Journal of the Neurological Sciences 358 (2015) 532–534

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Letter to the Editor

Negative myoclonus in a child with anti-NMDA receptor encephalitis☆,☆☆

Keywords:
Anti-NMDA receptor encephalitis
Negative myoclonus
Video EEG

1. Introduction

Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis was increasingly recognized as a distinct auto-immune entity with clinical significance in the past few years, which was characterized by acute or subacute neuropsychiatric and neurological symptoms, and progressed to death or disability in many cases [1,2]. The clinical manifestations, however were variable, which resulted in the difficulty of diagnosis or confusion with other neurological disorders, especially in pediatric patients [3,4].

We report on a child with negative myoclonus (NM) as the initial presentation of anti-NMDA receptor encephalitis.

2. Case report

A 7-year-old previously healthy boy presented with episodes of sudden drop of the right wrist while playing the piano. Within days, these episodes became more frequent up to dozens of times per day and evolved to involve his entire right arm.

On admission, neurologic examination revealed intermittent flapping movements of the right arm when the patient was asked to outstretch his arms, as shown in the Supplemental video (Online Resource 1). His neurologic exam, including mental status, was otherwise normal. No psychiatric symptoms or autonomic dysfunctions were observed.

Scalp EEG demonstrated delta activity in the left parietal and central regions, but no interictal epileptiform discharges. The patient was asked to outstretch his arms while on EEG and on surface EMG on bilateral deltoideus triangularis and, continuous bursting motor unit action potentials on right deltoideus triangularis were interrupted intermittently by short EMG silence period (SP) in line with quick transient drop of right arm. These are the essential features of NM. However, no obvious EEG changes were visualized pre-, during and post-SP (Fig. 1A).

To observe the EMG–EEG coupling, EMG SP onset-triggered EEG averaging was performed with customized MATLAB code. The raw EEG was firstly pre-processed by a bandpass filter between 0.5 and 60 Hz, notch at 50 Hz (power line supply artifact in China), followed by careful removal of eye artifacts with independent component analysis and rejecting the EEG epochs with significant artifacts. 46 times of SP on surface EMG were detected by visual inspection followed by manually marking onsets of SP. Subsequently, EEG epochs were extracted with 150 ms before and 200 ms after SP onset. As a result, time-locked negative shape waves appeared predominantly on the left parietal, the center of parietal and the left central area after all 46 EEG epochs were averaged (Fig. 1B). The earliest appearance of shape peak was 52 ms preceding EMG SP onset on the left parietal region predominantly. EMG SP last 124.6 ± 47.3 ms.

Radiologic re-examination showed slightly high signal on the left frontal and parietal cortex, especially the posterior central gyrus (MRI Flair) (Fig. 1D), which consistent with the maximal negative shift on the same location of voltage map (Fig. 1C).

Patient serum and CSF samples were screened for anti-NMDA IgG antibodies by indirect immunofluorescence (IIF) using EU 90 cells transfected with the NMDAR1 subunit (NR1) of the NMDA complex and immobilized on BIOCHIPs (Euroimmun AG, Lubeck Germany). Samples were classified as positive or negative according to the intensity of surface immunofluorescence of transfected cells compared to non-transfected cells based on the manufacturer's recommendations for reading and interpretation [5]. Finally, clinical diagnosis of anti-NMDA receptor encephalitis of the patient was revealed by strong positivity for anti-NMDA receptor antibodies of CSF. Notably, no tumor was detected by comprehensive laboratory investigation as well as radiological examination.

Clinically, the patient progressively presented weakness of right limbs, generalized tonic–clonic seizure (GTCS), language deficits in the following few days. The patient was promptly treated with IVIG (0.4 g/kg/day, 5 days). The frequency of NM decreased and no further worse of other symptoms. One week later, additional course of IVIG was given again, followed by tempered oral prednisone (initial dose was 45 mg/day). All the symptoms improved gradually. Particularly, NM remised after the combination therapies. At the one-year follow-up, the patient goes to school without significant neurological deficits.

3. Discussion

Our patient presented with prominent negative myoclonus seizures, a presentation that, to the best of our knowledge, has not been previously described for anti-NMDA receptor encephalitis.

The identification of anti-NMDA receptor encephalitis has changed the diagnostic approach and therapy strategies towards epilepsy since the first description in 2007 [6]. Even with the rapid contribution of literature to this topic, the prevalence of anti-NMDA receptor encephalitis is likely to be underappreciated. Anti-NMDA receptor encephalitis can present in variable and difficult to identify ways. The current patient presented predominantly NM associated with anti-NMDA receptor antibody. In particular, our patient had no encephalopathy, movement disorders, or focal seizures, although

☆ All authors have seen the manuscript and agreed with the contents.

☆☆ Study funding: National Natural Science Foundation of China (CN) 81271447 and 81271448.

http://dx.doi.org/10.1016/j.jns.2015.10.006

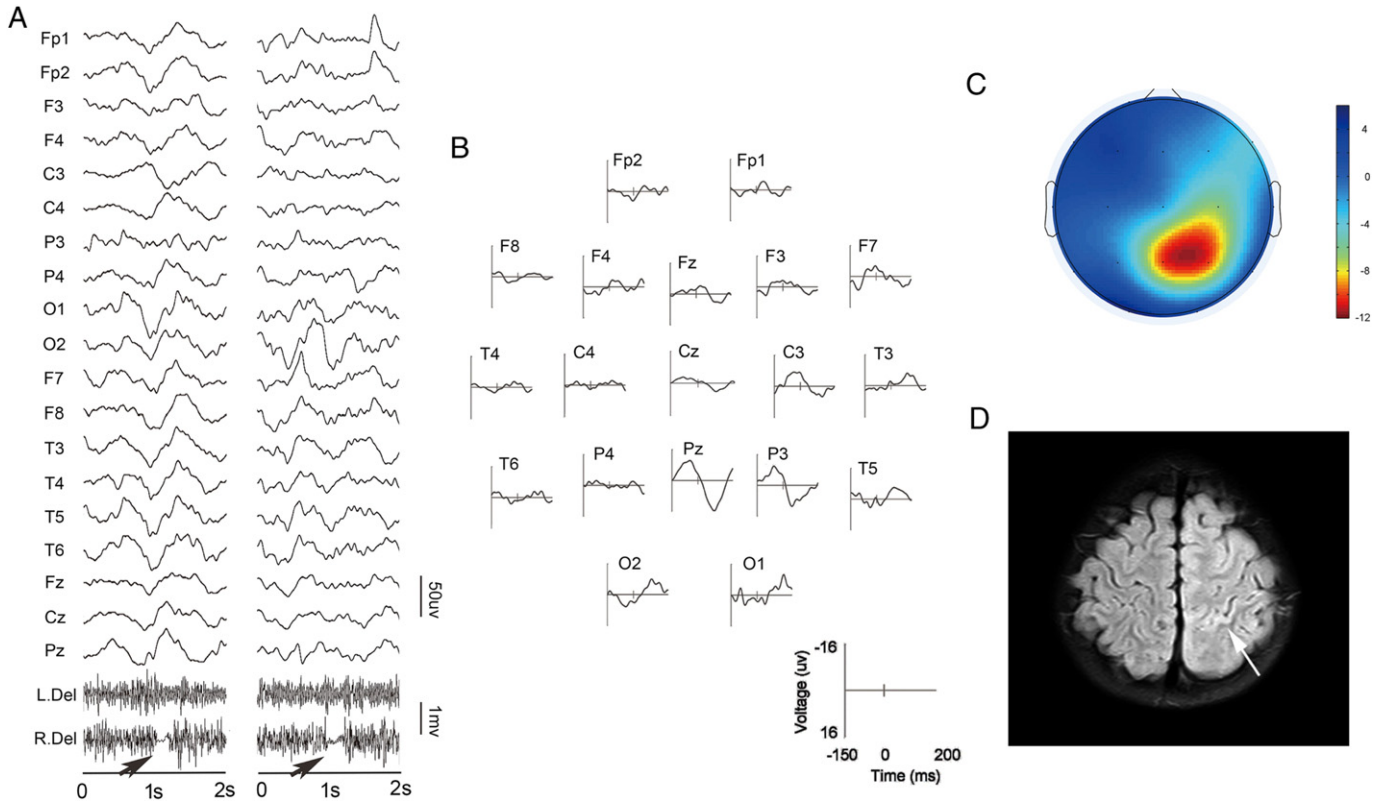

Fig. 1. The electrophysiological findings of negative myoclonus. A) Two example epochs of EEG with surface EMG recording during negative myoclonus (NM) in the patient. There were transient EMG silence period with simultaneous NM, but no obvious EEG changes were identified (black arrow). B) The topoplot map of NM-related potentials after averaging 46 epochs of EEG. Significant sharp wave preceding NM onset could be detected on Pz, P3, and C3. The earliest peak was −52 ms on P3. C) Voltage map of −52 ms preceding NM onset. The maximal negative shift was on the left parietal consistent with the slight increased signal on the same location on MRI flair (D) (white arrow).

later in his course shared the common acute progressive clinical development. However, the sequence symptoms of prominent NM, weakness of right limbs, GTCS and language deficit were quite different from the common clinical traits manifesting as psychosis, memory deficits, seizures, abnormal movements and autonomic and breathing instability [3,4], suggesting neocortex was involved preferably than the limbic system in this patient.

The current observation extends the clinical spectrum of anti-NMDA receptor encephalitis presentations in children. The likely physiopathology of this presentation is based on antibody-mediated neuronal dysfunction, and, to the best of our knowledge, NM has not been previously described in patients with anti-NMDA receptor encephalitis. The present patient's clinical and electrophysiological characteristics illustrated an initial prominent NM. Clinically, NM was likely to be overlooked because NM could be observed only from the affected muscle in tension [7]. In particular, even if EMG silent period was observed, there are still plenty of patients who lack the identifiable abnormal EEG signal since the cortical area involved in generating NM is very limited [8]. The application of SP locked averaging can be effective in the extraction of a cortical potential preceding NM from the background EEG activity, and to better delineate the tempo-spatial relationships between the EEG and the EMG events, as showed in current study. The origin of NM on parietal, revealed by averaging analysis, was consistent with the findings of the previous study [9], which suggested that the lesion caused by anti-NMDA receptor encephalitis could initiate on very limited focal cortex.

This case report emphasizes that in patients, especially children with otherwise unexplained acute progressive transient atonia of limb, NM in the context of anti-NMDA receptor encephalitis is a diagnostic possibility, which may lead to early diagnosis and treatment.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2015.10.006.

Ethical standard

The patient gave his informed consent prior to his inclusion in the study. Details that might disclose the identity of the patient under study were omitted.

Conflicts of interest

The authors have no conflict of interest to disclose.

References

[1] J. Dalmau, E. Lancaster, E. Martinez-Hernandez, M.R. Rosenfeld, R. Balice-Gordon, Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis, Lancet Neurol. 10 (2011) 63–74.
[2] N.R. Florance, R.L. Davis, C. Lam, C. Szperka, L. Zhou, S. Ahmad, C.J. Campen, H. Moss, N. Peter, A.J. Gleichman, C.A. Glaser, D.R. Lynch, M.R. Rosenfeild, J. Dalmau, Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents, Ann. Neurol. 66 (2009) 11–18.
[3] S. Bigi, M. Hladio, M. Twilt, J. Dalmau, S.M. Benseler, The growing spectrum of antibody-associated inflammatory brain diseases in children, Neurol. Neuroimmunol. Neuroinflamm 2;2 (3) (2015) e92, http://dx.doi.org/10.1212/NXI.0000000000000092 (eCollection 2015).
[4] T.T. Sands, K. Nash, S. Tong, J. Sullivan, Focal seizures in children with anti-NMDA receptor antibody encephalitis, Epilepsy Res. 112 (2015) 31–36.
[5] R. Wang, H.Z. Guan, H.T. Ren, W. Wang, Z. Hong, D. Zhou, CSF findings in patients with anti-N-methyl-D-aspartate receptor-encephalitis, Seizure 29 (2015) 137–142.
[6] J. Dalmau, E. Tüzün, H.Y. Wu, J. Masjuan, J.E. Rossi, A. Voloschin, J.M. Baehring, H. Shimazaki, R. Koide, D. King, W. Mason, L.H. Sansing, M.A. Dichter, M.R. Rosenfeld, D.R. Lynch, Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma, Ann. Neurol. 61 (2007) 25–36.
[7] G. Rubboli, C.A. Tassinari, Negative myoclonus. an overview of its clinical features, pathophysiological mechanisms, and management, Clin. Neurophysiol. 36 (2006) 337–343.

[8] G. Rubboli, R. Mai, S. Meletti, S. Francione, F. Cardinale, L. Tassi, G. Lo Russo, M. Stanzani-Maserati, G. Cantalupo, C.A. Tassinari, Negative myoclonus induced by cortical electrical stimulation in epileptic patients, Brain 129 (2006) 65–81.
[9] S. Noachtar, H. Holthausen, H.O. Luders, Epileptic negative myoclonus. Subdural EEG recordings indicate a postcentral generator, Neurology 49 (1997) 1534–1537.

Xiaoxuan Li
Dongyan Wu
Department of Neurology, China–Japan Friendship Hospital, Beijing, China
E-mail addresses: magrate1019@126.com (X. Li), wudongyan2008@sina.com (D. Wu).

Iván Sánchez Fernández
Division of Epilepsy and Clinical Neurophysiology, Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States
E-mail address: Ivan.Fernandez@childrens.harvard.edu.

Jia Chen
Pingping Jin
Department of Neurology, China–Japan Friendship Hospital, Beijing, China
E-mail addresses: sophumun@163.com (J. Chen), 18811771755@163.com (P. Jin).

Zhongshu Zhou
Department of Pediatrics, China–Japan Friendship Hospital, Beijing, China
E-mail address: wwenwen@hotmail.com.

Ye Wu
Department of Pediatrics, Peking University First Hospital, Beijing, China
E-mail address: dryewu@263.net.

Jinsong Jiao
Liankun Ren*
Department of Neurology, China–Japan Friendship Hospital, Beijing, China
*Corresponding author.
E-mail addresses: jiao_jinsong@126.com (J. Jiao), rlkbrain2000@yahoo.com (L. Ren).

14 August 2015