubellavirus (Gahr et al., 2015), Mumps virus (Armangue et al., 2013), Densovirus (Phan et al., 2016), Enterovirus (Armangue et al., 2013), *Mycobacterium tuberculosis* (Goenka et al., 2017), Mycoplasma Pneumoniae (Venâncio et al., 2014; Veciana et al., 2015; Gable et al., 2009), Chlamydia Pnuemoniae (Prüss et al., 2010), Legionella Pneumoniae (Prüss et al., 2010), Campylobacter jejuni (Peng et al., 2017), Toxoplasma Gondi (Cai et al., 2018), *Angiostrongylus cantonensis* (Peng et al., 2017), Japanese encephalitis virus (Tian et al., 2019; Shaik et al., 2018; Ma et al., 2017).

Another major pathogenic hypothesis linking HSV CNS infection and anti-NMDARE is that the virus-induced neuronal destruction may expose and present abundant NMDAR epitopes to the systemic immunity, initiating a primary autoimmune response (Nosadini et al., 2017; Cai et al., 2018; Armangue et al., 2018; Peng et al., 2017; Prüss et al., 2012). This may hold true despite the absence of overt brain changes detectable at MRI, like in our case. This hypothesis may well serve our literature cohort, especially as regards the four cases of anti-NMDARE after herpes family CNS infections (VZV, HHV6, EBV), which account for almost 30% of all the reviewed cases (Schmacher et al., 2016; Spatola et al., 2017; Linnoila et al., 2016; Schabitz et al., 2014). Nevertheless, this hypothesis is challenged by the results of a recent study, suggesting a meaningful association between nonencephalitic HSV-1 infection and development of anti-NMDARE (Salovin et al., 2018).

Finally, another hypothesis linking infectious and autoimmune encephalitis is that of a non-specific B-cell activation following the infection.

Some similarities could be drawn between the literature cohort of patients with biphasic disease with anti-NMDARE preceded by HSE (Nosadini et al., 2017) and the present literature cohort of patients with biphasic disease with anti-NMDARE preceded by non-HSV CNS infection. The time interval between infectious encephalitis and anti-NMDARE was similar in the two cohorts (median 28 versus 25 days), with wide expression of typical symptoms of anti-NMDARE in both cohorts (Supplementary Table 1). Similarly to the cohort of anti-NMDARE preceded by HSE, pediatric patients in our literature cohort had more movement disorder and less psychiatric symptoms than adult patients; moreover, in our literature cohort children had more encephalopathy and more sleep disturbances than adults. Although, definite conclusions cannot be drawn in view of the limited number of cases. As regards treatment for anti-NMDARE, while most patients received first-line immune therapy in both cohorts, second-line

treatments were used in 52.5% of patients with anti-NMDARE preceded by HSE, and in only 14% in the present cohort. In the two cohort none of the patients developed a relapse of infectious encephalitis, while 2 patients had a relapse of anti-NMDARE in the subgroup with anti-NMDARE following HSE.

5. Conclusion

Anti-NMDARE has been increasingly described following HSE, while more recently other non-HSV CNS infections have been reported as potential triggers for anti-NMDARE. We reported the first case of TBE followed by anti-NMDARE and identified 13 additional published cases of anti-NMDARE preceded by non-HSV CNS infections. While this remains a very rare phenomenon, the possibility of autoimmune encephalitis should be kept in mind with re-emergence of neurological symptoms after HSV and non-HSV CNS infections. Much remains to be understood on the pathogenesis of post-infectious brain autoimmunity, although it is noteworthy that the timing of re-emergence of neurological symptoms after non-HSV CNS infection in our literature review was similar to that described for anti-NMDARE following HSE (Nosadini et al., 2017), supporting a possible shared pathogenesis for infection-triggered autoimmunity.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2019.03.011.

Funding

None.

Competing interests

None declared.

Acknowledgment

We thank the Pediatric Research Institute "Città della Speranza", Padova, Italy for supporting our Neuroimmunology group and Lab.

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