

A 15-year epileptogenic period after perinatal brain injury

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Summary

Seizures are a frequent acute neurological event in the neonatal period. Up to 12 to 18% of all seizures in newborns are due to perinatal stroke and up to 39% of affected children can then develop epilepsy in childhood. We report the case of a young patient who presented stroke-related seizures in the neonatal period and then developed focal symptomatic epilepsy at 15 years of age, and in whom the epileptic focus was found to co-localize with the site of his ischemic brain lesion.

Such a prolonged silent period before onset of remote symptomatic epilepsy has not previously been reported. This case suggests that newborns with seizures due to a neonatal stroke are at higher risk of epilepsy and that the epileptogenic process in these subjects can last longer than a decade.

KEY WORDS: children, EEG, epilepsy, neonatal seizures, perinatal stroke, seizure.

Introduction

Seizures occur more often in the neonatal period than at all other ages and they are a frequent neurological complication in the neonatal intensive care unit. Population-based studies indicate an incidence rate of neonatal seizures (NSs) of 1.8 to 3.5 per 1000 live births (Chapman et al., 2012). Newborns with seizures carry an increased risk of long-term morbidity such as developmental delay, cerebral palsy and post-neonatal epilepsy (PNE) (Pisani et al., 2012). Estimates on rates of PNE

after NSs vary widely, ranging from 17 to 56%, depending on selection criteria and the duration of follow-up (Pisani et al., 2012; Pisani et al., 2015; Mizrahi and Watanabe, 2005). Perinatal stroke accounts for 12 to 18% of all etiologies causing seizures in this age group (Walsh et al., 2011) and affected newborns seem to be at increased risk of childhood epilepsy, with a rate of up to 39% (Sehgal, 2012). Most children with NSs experience early spontaneous recurrent epileptic seizures. Almost 3/4 of seizures occurred within the first year of life (Ellenberg et al., 1984; Fox et al., 2016) and the others usually before the age of 5 (Pisani et al., 2012).

We report the case of a young boy with onset of epilepsy at the age of 15 years, found to be related to an ischemic lesion due to a perinatal stroke with seizures in the neonatal period.

This observation suggests that whilst the risk for PNE is maximal in the first 5 years of life, in some patients seizures can appear much later in life.

Case report

This patient is the only child of unrelated parents, born at term by physiological delivery after an uneventful pregnancy. On the second day of life he started to present recurrent hemiclonic seizures, with alternating lateralization. At this age, video-EEG recordings documented focal ictal discharges in the right centro-parietal area and, less frequently, in the homologous region of the contralateral hemisphere. The seizures continued after both intravenous pyridoxine and diazepam administration and were controlled with phenobarbital. Blood and cerebrospinal fluid analysis were unremarkable and cerebral magnetic resonance imaging (MRI) did not reveal abnormalities. Drugs were then gradually discontinued and the patient was discharged at 1 month of age. Neurological follow-up was carried out through periodic evaluations until 24 months of age, disclosing only a slight language delay.

At 15 years of age, the patient experienced an unprovoked episode characterized by a sudden painful paresis of his left arm and shoulder followed by vision blurring, loss of responsiveness for a few minutes, then left head and eye deviation, and finally a brief convulsive phase. During the post-ictal period he presented repeated vomiting and anterograde amnesia. He was admitted to the emergency department where he underwent a head computerized tomography scan and an EEG during wakefulness, both reported as normal. Therefore, the patient was discharged without treatment.

He was then referred to our service and underwent a full diagnostic work-up. Neurological examination showed a slight asymmetry of deep tendon reflexes (predominant on the left side). The cutaneous plantar reflex was silent on the left side. A sleep-deprived EEG revealed spo-

radic sharp waves over the left hemisphere, and right fronto-central spikes, whose source was estimated to lie in the peri-rolandic region of the right hemisphere. The neuropsychological evaluation documented a borderline cognitive level (IQ=79). Brain MRI disclosed signal abnormalities in the right peri-rolandic region, with a focal ischemic lesion involving the right precentral operculum (Fig. 1), compatible with the electrical source imaging of the epileptiform abnormalities (Fig. 2).

A chronic treatment with lamotrigine was started. The patient, now followed-up in another hospital, is still on treatment and has been seizure free for 6 years.

Discussion

Our report raises an important issue: how long can the epileptogenic latent period last? This patient had a history of perinatal stroke and NSs and presented with an acute epileptic seizure at 15 years of age. In the perinatal period, imaging was interpreted as normal, and the diagnosis of perinatal ischemic stroke was made only retrospectively. Patients with perinatal stroke can present acute symptoms in the first week of life; these consist mainly of focal and repetitive acute symptomatic seizures in an otherwise well-appearing neonate (Walsh et al., 2011). As reported in the literature, a small and peripheral ischemic lesion can be missed at the imaging work-up and usually, in these subjects, NSs can recur, mainly localized to one side, and the background EEG activity can be normal (Rafay et al., 2009). This, as in our case, can happen after an uneventful pregnancy and peripartum period (Chabrier et al., 2011).

Perinatal stroke accounts for 12 to 18% of all seizures during the neonatal period (Walsh et al., 2011) and the majority of NSs are symptomatic markers of an underlying acute brain dysfunction. The NSs in our patient suggested an acute neurological event and, in view of his perinatal history and the focal lesion shown on his MRI images, they were very likely due to his perinatal stroke. Thereafter, the patient became seizure free, as do most newborns with this kind of lesion, and developed a mild neurological impairment. Thus, his anticonvulsant therapy was discontinued early, in the first month of life. However, a late unprovoked seizure occurred, confirming that children with perinatal stroke can have a good short-term outcome, although, in up to 46% of them (particularly after an arterial ischemic stroke), spontaneous seizures may recur even after a long latent period (Sehgal, 2012). Furthermore, the “practical clinical definition of epilepsy” allows the diagnosis of epilepsy after a single seizure in situations with a probability of further seizures of at least 60% (Fisher et al., 2014). This may include our child who presented with a single seizure combined with a remote symptomatic etiology and an epileptiform EEG study (Stroink et al., 1998). Although we cannot completely exclude the occurrence of two independent events in this patient, his perinatal history and the area of the lesion, which is consistent with the focus of the epileptic EEG abnormalities both in the neonatal period and later in life, strongly suggest that he suffered from PNE after a perinatal stroke.

Epilepsy is a common endpoint of many forms of acquired brain pathology (Goldberg and Coulter, 2013). Brain injuries are often followed by a latent period of

variable duration before the appearance of epilepsy. In fact, epilepsy is believed to be the result of epileptogenesis, or chronic changes in neural networks favoring excitation. The epileptogenic process has been classically divided into 3 steps: inciting event, silent period, and onset of spontaneous recurrent seizures (Bender and Baram, 2007). In the present case, the occurrence of NSs, a sign of an acute brain injury, was followed by a long silent period before symptomatic epilepsy began. However, nearly 2/3 of newborns with NSs have their first spontaneous epileptic seizure during the first year of life (Pisani et al., 2012). It is also reported that up to 55% of hemiplegic patients with perinatal stroke can be expected to develop epilepsy by 10 years of age (Wanigasinghe et al., 2010). Furthermore, a recent study highlighted that, among children with a history of perinatal stroke and NSs, the 10-year cumulative incidence of a first remote seizure was 69% (CI 48-87%) and of active epilepsy 54% (CI 32-79%) (Fox et al., 2016).

Nevertheless, a seizure-free period lasting as long as 15 years, as in our patient, has not previously been described. Previously, the longest reported time before epilepsy onset in patients with perinatal stroke was 13 years (Wanigasinghe et al., 2010). Whatever the specific mechanisms of injury in epileptic patients, the main pathological features include either massive cell death that starts the epileptogenesis process, or repetitive and prolonged seizures that may alter the developing brain early in life to create epileptic neuronal circuits (Bender and Baram, 2007; Dudek et al., 2010). Both these conditions are absent in our case who presented only limited cortical brain injury and this can partially explain why the epilepsy began after many years.

Our patient was treated with both diazepam and phenobarbital during the neonatal period. Studies regarding the possible role played by antiepileptic drugs in neuroprotection and anti-epileptogenesis have given controversial results (Löscher and Brandt 2010; Radzik et al., 2015), thus we cannot exclude a possible influence of the treatment on the subsequent duration of the silent period. However, phenobarbital at least, being the first-line treatment for NS, has been used in other, previous patients reported in the literature on PNE after perinatal stroke, without resulting in such a long silent period (Golomb et al., 2007).

In our patient the EEG source analysis of interictal abnormalities indicated an epileptic focus that matched with the site of the lesion seen on the brain MRI images. Damage of the cerebral cortex is widely considered to be a *conditio sine qua non* for the development of epilepsy (Menon and Shorvon, 2009). Furthermore, a higher incidence of epilepsy in hemiplegia is reported in association with radiological evidence of cortical and subcortical damage than with periventricular changes only. This might also suggest that there is a need for careful long-term supervision of these children in whom there is also a cortical damage. The latter seems to determine the high morbidity in newborns with NSs and in some cases can be considered to represent the onset of a long epileptogenic process.

In conclusion, our report suggests that newborns with NS due to a perinatal stroke have a higher risk of epilepsy, with an epileptogenic process that can last longer than a decade.

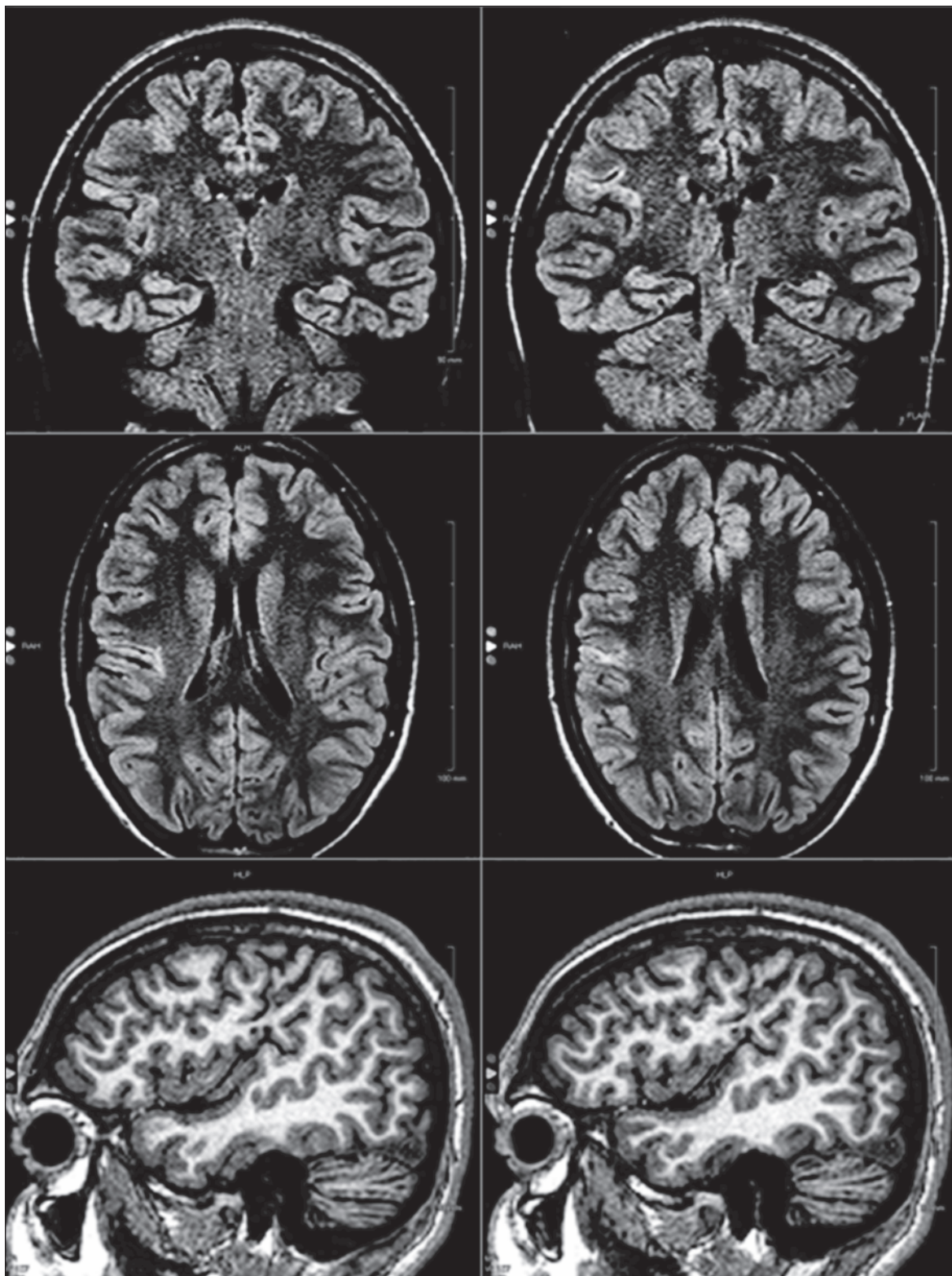


Figure 1 - Brain MRI findings.

Magnetic resonance imaging showed focal cortical damage of the right peri-rolandic region, with a focal ischemic lesion involving the right pre-central operculum in the form of a limited ulegyria. In T1-weighted images the morphological abnormality is evident, showing a "mushroom shape" associated with a focal band of hyperintensity in FLAIR in the subcortical white matter. This pattern is due to focal vascular damage with selective vulnerability of the sulcal portion of the gyri.

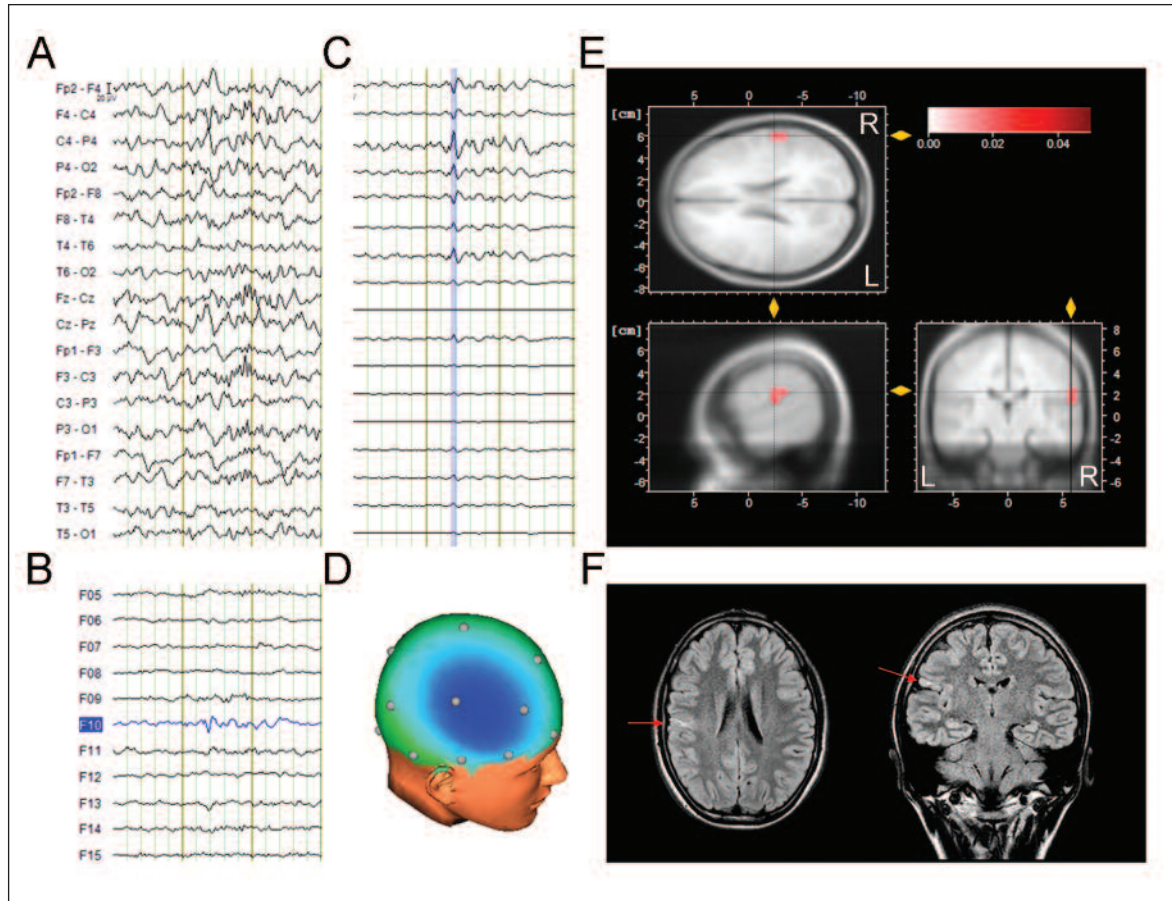


Figure 2 - EEG Source Analysis.

In A, a short 3-second fragment of sleep EEG in bipolar longitudinal montage is depicted, showing a paroxysmal focal epileptiform abnormality over the right fronto-central region. In B, the inspection of the same EEG fragment after Independent Component Analysis revealed that the epileptiform abnormality could be represented by a single component (F10). C shows the same EEG interval in which only the F10 component was back-transformed in order to emphasize the epileptic component, ignoring background oscillations. The topographic voltage scalp distribution of the paroxysmal abnormality is displayed in D and its source, estimated by means of LORETA algorithm, is illustrated in E. The estimated source of the interictal epileptiform abnormalities fits well with the lesion found on the patient's magnetic resonance imaging (F).

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