Case report
Persistent extreme delta brush in anti-NMDA-receptor encephalitis: Does it portend a poor prognosis?

Muthukani Sankaranarayanan, Shalin Shah, Pravin Thomas, Sudheeran Kannoth, Kurupath Radhakrishnan *
Department of Neurology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

A R T I C L E   I N F O
Article history:
Received 13 February 2019
Received in revised form 14 March 2019
Accepted 17 May 2019
Available online 06 June 2019

Keywords:
Anti-NMDA-R encephalitis
Autoimmune encephalitis
Electroencephalography (EEG)
Extreme delta brush
Gerstmann syndrome
Immunotherapy

A B S T R A C T
We describe an adolescent girl with non-paraneoplastic anti-NMDA-receptor encephalitis (ANMDARE), who despite persistence of the extreme delta brush (EDB) pattern for nearly 2 years in her serial EEGs, she exhibited a speedy and sustained response to immunotherapy. To the best of our knowledge, our patient had the longest persistence of the EDB pattern on EEG reported to date. Our patient illustrates that, although presence of EDB supports the diagnosis of ANMDARE, its presence and persistence may not be a reliable predictor of response to immunotherapy and overall clinical prognosis.

© 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction
Anti-N-methyl-D-aspartate receptor encephalitis (ANMDARE) is a disorder presenting with subacute onset of seizures, psychosis, memory and language deficits, abnormal movements, and breathing and autonomic disturbances [1,2]. Although initially identified in association with ovarian teratomas, in a majority of children and young adults, ANMDARE occurs without tumors [2]. Three-fourths of patients with ANMDARE make substantial recovery with early diagnosis, tumor resection and immunotherapy, but relapses may occur in a quarter of them [1].

In 2012, Schmitt et al. [3] described an electroencephalographic (EEG) pattern characterized by rhythmic 1–3 Hz delta activity with superimposed bursts of rhythmic 20–30 Hz beta activity overriding on each delta wave, which they named ‘extreme delta brush’ (EDB). This pattern since then is believed to be diagnostic of ANMDARE, occurs in 30% [3] to 58% [4] of patients with ANMDARE, and is associated with abnormal magnetic resonance imaging (MRI), high seizure burden, prolonged hospitalization and poor outcome [3].

We describe an adolescent girl with non-paraneoplastic ANMDARE, who despite persistence of EDB for nearly 2 years had a speedy and sustained response to immunotherapy.

2. Case report
A 16-year-old right-handed girl presented in November 2016 with the history of seizures and episodic confusion of 3 months duration. She had a few seizures at the age of 5 years and was diagnosed with benign rolandic epilepsy, for which she received carbamazepine for over one year. The drug was discontinued and she remained seizure-free from the age of 6 until seizure recurrence at the age of 16. The new onset seizures were characterized by motor restlessness and confusion lasting for nearly 2 min and occurred 2 to 3 times per week, and failed to respond to adequate doses of levetiracetam and clobazam. She was a brilliant student until the recent seizure recurrence, after which there was a dramatic decline in her school performance.

On neurological examination, the findings were confined to the higher mental function testing. She had profound difficulties with writing and calculation. She had right–left disorientation and could not identify her fingers. The rest of the neurological and systemic examinations, including the optic fundi, and motor and sensory systems were normal. A diagnosis of Gerstmann’s syndrome due to a rapidly evolving epileptogenic lesion involving the left angular gyrus region was considered.

A 3 Tesla MRI of the brain was normal (Supplementary Fig. 1). Her EEG revealed polymorphic left hemispheric slow activity, maximally over the left parietal region with EDB morphology (Fig. 1). Both the serum and cerebrospinal fluid (CSF) tested strongly positive for NMDA receptor antibodies (by indirect immunofluorescence on transfected cells at our laboratory). There was no evidence of ovarian lesions on
munotherapy with injections of rituximab 1 g/m2 was started and the progression to a generalized tonic right lower limb, along with posturing of the right upper limb with painful sensation that started in the right upper limb spreading to the right disorientation, and agraphia. Although the MRI and FDG-PET are diagnostic of Gerstmann syndrome:

3. Discussion

We have described here a confirmed case of non-paraneoplastic ANMDARE in an adolescent girl, who despite complete resolution of neurological symptoms and signs within 3 months of initiation of immunotherapy, had persistence of EDB and serum antibody positivity for over 2 years. Our patient presented with the four symptoms that are diagnostic of Gerstmann syndrome: finger agnosia, acalculia, left-right disorientation, and agraphia. Although the MRI and FDG-PET turned out to be normal, the EEG disclosed a focal disturbance of electrical function over the dominant hemisphere associated with EDB. Our case illustrates the immense value of scalp EEG, even in this era of advanced neuroimaging, providing not only the localization, but also the first hint to the etiology of the lesion.

Although ANMDARE is typically recognized as a multistage disease characterized by prodromal flu-like illness, followed by acute onset of neuropsychiatric manifestations, difficult to control seizures, movement disorders and autonomic instability [1,2], atypical forms of the disease with isolated focal manifestations are being increasingly reported both in children [5] and adults [6]. To the best of our knowledge, our patient’s presentation with Gerstmann syndrome is unique.

While brain MRI is unremarkable in 50% of patients with ANMDARE [1,2], EEG is abnormal in most [4,7]. In a recent study of 53 patients (35 adults and 18 children), only 2 (4%) patients had normal EEG [8]. Focal disturbance of electrical function was encountered in 73% patients. Overall, close to one-third of patients with ANMDARE show a EDB pattern, although its incidence has varied widely in different case series depending upon patient selection, clinical state and timing of EEG [3,4,7,8].

Generally, with immunotherapy, the EDB pattern gradually becomes less prominent and less frequent, and resolves completely within a few weeks or months [4,9]. In a serial EEG study of 5 children with ANMDARE and the EDB pattern, it resolved within 6 months in 3 children, but persisted in 2 of them [9]. While an infant of 6 months at onset, in whom the EDB pattern on EEG persisted for 10 months, was left with significant cognitive and motor impairment despite control of seizures with medication, a 14-year-old boy had the EBD pattern persist for 17 months and made a complete recovery [9]. To the best of our knowledge, our patient had the longest persistence of EDB reported to date.

Several studies have linked markedly abnormal initial EEGs, especially the presence of the EDB pattern, to prolonged hospitalization, high seizure frequency, abnormal MRI, poor response to immunotherapy and unfavorable outcome [3,7,8]. However, the adverse prognostic implication of this pattern is less apparent in some recent studies [4,10]. Because of its frequent co-occurrence with brief rhythmic discharges, and electrographic and electro-clinical seizures, EDB has been ultrasound of the abdomen and pelvis. Brain fluorodeoxyglucose–positron emission tomography (FDG-PET) was normal (Supplementary Fig. 2).

We treated the patient with injections of methyl prednisolone 1 g/day along with intravenous immune globulin (400 mg/kg/day) for 5 days. She had a seizure recurrence 10 days later characterized by a right lower limb, along with posturing of the right upper limb with progression to a generalized tonic–clonic seizure. Chronic second-line immunotherapy with injections of rituximab 1 g/m2 was started and the same dose was repeated after 2 weeks. There were no further episodes of seizures on oxcarbazepine monotherapy. Her scholastic performance came back to baseline within the next 3 months, and she completed her 12th grade examination with high scores 6 months after the initiation of immunotherapy. Her serial EEGs done at nearly 4–6 month intervals are depicted in Fig. 2. They revealed persistent focal electrical dysfunction over the left centro-temporo-parietal region with extreme delta brushes over the left fronto-centro-temporal region and infrequent left central spikes. In view of the persisting EDB, we continued biannual injections of rituximab (two doses of 1 g/m2, 2 weeks apart). Her serum and CSF anti-NMDA-R antibody remained positive when repeated in November 2018, at 2 years following commencement of immunotherapy. The EEG performed during the same time continued to show EDB (Fig. 2D). She continued to take oxcarbazepine 300 mg in the morning and 450 mg at night.

3. Discussion

We have described here a confirmed case of non-paraneoplastic ANMDARE in an adolescent girl, who despite complete resolution of neurological symptoms and signs within 3 months of initiation of immunotherapy, had persistence of EDB and serum antibody positivity for over 2 years. Our patient presented with the four symptoms that are diagnostic of Gerstmann syndrome: finger agnosia, acalculia, left-right disorientation, and agraphia. Although the MRI and FDG-PET turned out to be normal, the EEG disclosed a focal disturbance of electrical function over the dominant hemisphere associated with EDB. Our case illustrates the immense value of scalp EEG, even in this era of advanced neuroimaging, providing not only the localization, but also the first hint to the etiology of the lesion.

Although ANMDARE is typically recognized as a multistage disease characterized by prodromal flu-like illness, followed by acute onset of neuropsychiatric manifestations, difficult to control seizures, movement disorders and autonomic instability [1,2], atypical forms of the disease with isolated focal manifestations are being increasingly reported both in children [5] and adults [6]. To the best of our knowledge, our patient’s presentation with Gerstmann syndrome is unique.

While brain MRI is unremarkable in 50% of patients with ANMDARE [1,2], EEG is abnormal in most [4,7]. In a recent study of 53 patients (35 adults and 18 children), only 2 (4%) patients had normal EEG [8]. Focal disturbance of electrical function was encountered in 73% patients. Overall, close to one-third of patients with ANMDARE show a EDB pattern, although its incidence has varied widely in different case series depending upon patient selection, clinical state and timing of EEG [3,4,7,8].

Generally, with immunotherapy, the EDB pattern gradually becomes less prominent and less frequent, and resolves completely within a few weeks or months [4,9]. In a serial EEG study of 5 children with ANMDARE and the EDB pattern, it resolved within 6 months in 3 children, but persisted in 2 of them [9]. While an infant of 6 months at onset, in whom the EDB pattern on EEG persisted for 10 months, was left with significant cognitive and motor impairment despite control of seizures with medication, a 14-year-old boy had the EBD pattern persist for 17 months and made a complete recovery [9]. To the best of our knowledge, our patient had the longest persistence of EDB reported to date.

Several studies have linked markedly abnormal initial EEGs, especially the presence of the EDB pattern, to prolonged hospitalization, high seizure frequency, abnormal MRI, poor response to immunotherapy and unfavorable outcome [3,7,8]. However, the adverse prognostic implication of this pattern is less apparent in some recent studies [4,10]. Because of its frequent co-occurrence with brief rhythmic discharges, and electrographic and electro-clinical seizures, EDB has been
labeled as an ictal rather than an interictal phenomenon [11]. Our patient did not have any of these clinical or EEG characteristics, despite the early presence of EDB and its persistence for 2 years.

EDB may not be unique for ANMDARE and has been reported in febrile infection-related epilepsy syndrome, hypoxic encephalopathy, brain tumor, focal cortical dysplasia, stroke and glycine receptor antibody-associated epilepsy [4,12]. Furthermore, benzodiazepine and barbiturate induced beta activity may be misread as EDB. EDB has also been documented in association with methotrexate toxicity [13]. Our patient received none of these drugs. A recent report suspected that EDB might represent an electromyographic artifact due to rhythmic contractions of the frontalis muscle, occurring in synchrony with frontal delta activity [14]. However, its unilaterality, stereotyped morphology in multiple EEG recordings and fronto-centro-temporal distribution would strongly argue against this possibility in our patient.

Although immunotherapy for autoimmune encephalitis remains to be standardized, a recent systematic review concluded that patients treated with dual first-line immunotherapeutic drugs fared better and had lesser chance of relapse in the long-term [15], which prompted us to treat our patient aggressively. It is unclear whether ANMDARE patients with persistence of EDB, despite complete resolution of symptoms, need prolonged immunotherapy to avert relapse. In the absence of reliable guidelines, although our patient was free of neurological symptoms for over one and a half years, in view of persisting EEG abnormalities and positive serum and CSF anti-NMDA-R antibody, fearing relapse, we decided to continue immunoprophylaxis with rituximab.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2019.100324.

**Declaration of Competing Interest**

None of the authors have any conflict of interest to declare.

**References**

[1] Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63–74. https://doi.org/10.1016/S1474-4422(10)70253-2.

[2] Irani SR, Bera K, Waters P, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010;133:1655–67. https://doi.org/10.1093/brain/awq113.

[3] Schmitt SE, Pargeon K, Frechet ESS, Hirsch LJ, Dalmau J, Friedman D. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. Neurology 2012;79:1084–100. https://doi.org/10.1212/WNL.0b013e31826f8cd8.

[4] Jeannin-Mayer S, André-Obadia N, Rosenberg S, et al. EEG analysis in anti-NMDA receptor encephalitis: description of typical patterns. Clin Neurophysiol 2019;130:289–96. https://doi.org/10.1016/j.clinph.2018.10.017.
[5] do Valle DA, Galeazzi JSP, Machado MR, et al. Clinical variability of children with anti-N-methyl-D-aspartate receptor encephalitis in southern Brazil: a cases series and review of the literature. Neurol Sci 2019;40:351–6. https://doi.org/10.1007/s10072-018-3648-z.

[6] Constantinides VC, Kasselimis DS, Paraskevas GP, et al. Anti-NMDA receptor encephalitis presenting as isolated aphasia in an adult. Neurocase 2018;24:188–94. https://doi.org/10.1080/13554794.2018.1524915.

[7] Gillinder L, Warren N, Hartel G, Dionisio S, O’Gorman C. EEG findings in NMDA encephalitis — a systematic review. Seizure 2019;65:20–4. https://doi.org/10.1016/j.seizure.2018.12.015.

[8] Sonderen A, Arends S, Tavy DJ, et al. Predictive value of electroencephalography in anti-NMDA receptor encephalitis. J Neurol Neurosurg Psychiatry 2018;89:1101–6. https://doi.org/10.1136/jnnp-2018-318376.

[9] Yildirim M, Konuskan B, Yalnizoglu D, Topaloglu H, Erol I, Anlar B. Electroencephalographic findings in anti-N-methyl-D-aspartate receptor encephalitis in children: a series of 12 patients. Epilepsy Behav 2018;78:118–23. https://doi.org/10.1016/j.yebeh.2017.05.022.

[10] Zhang Y, Liu G, Jiang MD, Li LP, Su YY. Analysis of electroencephalogram characteristics of anti-NMDA receptor encephalitis patients in China. Clin Neurophysiol 2017;128:1227–33. https://doi.org/10.1016/j.clinph.2017.04.015.

[11] Veciana M, Becerra JL, Fossas P, et al. EEG extreme delta brush: an ictal pattern in patients with anti-NMDA receptor encephalitis. Epilepsy Behav 2015;49:280–5. https://doi.org/10.1016/j.yebeh.2015.04.032.

[12] Baykan B, Tuncer OG, Vanli-Yavuz EN, et al. Delta brush pattern is not unique to NMDAR encephalitis: evaluation of two independent long-term EEG cohorts. Clin EEG Neurosci 2018;49:278–84. https://doi.org/10.1177/155009417693168.

[13] Schmidt LS, Kjaer TW, Schmiegelow K, Born AP. EEG with extreme delta brush in young female with methotrexate neurotoxicity supports NMDA receptor involvement. Eur J Paediatr Neurol 2017;21:795–7. https://doi.org/10.1016/j.ejpn.2017.05.008.

[14] van der Meulen AAE, van der Hoeven JH, de Jong BM, Elting JWJ. Extreme delta brushes in anti NMDA receptor encephalitis — muscle artefact or an EEG phenomenon? A case report. Clin Neurophysiol 2017;128:1835–6. https://doi.org/10.1016/j.clinph.2017.06.256.

[15] Nosadini M, Mohammad SS, Ramanathan S, Briot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother 2015;15:1391–419. https://doi.org/10.1586/14737175.2015.1115720.