Successful treatment of anti-N-methyl-D-aspartate receptor encephalitis presenting with catatonia

M Schimmel,[1] C G Bien,[2] A Vincent,[3] W Schenk,[1] J Penzien[1]

ABSTRACT

The case of a 12-year-old girl with the typical clinical symptoms of the recently described anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is reported. Within 6 weeks the full clinical spectrum of this condition presented with seizures, agitation, stupor, autonomic instability, dysphagia and hypoventilation leading to a diagnosis of pernicious catatonia. MRI and CSF glucose, protein and lactate were repeatedly normal. EEG revealed rhythmical slowing. No teratoma was detected. Recognition of the unique pattern of the clinical symptoms led to early consideration of this disease which was confirmed by detection of anti-NMDAR antibodies. After high dose prednisolone without clinical improvement, plasmapheresis was followed by a rapid reduction in antibodies and recovery within a few weeks. To our knowledge this is the youngest patient with anti-NMDAR encephalitis to have been described to date. We speculate that NMDAR antibodies may be directly involved in the pathogenesis of this disease.

[1] Department of Paediatrics, Klinikum Augsburg, Augsburg, Germany; [2] Department of Epileptology, University of Bonn, Bonn, Germany; [3] Neurosciences Group, Weatherall Institute of Molecular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK

Correspondence to: Johannes Penzien, Department of Paediatrics, Klinikum Augsburg, Stenglinstrasse 2, 86156 Augsburg, Germany; johann.penzien@klinikum-augsburg.de

Encephalitis is caused by infection or by immune mechanisms. In adults, immune-mediated encephalitides with specific antibodies against CNS cells (''onconeural antibodies'' indicative of paraneoplastic disease, or antibodies against potassium channels) are being recognised, including a new form of autoimmune encephalitis with antibodies against N-methyl-D-aspartate receptors (NMDAR).[1 2] Most patients have an associated ovarian teratoma. They are usually young women (14–44 years of age) and present with severe psychiatric symptoms, decreased consciousness, seizures, orofacial dyskinesia, autonomic instability and hypoventilation often requiring prolonged mechanical ventilation. Tumour extirpation and immunotherapy were mostly followed by a favourable course.[1–4]

We present the case of a girl with this clinical picture but no detection of a tumour. Anti-NMDAR encephalitis was suspected early on and plasma exchange was followed by excellent recovery.

CASE REPORT

A 12-year-old girl was admitted after one episode with paraesthesia and hypotonia of the left leg, and one episode with head-turning along with rhythmic clonic movements of all extremities without loss of consciousness. She had no medical history of interest, except for a 2-day episode of diarrhoea 3 weeks before. Following admission she showed one episode with cloni on the left extremities only and she was once seized with cloni of all extremities during the night. In between these episodes her behaviour and neurological examination were normal as were EEGs, brain MRI, CSF and somatosensory and motor evoked potentials. Psychological evaluation indicated emotional stress at school. She was discharged after 2 weeks with a diagnosis of suspected psychogenic seizures.

However, 2 days later she was admitted to a child psychiatry department with agitation, hyperventilation and intermittent ocular deviation. Within 2 weeks she developed major psychiatric symptoms and showed autonomic instability. Due to unstable vital signs she was transferred to the children's intensive care unit under the diagnosis of pernicious catatonia.

Upon admission, she was unresponsive to verbal commands while keeping her eyes open, showed paradoxical response (eg, eye opening on command while unresponsive to pain-inducing stimuli), insomnia, agitation, intermittent catatonic postures with hyperhidrosis, frequent chewing movements with tongue protrusion and staring episodes with rare blink (see supplementary video 1 ''Before PEX''). Episodes with hyperthermia up to 39°C, tachycardia and arterial hypertension occurred. She needed tube feeding and intermittent oxygen.

Blood cell count, general chemistry, thyroid function test and tumour markers (AFP, CEA, β-HCG, CA 125) were unrevealing as were thyroid and antinuclear antibodies, antibodies against double-stranded DNA, glutamic acid decarboxylase, gangliosides (GM1, GD1b, GQ1b) and antiviral and antibacterial antibodies except for IgM antibodies against *Campylobacter jejuni* (60 U/ml, normal values <40 U/ml). EEG now showed continuous slowing without epileptic activity. In CSF, oligoclonal bands were found with normal cell count and protein and glucose without evidence of disrupted blood–brain barrier or infection. Brain MRI was again unremarkable.

Presuming an autoimmunological pathogenesis, prednisolone 1 g/day for 5 days was given without beneficial effect. At this stage, 6 weeks after the first admission, CSF IgG antibody reactivity with hippocampal neuropil was detected using the indirect immunohistochemistry technique (fig 1A–B1). In brief, undiluted CSF was incubated with cryoprotected brain sections of rats perfused with 4% paraformaldehyde, and bound antibodies were detected by biotinylated anti-human IgG (sheep antibody; Amersham Pharmacia Biotech, Uppsala, Sweden) at a dilution of 1:200. Labelling was visualised with 3,3 diaminobenzidine-tetrahydrochloride. Subsequently, serum antibodies to NMDAR were demonstrated by a cell-based assay using NR1/NR2b transfected cells, essentially as reported previously[2] but at lower dilution (1:20), as

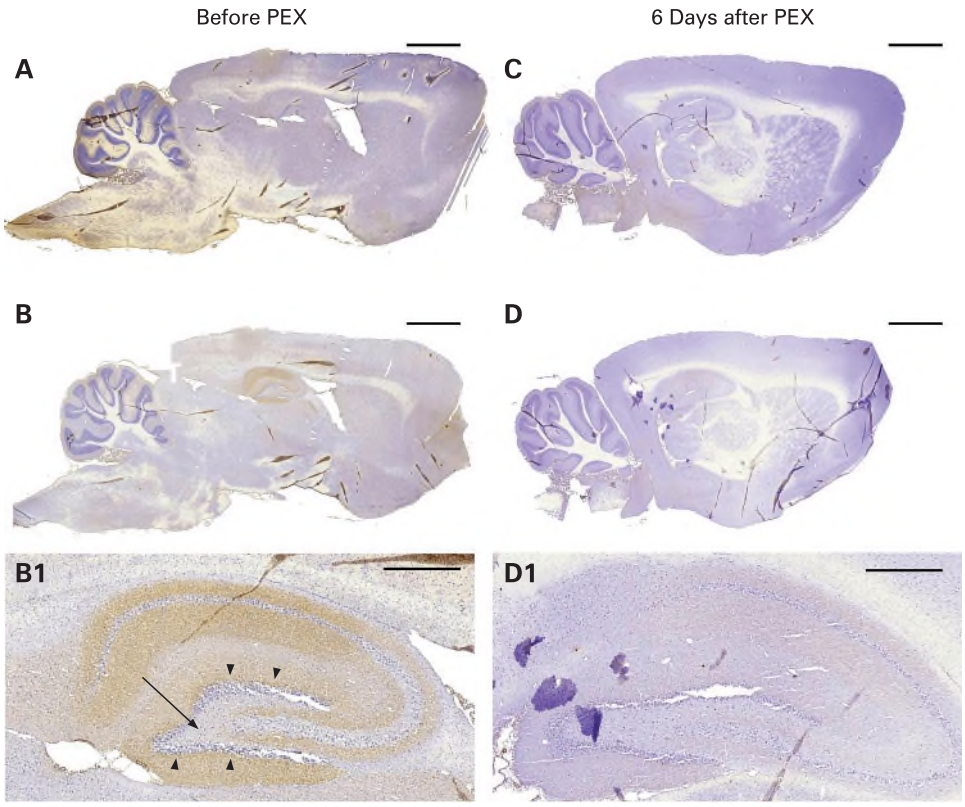

Figure 1 Indirect immunohistochemistry with patient's serum (A, C; dilution 1:500) and cerebrospinal fluid (B, D; undiluted) on sagittal rat brain sections. Whereas serum staining is not visible either before (A) or after (C) plasma exchange, there is marked CSF antibody reactivity with hippocampal neuropil before plasmapheresis (B, B1). Note that the antibodies spare the inner part of the hippocampal endfolium (arrow) but react with the inner aspect of the molecular layer adjacent to the granular cells of the dentate gyrus (arrowheads). This type of reactivity is typical for NMDAR antibodies.[2] After plasma exchange, only faint hippocampal neuropil reactivity remains (D, D1). B1 and D1 are magnifications of hippocampi from B and D, respectively. Bars: A–D: 2 mm, B1 and D1: 0.5 mm. PEX, plasma exchange.

performed for other antibodies.[5] Plasmapheresis was started 6 days after the last steroid dose with eight sessions over 13 days. After two sessions the patient started to speak single words, regained some walking ability and continued to improve over 4 weeks until almost full recovery (see supplementary videos "Before and after 2 days of PEX" and "After PEX"). EEG and MRI were normal. CSF antibody reactivity with hippocampal neuropil was no longer detectable (fig 1C–D1). The patient was transferred to rehabilitation 11 weeks after the first admission and was discharged 4 weeks later showing only minimal dysfunction of short-term memory. A repeated search for teratoma in the pelvis or in the mediastinum by ultrasound and CT remained negative.

DISCUSSION

We present the case of a 12-year-old girl with typical symptoms of anti-NMDAR encephalitis. To the best of our knowledge, this is the youngest patient with this condition described to date. In a progressive course of neuropsychiatric symptoms over 4–6 weeks, the clinical picture deteriorated to a catatonic state with autonomic dysfunction, hypoventilation, orofacial dyskinesia and dysphagia. Signs and symptoms in our patient are in accordance with cases already reported.[1–4] Despite intense search, no teratoma has been detected. According to recent data, a teratoma could be found in 65% of patients with anti-NMDAR encephalitis, and therefore the disease is, at least in some patients, paraneoplastic in nature.[1] In Iizuka's series, teratomas have been found up 7 years after the encephalitis.[3] Therefore, regular follow-up visits are scheduled.

Although the improvement was strongly time related to plasmapheresis, a causative effect of this intervention cannot be proven based on this single case. A delayed steroid effect or just a favourable natural course must be taken into account. However, the rapid clearance of CSF from hippocampal neuropil antibodies in parallel with clinical improvement is striking. In previous cases of anti-NMDAR encephalitis, remission has mostly been observed after tumour resection and/or immunotherapy, while some reported that untreated or only partially treated patients died.[2 4] Thus, we tentatively suggest that in our case recovery was at least hastened by plasmapheresis.

It may be speculated that this successful treatment is related to the NMDAR antibodies being the relevant pathophysiological agents. Although the NR1/NR2 heteromers of the NMDAR are expressed throughout the entire nervous system, the main epitope targets of patients with NMDAR autoimmunity are contained in NR1/NR2b heteromers, which are mainly expressed in the adult forebrain and the limbic system as well as the hypothalamus.[3] Kleinig *et al* hypothesised that the typical orofacial clinical symptoms are related to interruption of forebrain corticostriatal inputs which remove the tonic inhibition of brainstem pattern generators.[4] As a consequence, primitive patterns of bulbar and limb movement are released. Inhibition of NMDAR by antagonists in man is reported to be followed by schizophrenia-like symptoms, and NR1 knockout animals die of hypoventilation.[3] These observations may serve as arguments that the NMDAR antibodies are directly involved in the pathogenesis of this disease. The clinical homogeneity of the patients with anti-NMDAR encephalitis and the disappearance of the antibodies after recovery support this suggestion. However, it remains unclear how these antibodies can cross the blood–brain barrier. It is likely that other factors are involved. The preceding infection with *C jejuni*, has not been reported previously in this condition, but might be one such factor.

We conclude that anti-NMDAR encephalitis is a treatable disorder which can occur in children and may not be paraneoplastic. The presenting features are now well described and the diagnosis can be confirmed by detection of antibodies to hippocampal neuropil and NMDAR. Early diagnosis may be

important for successful immunotherapy, as well as detection and therapy of an underlying tumour in those cases that are paraneoplastic.

Acknowledgements: We are grateful to Dr Sarosh Irani for performing the NMDAR antibody test and to Dr Susan Maxwell and Professor David Beeson for providing the NMDAR constructs.

Funding: None.

Competing interests: AV's department receives royalties and payments for antibody tests.

REFERENCES

1. **Dalmau J,** Rosenfeld MR. Paraneoplastic syndromes of the CNS. *Lancet Neurol* 2008;**7**:327–40.
2. **Dalmau J,** Tüzün E, Wu HY, *et al*. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;**61**:25–36.
3. **Iizuka T,** Sakai F, Ide T, *et al*. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. *Neurology* 2008;**70**:504–11.
4. **Kleinig TJ,** Thompson PD, Matar W, *et al*. The distinctive movement disorder of ovarian teratoma-associated encephalitis. *Mov Disord* 2008;**23**:1256–61.
5. **Waters P,** Jarius S, Littleton E, *et al*. Aquaporin-4 antibodies in neuromyelitis optica and longitudinally-extensive transverse myelitis. *Arch Neurol* 2008;**65**:913–19.