LETTER TO THE EDITOR

To The Editor

A Story That Begins Too Soon: A Girl with Untreated Anti-N-Methyl-D-Aspartate Receptor Encephalitis for 14 Years

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Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis (anti-NMDARE) is a treatable antibody-mediated neurological disease, first definitively described with respect to its association with the NMDAR antibody in 2007.[1] In children, it is characterised by a broad clinical spectrum mainly presenting with subacute onset of altered mental status or psychiatric symptoms. Progression occurs to seizures and movement disorders, up to coma in severe cases.[2] Prompt initiation of immunotherapy and the detection and removal of an associated teratoma have been associated with recovery (or mild persistent symptoms still allowing for return to activities of daily living).[3]

We report a case of non-paraneoplastic anti-NMDARE in a young female, recognising that this can provide an opportunity to understand the natural history of this condition if left untreated in children.

In 2004, a 4-year-old, right-handed girl presented to the emergency department of a large tertiary paediatric hospital with fever, worsening headache, confusion and new-onset seizures. She had otherwise been healthy and developmentally normal with no remarkable medical history. She developed refractory seizures, required prolonged intensive care unit (ICU) admission and spent 3 months in hospital. She was diagnosed with an encephalitis of unknown origin and received full supportive treatment as no pathogen had been recovered from her blood or cerebrospinal fluid (including herpes simplex virus). She was not started on any immunosuppressive treatment. Her initial (and 10-day follow-up) brain MRI showed diffuse leptomeningeal enhancement, followed by diffuse brain atrophy noted 3 months later. We were unable to determine whether screening for ovarian teratoma or any neural antibody testing had been performed at this time, although testing for anti-NMDAR would not have been available. Soon after her initial presentation, she became non-verbal, developed severe behavioural disturbances with episodes of agitation with significant uncoordinated movements concerning dyskinesia, and underwent intensive inpatient rehabilitation for 6 months. Upon discharge from rehabilitation, she was taking a few steps with a walker and was more responsive albeit with minimal communication skills.

She remained seizure free for 1 year and her anti-seizure medication was weaned off before representing with multifocal, motor seizures. Carbamazepine was initiated but was later switched to valproic acid to aid with better seizure management. In 2009, she had short admission for relapse of abnormal movement and orofacial dyskinetic movements. Still undiagnosed, her symptoms stabilised by adjusting her maintenance medication. No further relapses were reported, and no dyskinesia is currently described.

In 2014, 10 years after her original presentation, her new care team at another paediatric tertiary hospital (MS) considered the diagnosis of anti-NMDARE based on her history and presentation. For diagnostic confirmation, cerebrospinal fluid (CSF) was collected and was positive for NMDAR antibodies by cell-based assay. Titre was not reported. An abdominal ultrasound was negative for ovarian teratoma. Severe intellectual disability was confirmed in formal neurocognitive evaluation. Given the time lapse since presentation, it was felt her symptoms were not due to active central nervous system (CNS) inflammation, but rather chronic sequelae of previous CNS inflammation, so she did not receive immunotherapy.

In 2019, at age 16, we (SL, MNN) saw her and noted ongoing significant behavioral aggression and poorly controlled seizures on valproic acid, largely due to non-compliance. Her medication was switched to lamotrigine which improved her compliance and seizure control. A repeat lumbar puncture was completed in 2020 to look for evidence of active CNS inflammation. Her CSF was again positive for NMDAR antibodies (EUROIMMUN fixed cell-based assay, CSF dilution of 1:1), but there was no CSF pleocytosis or oligoclonal bands to indicate active CNS inflammation. Her EEG showed diffuse slowing and an MRI redemonstrated diffuse brain atrophy. While diagnosis of severe intellectual disability was reaffirmed, there were few identifiable gains in her life skills. Her communication currently consists largely of pulling caregivers to a desired item and pushing items away to say "no." While initially wheelchair-bound and G-tube dependent, she can now walk with support and tolerates oral feeds. She is dependent on caregivers for self-care. She is currently on aripiprazole and clonidine for behavioural aggression.

We present the case of an 18-year-old girl with persistent CSF NMDAR antibody positivity 14 years after her original presentation of presumed anti-NMDARE at age 4, having never been treated with immunotherapy. She presented initially at a time when anti-NMDARE was still largely unknown to the medical community. In review of cases of encephalitis of unknown origin, NMDAR antibodies have been reported in up to 1% of patients admitted to an ICU.[4] Poor prognostic factors in children with anti-NMDARE have been identified as "ICU stay" and "longer duration from symptom onset until initiation of treatment" as was the case with our patient.[5] Anecdotal evidence also shows that patients without a teratoma have a lower likelihood of significant improvement.[3] Rarity of such cases with a prolonged path to diagnosis, together with lack of evidence to initiate immunotherapy beyond the acute phase,[6] shifted the focus of her therapy toward symptom management exclusively. Widespread changes reported on electrophysiological and neuroimaging studies in this untreated case suggest the extensive influence of NMDARs on the developing brain, explaining her severe disease phenotype given young age of untreated disease onset.[7] This is different from rare, reported adult cases of full spontaneous disease recovery despite persistent antibodies, in the absence of immunotherapy.[8] It has been shown that patients can demonstrate persistent antibodies in the CSF even after recovery, indicating that anti-NMDAR CSF positivity in isolation is not diagnostic of active CNS inflammation causing symptoms. Increase in anti-

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NMDAR CSF titre may provide supportive evidence of active disease, but this could not be determined in this case because no titre was available for the first positive result in 2014.[9] Given the delayed diagnosis and inability to locate prior CSF samples in this case, the significance of persistent antibody positivity with respect to whether active CNS inflammation is contributory to our patient's symptoms is unclear. We favour her ongoing symptoms to be related to chronic sequelae of previous CNS inflammation due to 1) evidence of cerebral injury indicated by diffuse brain atrophy on MRI, 2) absence of CSF pleocytosis and 3) long disease duration without clear clinical fluctuations or evidence of discrete relapse in recent years. Nonetheless, given this unique clinical situation, an immunotherapy trial was offered to the patient's family after thoroughly reviewing the uncertainty surrounding the potential for any therapeutic benefit at the time of their most recent evaluation in 2021 (AB); the family is actively contemplating whether they would like to pursue this.

To conclude, our case highlights the severe clinical outcome of untreated, paediatric anti-NMDARE manifesting at a young age and progressing to an advanced stage within a few weeks of disease onset, with no return of normal function. To our knowledge, this case represents the longest duration of untreated anti-NMDARE in a paediatric patient published in the literature, and emphasizes the importance of timely diagnosis as well as early initiation of immunotherapy.

Disclosures

All authors have no disclosures to declare.

Sean Leonard
Department of Paediatrics, Western University, London, Ontario, Canada

Adrian Budhram
Department of Clinical Neurological Sciences, Western University, London, Ontario, Canada

Michael Shevell
Department of Pediatrics & Neurology/Neurosurgery, McGill University, Montreal, Quebec, Canada

Maryam Nabavi Nouri
Department of Paediatrics, Western University, London, Ontario, Canada

Department of Clinical Neurological Sciences, Western University, London, Ontario, Canada

Correspondence to: Maryam Nabavi Nouri, CHWO, Rm B1-177, 800 Commissioners Road East, London, Ontario, Canada, N6A 5W9. Email: maryam.nouri@lhsc.on.ca

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