Case report

Autoimmune encephalitis: the clinical evolution as a key to the diagnosis

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SUMMARY

Anti-N-methyl D-aspartate receptor (NMDAR) encephalitis is a devastating disease, that despite being increasingly diagnosed, there are no consensus guidelines for the optimal management. A previously healthy 3-year-old-boy brought to the emergency department due to seizures. Neurological examination was normal, and electroencephalogram (EEG) suggested focal epilepsy. Anticonvulsive medication was initiated. He progressively lost age-appropriate language skills, presented behavioural changes and psychiatric symptoms. Neurological examination at that time revealed symmetric gross motor weakness of the lower limbs. Brain and spinal cord MRI and cerebrospinal fluid were normal. Repeated EEG showed global lentification. Steroid therapy was initiated for the suspicion of autoimmune encephalitis, later confirmed as NMDAR encephalitis. He became clinically improved after 10 days of treatment but only returned to his baseline after 3 months of disease onset. The authors emphasised the variable course of the disease and possible late response to treatment.

BACKGROUND

Anti-N-methyl D-aspartate receptor (NMDAR) encephalitis is a rare autoimmune disease characterised by severe neurological and psychiatric symptoms. The possible vast spectrum of presentation makes diagnosis more difficult, becoming an under-recognised pathology. Its pathogeny comprises the production of an autoantibody to the NMDA-type glutamate receptor, involved in synaptic transmission and plasticity, known to play a role in neuropsychiatric diseases.

Neuroimaging and electroencephalogram (EEG) are non-specific. Therefore, the diagnosis implies a high index of suspicion, and it is based on detection of anti-NMDAR antibodies.

Early recognition and prompt treatment can improve outcome; however, there are limited reports regarding the optimal management of these children, natural history of disease and response to treatment.

CASE PRESENTATION

A previously healthy 3-year-old Caucasian boy presented to the emergency department (ED) with an acute onset of brief shakes of the right hemibody. There was no epidemiological context of disease, recent vaccinations or medication ingestion. Family history was unremarkable for neurological

or autoimmune diseases. Physical examination, including neurological examination was otherwise normal. Brain CT scan was normal, and EEG revealed paroxystic temporo-occipital activity suggestive of focal epilepsy; he was discharged from hospital medicated with sodium valproate.

Eleven days later, he returned to ED because of insidious axial hypotonia with progressive loss of gait, need for support to remain seated and gradual increase of motor discoordination. He revealed a good general condition and normal vital signs. Neurological examination revealed symmetric gross motor weakness of the lower limbs, feet lag as he walked and instability when he seated; deep tendon reflexes were present and symmetric, and cutaneous plantar reflexes were flexor bilaterally. There were no apparent cranial nerve abnormalities or cerebellar dysfunction.

Laboratory studies including blood cell count, liver and renal function, serum electrolytes, glucose, C-reactive protein, total creatinine kinase and myoglobin were normal. Valproate levels were in a therapeutic concentration (86.55 µg/mL). Acid-base balance was normal. At this moment in time, he was hospitalised, and the antiepileptic medication was changed to carbamazepine.

Diagnostic testing, including brain and spinal MRI, immunological (IgG, IgA, IgM; antinuclear, antithyroglobulin and antiperoxidase antibodies) and metabolic study (ammonia, lactate, pyruvate, lactate/pyruvate ratio, organic acid, amino acid, acylcarnitines profile and biotinidase enzymatic activity) were normal.

Serology excluded recent or active infection with cytomegalovirus, Epstein-Barr virus, herpes simplex virus type 1 and 2, *Borrelia burgdorferi* and parvovirus.

Cerebrospinal fluid (CSF) cytology and biochemistry were normal; CSF cultures were sterile and PCR was negative for herpes virus type 1 and 2 DNA, varicella zoster DNA, Epstein-Barr DNA, cytomegalovirus DNA, enterovirus RNA and *Mycoplasma pneumoniae* DNA. Immunological assay detected oligoclonal bands type 4 pattern, which had correspondence in the serum sample (mirror pattern), suggesting a systemic inflammatory response.

At day 9 (day 19 of illness), he became severely agitated with intense and disproportionate tantrums and visual hallucinations.

With the suspicion of autoimmune encephalitis, lumbar puncture was repeated, and CFS revealed 11/uL white cell count, glucose level 53 mg/dL and

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protein level 25 mg/dL. Repeated EEG showed global lentification. In this context, a 5-day course of intravenous methylprednisolone (30 mg/kg/day) was started (day 22 of illness), and levetiracetam was associated to the previous antiepileptic medication. Despite therapy, neuropsychiatric dysfunction progressed with deterioration of consciousness, speech and swallowing difficulties, orofacial dyskinesia and choreoathetoid movements of the limbs. So, a 5-day course of intravenous IG (IVIG) was started (0.4 g/kg/day).

At day 5 of steroid therapy, anti-NMDAR autoantibodies came out positive in the CSF and blood, allowing the definite diagnosis of NMDAR encephalitis.

Seven days after initiating steroid therapy, he kept severely agitated state, intensification of the choreoathetoid movements of the limbs and started to have solid dysphagia.

After completing methylprednisolone course, oral prednisolone (2 mg/kg/day) was initiated.

Abdominal and scrotal sonography revealed no signs of neoplastic lesions.

Clinical improvement became apparent after 11 days of IVIG onset and 10 days of steroid with progressive improvement of motor coordination and speech. At the time of discharge, he has already presented adequate tolerance for solid food. He was discharged after 4 weeks.

OUTCOME AND FOLLOW-UP

At follow-up, there was a remarkable improvement, particularly in motor coordination with recuperation of stable gait at the day 57 of corticotherapy (75 of disease), progressive improvement of speech, maintaining at this point only dystonia of the left superior member.

After 80 days of corticosteroid (98 of disease), he returned back to his baseline, and we started to progressively reduce the prednisolone dose, until suspending after a total of 6 months of steroid therapy.

DISCUSSION

Anti-NMDAR encephalitis is an autoimmune disease resulting from the inactivity of the extracellular portion of NR1 subunits of NMDARs by autoantibodies; this protein is involved in memory function and synaptic plasticity, resulting in the characteristic neuropsychiatric symptomatology.^{1,2}

Anti-NMDAR encephalitis corresponds up to 21% of encephalitis. Although the specific cause remains unknown, most reports have postulated a virus-induced aetiology.³⁻⁶

Its clinical presentation typically begins with a prodrome of influenza-like symptoms.^{2,6,7} In children, neurological and psychiatric symptoms occur later, being the neurological symptoms more prevalent, as occurred in our patient.^{1,2,7,8} Sleep disorders, especially insomnia, are also common. The psychiatric symptoms in younger children are usually characterised by behavioural abnormalities, whose detection can be difficult once these symptoms can be associated with age, in this population.^{1,9,10}

Differential diagnosis represents a major challenge because symptoms may overlap with other disorders and initial laboratory tests may not provide directive findings.¹¹ As in this case, clinical presentation could have led to the presumptive diagnosis of epilepsy, psychosis or viral encephalitis.

Despite the diagnostic tests that are usually carried out at workup, they are often non-specific; the definitive diagnosis implies the detection on serum or on CFS of anti-NMDAR antibodies. However, in the setting of clinical suspicion, the beginning

of the treatment should not be delayed by these results, because treatment precocity affects prognosis and recovery.^{1,7,12,13}

With regard to treatment, corticosteroids, IVIG or plasmapheresis are first-line choices; however, they fail in half of all children.^{1,8} In our patient, we verified an adequate response to first-line therapy, however, the authors intend to point out, the fact that the presented child, even under steroid therapy, showed a clinical worsening and that clinical improvement arose only after 10 days of initiating steroid therapy.

Second-line therapy, like rituximab, cyclophosphamide and mycophenolate is often needed. They should be reserved for those who are refractory or have relapses with first-line immunotherapy.^{1,8}

Prompt recognition and early use of high-dose steroid treatment can shorten the duration of the disease and possibly prevent complications; however, there are still gaps in knowledge, specifically, when to add disease-modifying therapy and how long to remain immunotherapy in patients who have returned to their baseline.⁸ In our patient, we continued immunotherapy for 3 more months, after our child has returned to his neurological baseline.

Once discharged, most patients make a complete recovery or experience some mild deficits. Significant recovery will usually span a 3–4-month period with treatment. Cognitive dysfunction and other psychiatric symptoms are the slowest to solve.^{14,15}

Relapses are not uncommon, most of them have been reported in the first 2 years and more likely to be monosymptomatic.

Anti-NMDAR encephalitis should be considered in children presenting with acute onset of prolonged or difficult to control seizures, movement disorder or psychiatric symptoms, especially if preceded by viral infections. Because of the overlap of presentation with other causes of encephalitis and high mortality if untreated, a high index of suspicion should always be presented and an early treatment initiated.

The authors pretend to emphasise the variable course of the disease and response to treatment and that clinical worsening can happen under therapy before gradual recovery initiates.

Clearly, a greater understanding of the presentation, course of illness, treatment options, as well as the expected response to therapeutics is needed.

Learning points

- ▶ A high index of suspicion is important for a correct and timely diagnosis.
- ▶ Early beginning of the treatment determines the prognosis.
- ▶ Response to treatment and clinical worsening can happen under therapy before recovery begins.

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