Long-term management of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in young children—still a matter of debate

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Background: Anti-NMDAR encephalitis is the best-characterized and most common antibody-mediated encephalitis. With early aggressive immunosuppression, prognosis is usually good, although recurrences have been reported in up to 20–25% of patients, mostly in patients without teratoma. Guidelines for the best medical management are still lacking, especially concerning its duration, the comparative efficacy of individual treatments and the role of corticoid-sparing agents. It is also unclear if tumors should be sought after an initial negative screening in males and females younger than 18.

Case report: We report the case of a 30-month boy with previous speech delay, who presented with insidious onset of irritability, asymmetric dystonia and chorea, sleep disturbance and consciousness fluctuations. Infections and metabolic disturbances were excluded. NMDAR antibodies were identified in serum and CSF. MRI showed right insular and frontal cortex T2-hyperintensity. Tumor screening was negative. He was initially treated with methylprednisolone pulses and IVIG and then kept on monthly IVIG and prednisolone 1mg/Kg/day, followed by slowly tapering after 2 months of sustained clinical improvement. Follow-up MRI disclosed some brain atrophy and the patient remains with a significant speech delay after 5 months. Despite the good response to first-line treatments, as in this case, steroid side effects in children may be severe and irreversible. On the other hand, quick withdrawal may compromise recovery and increase relapse probability, especially in cases without associated tumor.

Conclusions: This case is illustrative of the difficulties faced by clinicians in the long-term management of NMDAR-encephalitis, namely in respect to the need and best choice of second-line treatments.

Keywords: Anti-NMDAR encephalitis, Autoimmunity, Cognitive disturbance, Movement disorders.

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Introduction

Since its first description in 2007 [1], anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been increasingly recognized and it is currently the best-characterized and most common antibody-mediated encephalitis [2, 3]. It affects mostly children and young adults and presents as a multistage illness with a frequent flu-like prodromal phase followed by a variable constellation of neuropsychiatric manifestations, seizures, consciousness fluctuations, hypoventilation, dysautonomia, movement disorders, and short-term memory and language disturbances [2, 4]. The presence of an underlying tumor is less frequent in patients under 18 years, especially in males [5] and despite the general good response to first-line treatments, those patients without teratoma tend to respond less to immunotherapy and have a higher risk of symptom recurrence [2, 3, 6]. Although several studies have suggested that early aggressive immunotherapy prevents disability and relapses, guidelines for the best medical management, concerning its duration, immunosuppressant selection based on comparative efficacy and response monitoring, are still lacking [3, 5]. Additional concerns raise when treating children that may become chronically exposed to these drugs [5].

Case Report

We report the case of a 30-month boy with previous speech and motor delay who was admitted with an insidious history of irritability, orolinguual dyskinesia and left hemibody dystonia and chorea. During hospitalization, similar involuntary movements spread to the right limbs, yet maintaining predominant movements on the left hemibody. He also developed consciousness fluctuations with excessive somnolence alternating with irritability and sleep disturbance, which slowly improved under clonal hydrate. Speech regression with frank verbal fluency reduction and echolalia became a predominant feature. Infections and metabolic disturbances were excluded. Cerebrospinal fluid (CSF) analysis showed normal glucose and protein levels, 40 cells/μL (100% mononuclear leucocytes), 680 erythrocytes/μL, negative cultures and negative protein chain reaction for herpes simplex. NMDAR antibodies were identified both in CSF and serum. Cerebral MRI revealed right insular and mesial/lateral posterior frontal cortex T2-hyperintensity (Figure 1). Tumor screening with abdominal and testicular echography were negative. EEG depicted an excessive slow activity in right derivations, mainly in anterior and paracentral ones, in agreement with MRI findings. He was initially treated with methylprednisolone (30mg/Kg/day) and IVIG (0.4g/Kg/day) for 5 days and further kept on monthly IVIG and prednisolone 1mg/Kg/day, with slow but consistent clinical improvement. At discharge, 21 days after admission, he maintained significant speech disturbance and mild choreic movements and dystonia of left limbs. Tapering of prednisolone was started after 2 months of sustained clinical improvement and monthly IVIG was stopped after 6 cycles. Follow-up MRI at 3 months disclosed some brain atrophy, without cortical or parenchymal signal intensity changes (Figure 2).

Figure 1. Cerebral MRI at symptom onset: FLAIR image showing right insular (arrow), mesial frontal and precentral gyral cortex hyperintensity (arrowheads).
months after initial treatment, steroid tapering was complete, anti-NMDAR antibodies were negative in serum and CSF, but the patient still presented a significant speech disturbance (frequent monosyllabic vocalizations and remarkable lack of word formation), as well as poor global motor skills, without other symptoms that could suggest clinical relapse.

**Discussion**

This case is illustrative of typical neurological predominant (rather than psychiatric) childhood anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis [5], albeit the patient never having had epileptic seizures, reported in about half of children under 12 years [6]. Despite the significant and sustained clinical improvement after initial first-line treatment, the patient still maintains a significant speech disturbance. It is uncertain if it was a previous unrecognized feature of its autoimmune encephalitis or if otherwise it was primarily unrelated to the disease, but further exacerbated by it. Although it has been well documented that steroid side effects in children may be severe and irreversible, little is known about its chronic immunological consequences. Further difficulties and concerns arise when full clinical recovery is not achieved after initial treatment. Notwithstanding the previous studies suggesting that second-line treatment with rituximab may decrease the probability of relapses and improve outcome in non-responders [6], no validated clinical criteria or biomarkers exist to evaluate this probability or monitor response to treatment. This case is illustrative of the challenges faced by clinicians in the long-term management of NMDAR-encephalitis, namely in respect to the need and best choice of second-line treatments.

**Abbreviations**

NMDAR: N-methyl-D-aspartate receptor; CSF: Cerebrospinal fluid

**References**