EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 18 (2014) 449–452

Official Journal of the European Paediatric Neurology Society

Case study

Resective surgery in the treatment of super-refractory partial status epilepticus secondary to NMDAR antibody encephalitis

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ARTICLE INFO

Article history:
Received 7 April 2013
Received in revised form
15 December 2013
Accepted 26 January 2014

Keywords:
Anti-NDMAR
Encephalitis
Lobectomy
Seizures
Status epilepticus
Surgery

ABSTRACT

Background: Anti-NMDAR encephalitis is an increasingly described clinical entity in children, comprising 40% of all cases. We present a case of super-refractory status epilepticus secondary to anti-NMDAR encephalitis treated with emergent resective surgery.
Case study: A 7 years-old boy presented with progressive abnormal irritability. On the day after admission he had multiple seizures, characterized by head and eye version to the right. EEG revealed left parietal-occipital continuous paroxysmal activity. Anti-NMDAR antibodies were positive in CSF and serum. After almost 3 months in the Intensive Care Unit, in barbituric coma, and given the failure of all treatment regimens, a preoperative evaluation was conducted. Ictal SPECT showed significant hiperperfusion and brain FDG-PET a cortical hypometabolism in the left occipital lobe; a left occipital lobectomy was performed. In the next days it was possible to progressively suspend Thiopental. Currently, patient presents right homonymous hemianopsia, eats by his own hand but needs help in almost all other activities.
Discussion: Status epilepticus (SE) in the setting of anti-NMDAR encephalitis is unusual but described. Whilst the role of surgery in the management of refractory focal epilepsy is establis hed, it is seldom used in the treatment of SE. In the patient with refractory SE (RSE), awareness of surgery as a potentially *life saving* treatment is an important issue. To our knowledge, this is the first report of a partial RSE secondary to anti-NMDAR encephalitis treated with resective surgery and illustrates the need to consider anti-NMDAR encephalitis as a cause of super-refractory SE.

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1090-3798/$ – see front matter
http://dx.doi.org/10.1016/j.ejpn.2014.01.013

1. Background

In the last years, encephalitis associated with antibodies against *N*-methyl-D-aspartate receptor (NMDAR) emerged as an important diagnostic entity in neurology field. NMDAR are ligand-gated cation channels with crucial roles in synaptic transmission. These receptors are heteromers of NR1 subunits that bind glycine and NR2 subunits that bind glutamate and are expressed on neurons throughout the brain.[1] Antibodies against NR1–NR2 heteromers can result in a characteristic neuropsychiatric syndrome, the so-called anti-NMDAR encephalitis; NMDAR antibodies in serum and CSF are highly specific for this condition. Anti-NMDAR encephalitis is increasingly described in children, comprising 40% of all cases. It can be severe and even fatal, but it is potentially reversible. Responses to immunotherapy are variable, usually slow but despite the severity of symptoms and prolonged clinical course, most patients recover if the disorder is promptly recognized and treated.

Seizures are a common feature of anti-NMDAR encephalitis, occurring in about three-fourths of patients, and they can be one of the first signs of the disease. The majority of patients develop generalized tonic-clonic seizures but some exhibit complex partial type. Auto-immune epilepsy is an uncommon cause of status epilepticus (SE) but it should be considered among the many possible etiologies; it seems that anti-NMDAR encephalitis is one of the most common forms of auto-immune encephalitis that can be associated with SE. Here we present a case of super-refractory status epilepticus (RSE) secondary to anti-NMDAR encephalitis treated with emergent resective surgery.

2. Case study

The patient is a 7 years-old boy, previously healthy, with normal psychomotor development and with an irrelevant family history. Three days prior to admission, parents described fever, odinofagy and otalgy. They also described a progressive abnormal irritability, with episodes of aggressive behavior. On the admission day he had an apparently primary generalized tonic-clonic seizure; he was sleepy and febrile (38–39 °C). The Cerebral Spinal Fluid (CSF) study revealed a minor increase in protein content (0.58 g/dL) and pleocytosis (54 cells, lymphocytes predominance); brain CT and Electroencephalogram (EEG) were normal.

Given the suspect of viral encephalitis, treatment with intravenous acyclovir was initiated. On the next day, patient presented stereotyped seizures, with eye and head version to the right (20–30 s duration), two of them with secondary generalization. He was refractory to two successive bolus of phenytoin and to a bolus of valproic acid. The EEG revealed left parietal-occipital continuous paroxysmal activity (Fig. 1(a)). He was admitted to the Pediatric Intensive Care Unit (ICU) and it was started therapy with propofol, midazolam, phenobarbital and valproic acid. Nonetheless, he maintained frequent episodes of cephalic version and conjugate eye deviation to the right, with almost continuous left parietal-occipital continuous paroxysmal activity. In this context, thiopental was used until a *burst-suppression* pattern was reached. Cerebral MRI (day 2) was normal. Anti-NMDAR and anti-voltage-gated potassium channel complex (VGKC) antibodies in serum and CSF were requested. Extensive infectious (serological and PCR) studies were negative. The immunological study was normal/negative and cerebrospinal fluid cytology was negative for malignant cells.

On day 25 he developed orofacial diskinetic and coreoathetosic movements of both arms (video-EEG with no correlation with these movements). On day 38 the results of anti-NMDAR antibodies was positive in CSF and serum and a diagnosis of anti-NMDAR encephalitis was made. Computed tomography of the chest, abdomen and pelvis were negative and testicular ultrasound was normal. Total body PET-CT revealed no abnormalities. Repeated MRI (day 41; Fig. 1(b)) revealed mild hyperintensity of the left temporal-occipital cortex.

Several therapeutic options were sequentially tried: metyhprednisolone, immunoglubulins, plasmapheresis and rituximab, with no evidence of benefit. Each attempt to minimize the depth of thiopental coma resulted in resumption of electrical partial SE. Multiple combinations of anti-epileptic drugs (levetiracetam, phenytoin, phenobarbital, valproic acid, vigabatrin, carbamazepine, lamotrigine, zonisamide and felbamate) and even ketogenic diet were attempted, with no success. From day 85, he presented a progressive heart failure, with decreased ejection fraction, most probably related to prolonged therapy with thiopental. Given the failure of all treatments at this time, the possibility of surgery was considered and discussed with parents. A preoperative evaluation was conducted: ictal SPECT (Fig. 1(c)) showed a significant hiperperfusion in the left occipital lobe; brain FDG-PET revealed a parietal-occipital cortical hypometabolism. The decision was to move on and to remove the epileptic focus under electrocorticography (ECOG) guidance for refractory partial SE. At day 100, intra-operative ECOG showed continuous spike activity involving the whole left occipital lobe and a left occipital lobectomy was performed. Neuropathological examination revealed moderate inflammatory changes without definitive evidence of dysplasia or tumor.

In the next following days it was possible to progressively suspend thiopental coma. There was a progressive reduction in the frequency of seizures and there was no evidence of electroencephalographic SE. He was discharged from ICU 12 days after surgery and 26 days later he was discharged home. Currently, and with 9 years of age, the boy has right homonymous hemianopsia, is dysphasic, eats by his own hand but needs supervision in almost all other activities. He is now medicated with levetiracetam, carbamazepine, phenobarbital and clobazam and presents frequent partial seizures (2–3/week). The clinical manifestations are variable, but the parents describe two main types: a) left versive seizure > right arm clonic seizure; b) bilateral assymmetric tonic seizure. Follow-up EEG disclosed right frontal but also left temporal-frontal paroxysmal activity.

3. Discussion

We present a case where anti-NMDAR encephalitis was suspected due to the “typical” combination of signs/symptoms:

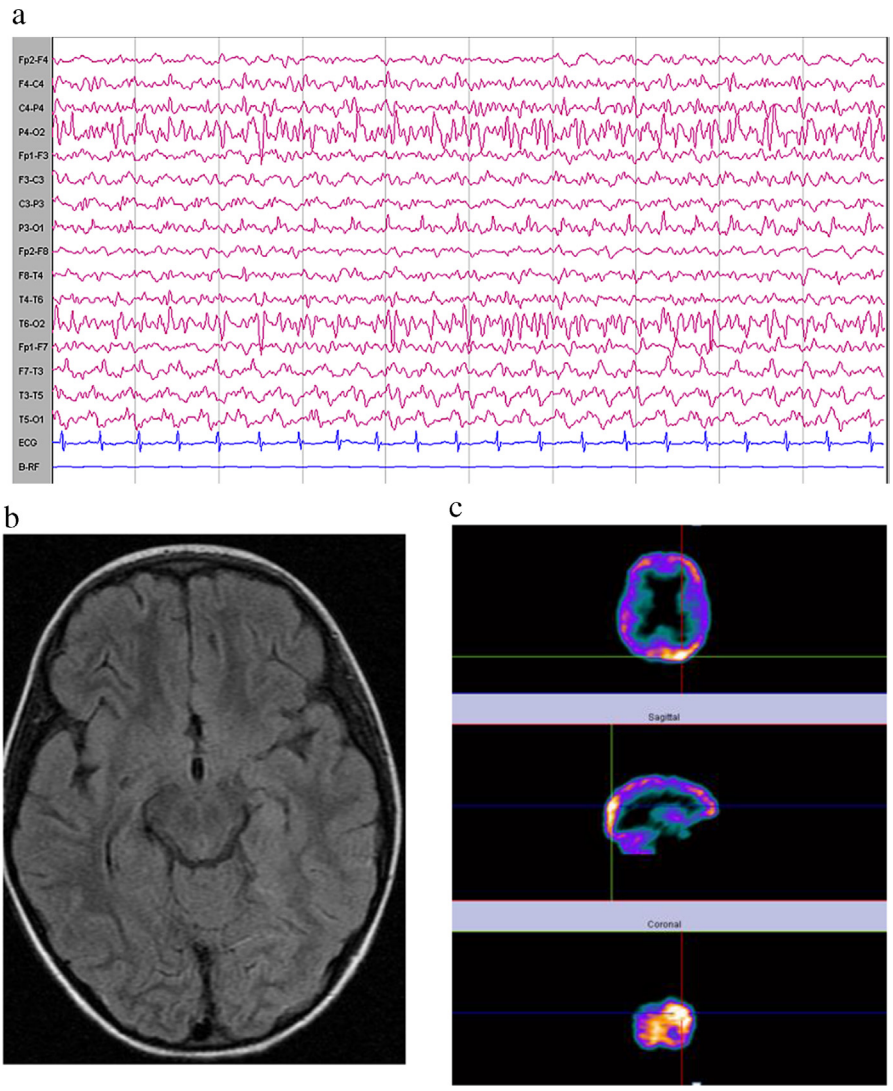

Fig. 1 – (a). EEG: left parietal-occipital continuous paroxysmal activity. (b). MRI (day 41): T2/FLAIR sequence – slight hyperintensity and thickening of the left temporal-occipital cortex. (c). Ictal SPECT (injection 2 s after seizure onset, 99 mTc-ECD): left occipital hyperperfusion. The ictal EEG showed a left occipital focus, with subsequent spread to adjacent regions.

previous infection, abnormal behavior, pleocytosis, seizures and movement disorder. Thirty-eight days after the initial presentation, CSF and serum tested positive for anti-NMDAR antibodies; the presence of anti-NMDAR antibodies was assessed as previously described (Oxford, Vincent A.).[2]

In 1988, Shiomi et al. reported cases of encephalitis with recurrent seizures.[3] The authors defined this type of encephalitis as characterized by repetitive, refractory seizures during acute phase, and designated it as *acute encephalitis with refractory, repetitive partial seizures* (AERRPS). In the original series, most children presented with brief (1–5 min) refractory partial seizures, repeating periodically every 5–10 min, and evolving into SE. The overall prognosis of AERRPS was generally poor; seizures were poorly controlled and continuously evolve into residual epilepsy without a latent period. The post-encephalitic epilepsy was also characterized by frequent and refractory partial seizures. A significant proportion of these patients tested positive for anti-NMADR antibodies. It is possible that this can represent a phenotypic expression of anti-NMDAR encephalitis and our patient can be a good example of it.

Super-refractory SE is defined as SE that continues or recurs 24 h or more after the onset of anesthetic therapy, including those cases where SE recurs on the reduction or withdrawal of anesthesia. General anesthesia is usually the recommended treatment, at a dose that results in EEG *burst-suppression*, but prolonged high-dose suppressive therapy is associated with significant mortality and morbidity.[4] The mortality and morbidity rates increases the longer the episode continues, due to a set of complications both from RSE and also its treatment. These complications include hypotension, cardiorespiratory collapse and failure, infection or deep vein thrombosis.

SE in the setting of anti-NMDAR encephalitis is unusual but already described, and two of the reported patients have died.[1] The diagnosis of autoimmune status epilepticus (ASE) should

be remembered whenever faced with an "explosive" onset of seizures, with quick progression to SE. Anti-epileptic therapy for ASE does not differ from the treatment of SE from other causes. There are few trials supporting one form of therapy over another and as a consequence, therapy is largely based upon expert opinion. Whereas the role of surgery in the treatment of refractory focal epilepsy, especially temporal lobe epilepsy, is established, it is very rarely used in the treatment of partial SE.[5] However, surgical therapy can be a successful option in cases of focal SE, when medical therapy has failed. A recent review paper about ASE causes and treatment, considers resective surgery a treatment option, preserving the fact that should be completed by an experienced team and using intra-operative ECOG as a support.[6]

In this particular case, there was evidence (based on clinical findings, EEG and neuroimaging) supporting a focal or unihemispheric origin of SE. The failure of aggressive medical management in controlling SE led to the consideration of resective surgery, in a child that suffered from an autoimmune disease which, as mentioned, is potentially reversible. We are well aware that in SE, and especially in ASE, there is a possibility of widespread epileptogenic areas and that the outcome after emergency surgery can be poor, as was the case. Nevertheless, in the individual patient with RSE, awareness of surgery as a potentially *life saving* treatment is an important issue and deserves to be considered and discussed with patient family.

To our knowledge, this is the first report of a partial RSE secondary to anti-NMDAR encephalitis treated with resective surgery. It illustrates the need to consider anti-NMDAR encephalitis as a cause of super-refractory SE as well as to consider emergent surgery as an option, although always keeping in mind that a poor functional and seizure outcome is a possibility.

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