Intrathecal treatment of anti-*N*-Methyl-D-aspartate receptor encephalitis in children

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ABBREVIATIONS

mRS	Modified Rankin scale
NMDAR	*N*-Methyl-D-aspartate receptor
PET	Positron emission tomography

Anti-NDMA receptor (NMDAR) encephalitis is an auto-immune condition. There is no uniformly agreed treatment strategy for the disorder in children. We report the use of intrathecal treatment with methotrexate and methylprednisolone in three children (one male, two females, age 10y, 11y, and 14y) with anti-NMDAR encephalitis, who did not respond to steroids, plasmapheresis, or rituximab. There was significant clinical improvement and stabilization of the anti-NMDAR antibody titers in cerebrospinal fluid (CSF) and blood in two patients. In the third patient, although anti-NMDAR antibody titers in CSF decreased, clinical recovery was less satisfactory. Intrathecal treatment with methotrexate and methylprednisolone seems to be a promising alternative treatment for some paediatric cases of resistant anti-NMDAR encephalitis.

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an immune-mediated neurological disease that can occur in previously healthy children. It is caused by the production of antibodies against the NR1 subunit of the NMDAR, a ligand-gated cation channel involved in synaptic transmission. Antibody binding to NMDAR causes a selective and reversible decrease of NMDAR clusters in postsynaptic dendrites.[1,2] In children, NMDAR encephalitis is the most frequent, non-infectious cause of encephalitis, as observed by the California Encephalitis Project,[3] and is rarely associated with an underlying tumour.[4,5] Most children with NMDAR encephalitis respond to first-line (steroids and/or immunoglobulins [Ig] and/or plasma exchange) and second-line treatments (rituximab, cyclophosphamide, azathioprine or mycophenolate mofetil); however, some cases are resistant to these treatments. We report three children with severe anti-NMDAR encephalitis who did not respond to initial therapies, and describe their responses to intrathecal treatment. The parents of the three children gave their consent to publication of this report.

CASE REPORTS

Case 1

A previously healthy 10-year-old male presented with partial seizures which responded to oxacarbazepine treatment. One month later he progressively developed agitation, behavioural modifications, choreic movements, fluctuating levels of consciousness, cognitive deterioration, and visual hallucinations (Table I). Cerebrospinal fluid (CSF) analysis identified anti-NMDAR antibodies (1/1000; Fig. S1, online supporting information) and was otherwise normal, confirming anti-NMDAR encephalitis. No tumour was identified. The patient was initially treated with intravenous (IV) rituximab (375mg/m^2), but relapsed 1 month later, with altered consciousness prompting plasma exchange. There was improvement in the patient's cognitive status, but hallucinations, disorientation and behavioural disorders (perseveration, abnormal sexual behaviour, and poor emotional regulation) persisted, suggesting an insufficient response, motivating another injection of 375mg/m^2 rituximab. Five months after initial presentation, no clinical improvement was observed. Intrathecal injections of methotrexate and methylprednisolone were initiated (see Fig. S1). There was significant clinical improvement following the third injection (8mo after first presentation), associated with a decrease in the serum anti-NMDAR titer (Fig. 1a). After 1 year of follow-up, the child recovered completely and was able to attend school. Neuropsychological assessment showed a normal verbal comprehension index but with limitations to memory and information processing. A secondary increase of antibody titers in blood was observed 1 month after the end of the intrathecal treatment but the titers then remained stable and had decreased by the last follow-up visit. The patient's clinical condition was good, with a score of 1 on the modified Rankin scale (mRS). No further treatment was required during a follow-up of more than 2 years after disease onset.

Case 2

An 11-year-old female without medical history presented with generalized seizures, ataxia, behavioural disorders, and delusional speech leading to high doses of IV steroids (Table I). Five months later, a relapse with aggressiveness and hallucinations occurred and anti-NMDAR antibodies were finally detected in the CSF, which was otherwise normal. IV immunoglobulins (immunoglobulins; 1g/kg for 2d) were given every month until another similar relapse occurred 9 months after disease onset, prompting plasma exchange followed by rituximab treatment because of insufficient clinical response. Similar treatments were repeated 12 months after disease onset following aggravation of behavioural disorders. Another relapse at 30 months motivated IV immunoglobulins followed 1 month later by rituximab and azathioprine treatment (100mg/d). Despite these treatments, memory difficulties, agitation, and behavioural disorders persisted and there was another relapse (increased aggressiveness, behavioural disorders) 3 years 9 months after disease onset. Extensive investigations for tumours (thoraco-abdominal computed tomography, pelvic magnetic resonance imaging [MRI], positron emission tomography [PET], exploratory laparascopy) were all negative and CSF was again positive for anti-NMDAR with a high protein concentration (0.88g/L). Intrathecal injections of methotrexate and methylprednisolone were started. One month later, the protein concentration in the CSF had declined to 0.28g/L. After four intrathecal injections there was a moderate reduction of aggressiveness and hallucinations; IV cyclophosphamide (500mg/m^2) was added because of insufficient clinical response. After 12 months of follow-up, the patient's clinical condition had improved (reduced hallucinations, no aggressiveness) and her mRS score decreased from 4 to 2 with a parallel decrease of the anti-NMDAR antibody titer in CSF (to 1/5; Fig. 1b).

What this paper adds

- Intrathecal treatment may be a useful add-on therapy for children with anti-NMDAR encephalitis.

Table I: Characteristics of the three patients

	Patient 1	Patient 2	Patient 3
Symptom at onset	Partial seizures	Generalized seizures	Generalized seizures
Time from presentation to diagnosis	1mo	4mo	3wks
Clinical evolution	Chorea, agitation, behaviour disorders, cognitive deterioration, hallucinations, fluctuating level of consciousness	Ataxia, behaviour disorders, hallucinations, aggressiveness, memory disturbance	Chorea, agitation, behaviour disorders, cognitive deterioration, hypoventilation, aphasia, fluctuating level of consciousness
Score on the modified Rankin scale			
At diagnosis	3	4	4
Before intrathecal treatment	4	3	5
3mo after intrathecal treatment	2	3	2
At the last medical examination	1	2	1
Investigations			
EEG	Focal right centro-parietal spikes	Generalized slow waves	Normal
MRI of the brain	Normal	Bilateral hippocampal intensity	Normal
Paraneoplastic investigations	Total body CT scan: normal Testicular ultrasound: normal	Total body CT scan: normal PET scan: normal Exploratory laparoscopy: negative	Total body CT scan: normal PET scan: normal
Anti-NMDAR antibodies			
CSF	Yes	Yes	Yes
Blood	Yes	Yes	Yes
Treatment before intrathecal			
Corticosteroids	No	Yes	No
Intravenous immunoglobulins	No	Yes	No
Plasma exchange	Yes	Yes	Yes
Rituximab	Yes	Yes	Yes
Other	No	Yes	No
Time from last immunomodulating treatment and intrathecal injections	5mo	18mo	3mo
Duration of follow-up after beginning of intrathecal treatment	28mo	18mo	7mo

EEG, electroencephalogram; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; NMDAR, *N*-Methyl-D-aspartate receptor; CSF, cerebrospinal fluid.

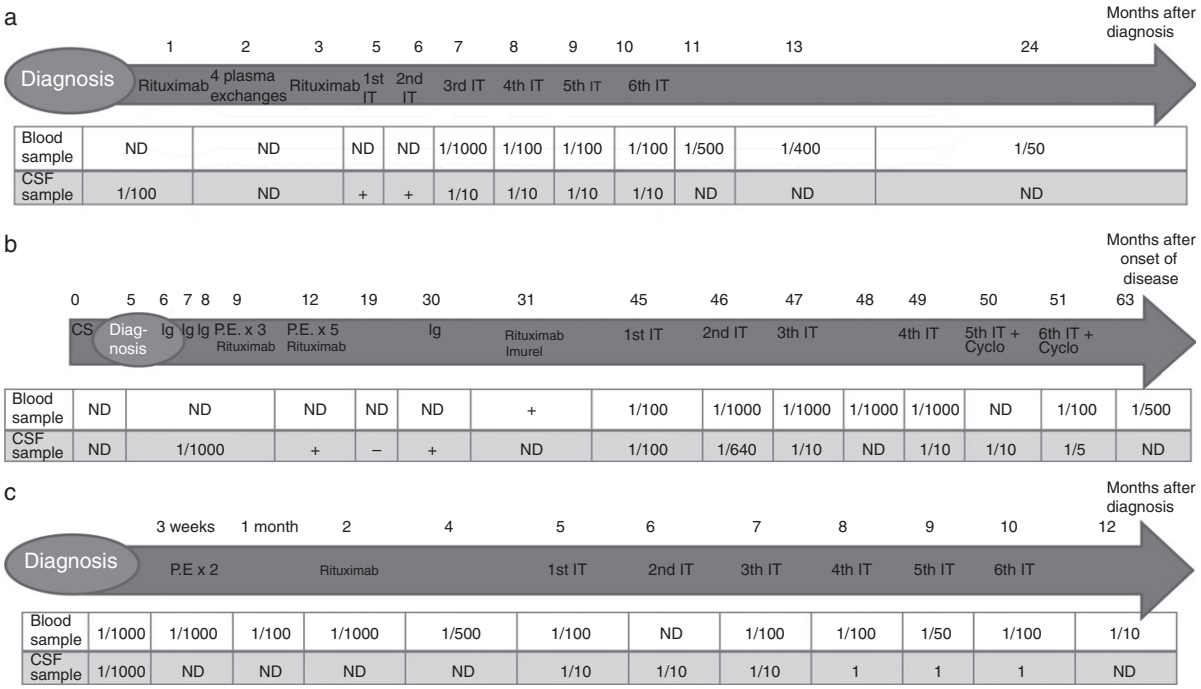

Figure 1: Treatments and evolution of anti-*N*-Methyl-D-aspartate receptor antibodies in case 1 (a), case 2 (b) and case 3 (c). IT, intrathecal injection; ND, not done; CSF, cerebrospinal fluid; +, positive; CS, corticosteroids; Ig, immunoglobulins; PE, plasma exchange; Cyclo, cyclophosphamide.

Case 3

A previously healthy 14-year-old female presented with recurrent generalized seizures (Table I). Behavioural difficulties, aphasia, abnormal movements including chorea, and oral dyskinesia developed rapidly with hypoventilation requiring respiratory assistance prompting plasma exchange. Cerebrospinal analysis demonstrated pleiocytosis (34 white cells/μL) with a normal protein concentration and no oligoclonal bands. Anti-NMDAR antibodies were detected, brain MRI was normal and no tumour was identified. There was no clinical improvement after plasma exchange, and rituximab treatment (375mg/m^2) was administered 3 weeks later. Hypoventilation disappeared and abnormal movements were reduced, leading to discharge from the intensive care unit. However, insufficient clinical response with persisting abnormal movements, aphasia, seizures, and altered consciousness and behaviour led to intrathecal treatment with methotrexate and methylprednisolone 3 months after the rituximab treatment. Three weeks later, a clear improvement in behaviour was observed, and the abnormal movements had disappeared. At last follow-up, 12 months after disease onset, the child was able to form sentences and understand simple orders (mRS score of 1). The antibody titers in serum and CSF were substantially lower (Fig. 1c).

DISCUSSION

Anti-NMDAR encephalitis is a well-recognized inflammatory disease affecting the brain; it can cause severe neurological sequelae. In the three cases reported here the usual treatments were not sufficient.

Our three patients did not receive similar treatment at onset because treatment was chosen by the clinician who received the patient and there is no established treatment strategy for this disease. Anti-NMDAR in children is rarely associated with tumours and recent studies suggested that, even though not significant, failure of first-line therapies is more frequent among children with anti-NMDAR encephalitis without tumour and that the relapse rate for such children is lower if treated with second-line immunotherapy.[6] A better improvement of outcome, measured by mRS score was also observed in the same study when second-line immunotherapy was used.[6] We have previously treated children with anti-NMDAR encephalitis with early rituximab injection and in our current experience the early use of rituximab seems to be more beneficial than steroids and immunoglobulin.[7] Safety and tolerance of immunotherapies are major concerns when using these treatments early. A recent retrospective cohort study of 2875 children in the USA who received rituximab demonstrated variability of the rates of sepsis and other life-threatening infections according to the underlying diseases, and they were particularly low in children with autoimmune diseases, suggesting that this treatment can be safely used in this condition.[8] Similar results were also observed in another international retrospective study in which a larger change in mRS (0–2) was observed in patients given early rituximab compared with those treated later.[9]

It would be useful to define when treatment should be escalated in children with anti-NMDAR encephalitis. We defined relapse as aggravation of previously existing neurological symptoms or appearance of new neurological symptoms in a child who had completely or partially recovered after 1 month or more; and insufficient treatment response as the absence of clinical modification within 2 weeks or more of plasma exchange or within 1 month or more of other immunotherapy with an mRS score 3 or greater. These definitions were used in our study to justify treatment escalation. Case 1 presented a relapse and insufficient clinical response, leading to treatment escalation, and the treatment of case 3 was based on an insufficient clinical response. Case 2 had several relapses, explaining the treatments, and neurological examination results between relapses were never normal, suggesting that some of the symptoms were neurological sequelae of the disease. Therefore, treatment escalation should be carefully assessed for each case.

Plasmocytes able to produce anti-NMDAR antibodies have been described in the central nervous system, suggesting that intrathecal treatment may be useful.[10] Intrathecal injections of methylprednisolone and methotrexate are commonly used for treatment of leukaemia, other tumours with carcinomatous meningitis (at high cumulative doses, 96–216mg of methotrexate) and lymphohistiocytosis with neurological involvement[11] (similar doses as in this protocol, cumulative doses of 36–72mg of methotrexate) and an adapted intrathecal treatment protocol[12] was established. In oncological studies, intrathecal or IV methotrexate may rarely induce neurological toxicity, including encephalopathy[13] which may occur at a median time of 9 days after intrathecal treatment.[14] Therefore, all children were screened for symptoms of infection before treatment. Neurological examination and liver function tests were also performed before every injection. All children had MRI at up to 3 and 6 months after intrathecal treatment to detect any infra clinical methotrexate-induced toxicity. No such toxicity was found in any of our patients.

Cerebrospinal markers of inflammation (high protein concentration and/or white cells) were present in cases 2 and 3. In case 2, the protein concentration normalized 1 month after initiation of intrathecal treatment; there was no pleiocytosis at the start of intrathecal treatment in case 3. Novel inflammatory markers, for example neopterins, which are increased in relapsing encephalitis, may be useful and might be investigated in future studies.[15] We observed that anti-NMDAR antibody titers in the CSF were reduced or stabilized after intrathecal treatment. In case 2, although the anti-NMDAR antibody titer in the CSF decreased, its level in blood remained stable, consistent with the treatment having a local effect.

Clinical recovery differed: intrathecal treatment was followed by clinical improvement in cases 1 and 3 (both recovered autonomy). In case 2, improvement was obtained only after further IV cyclophosphamide treatment. The natural history of this disease is highly variable and we cannot establish whether the clinical evolution observed was a consequence of the intrathecal treatment only. Moreover, intrathecal treatment was given at various times to these children and only the two children who received the treatment early responded significantly; case 2 responded partially and may have had associated neurological sequelae.

Low titers of antibodies persisted in both CSF and blood while these children were recovering clinically, as observed elsewhere.[16] These antibodies may be evidence of plasmocytes continuing to secrete without attaining a threshold required to induce the disease, or of a residual stage of the disease.

Local intrathecal treatment may be a useful add-on therapy for children with anti-NMDAR encephalitis that does not respond to first- and second-line treatments.

DISCLOSURES

Prof Marc Tardieu has served on advisory boards for Novartis, Biogen, Sanofi and Genzyme. Dr Kumaran Deiva participated in a retrospective study for Merck Serono.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Antibody detection techniques. Part 2 Intrathecal treatment for children presenting with anti-NMDA-R encephalitis resistant to initial treatments.

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