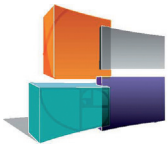
Anaesth Crit Care Pain Med 38 (2019) 195–198



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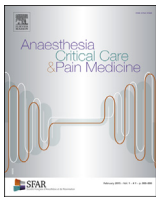

Letter to the Editor

A rare case of super-refractory epileptic status in pregnant woman: Schizencephaly

ARTICLE INFO

Keywords:
Schizencephaly
Pregnant
Status of refractory epilepticus
Super-refractory status epilepticus

ABSTRACT

Schizencephaly is an anomaly of the subtotal brain development, which occurs as the presence of a cleft lined with grey matter extending from subarachnoid space to the ventricles. It may be manifested by psychomotor retardation, paresis or partial seizures and drug-resistant convulsions. The clinical expression of schizencephaly depends on the bilaterality of the slit, its size and its seat. The diagnostic strategy of schizencephaly in the ante- and postnatal period has been revolutionised by MRI imaging, the only technique able to provide an accurate and complete lesional assessment, particularly in type I. We report the case of a 34-year-old pregnant woman at the 25th weeks of amenorrhea, who presented a super-refractory epileptic-status due to a right schizencephaly. The diagnosis of eclampsia was excluded. This case report is very particular cause of the late appearance of epileptic seizures in this pregnant woman who has never done so.

1. Introduction

Schizencephaly is an anomaly of subtotal brain development occurs as the presence of a cleft lined with poly-microgyric gray matter extending from subarachnoid space to the ventricles. The first anatomo-pathological descriptions were reported by Yakovlev and Wadsworth in 1946, who divided the schizencephaly into two types: open and closed-lip. Cerebral magnetic resonance imaging (MRI) is the examination of choice for diagnosis, anatomical shape and the presence of associated lesions [1]. It may be manifested by psychomotor retardation, paresis or partial seizures and drug-resistant convulsions [2–4].

We report the case of a 34-year-old pregnant woman at the 25th weeks of amenorrhea who presented a super-refractory epileptic-status due to a right schizencephaly.

2. Observation

We present a 34-year-old woman, pregnant at 25 weeks of amenorrhea, known diabetic balanced with diet. She has 2 children born of normal pregnancies and having a normal psychomotor development. The patient presented, in the week before admission, rebel headaches to usual analgesic treatments, followed two days later by the appearance of partial seizures in the upper left limb. The patient was admitted to a regional hospital for oversight and management. Evolution was characterised by persistent confusion and resistance to benzodiazepines (midazolam and diazepam). Computed tomography (CT) without contrast product was normal. The patient was transferred to our hospital for therapeutic care.

At admission, the patient was in a convulsive seizure involving the upper limb, the left hemi face and the eye, in the form of close shocks. The Glasgow coma scale was estimated to be 10 (spontaneous eye opening, motor response localising pain and no verbal response) without neurological deficit. The pupils were equals and reactive, the neck was supple and there are no traumatic signs or oedema of the lower limbs. Capillary blood glucose level was at 0.99 g/L, rectal temperature at 38.2 °C and there is no proteinuria or ketonesuria or nitrites in dipstick test. Blood pressure was 120/65 mmHg (MAP = 75 mmHg), respiratory rate is 26 c/min with oxygen saturation around 92% in air room increased to 98% under 6 L/min of oxygen by mask.

An initial dose of 5 mg of midazolam intravenously helped to stop the seizures temporarily for 15 min, requiring the injection of 10 mg of diazepam renewed 30 min afterwards. A loading dose of phenobarbital of 10 mg/kg and a maintenance dose of 5 mg/kg/day had been established. Re-reading of the CT scan had suspected a discreet deviation of the midline without visible process or intracranial hypertension (ICH) (Fig. 1). Obstetric examination had demonstrated a progressive mono-foetal pregnancy, estimated at 26 weeks without placental abnormalities or genital discharge. The family history had revealed the numbness of the upper left limb during the last two years.

The evolution was marked by the persistence of crises requiring the addition of full doses of clobazam and lamotrigine. The Serum electrolytes, renal and hepatic function, serum calcium and magnesemia and thyroid balances were normal. The glycosylated haemoglobin was 5.64%. Cerebrospinal liquid study remained sterile. The diagnosis of eclampsia was excluded.

The resistance of seizures to first and second line of antiepileptic (AE) drugs required sedation with midazolam 0.1 at 0.4 mg/kg/h

https://doi.org/10.1016/j.accpm.2018.06.002

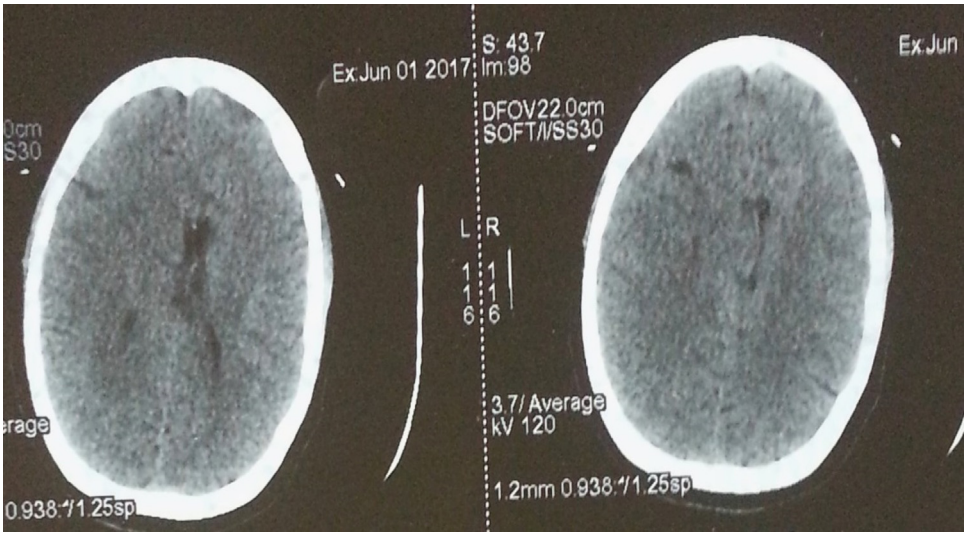

Fig. 1. CT images revealing a discreet deviation of the median line to the left.

and fentanyl 2 μg/kg/h, controlled ventilation and combination of clobazam and lamotrigine. An MRI (Fig. 2) showed an enlargement of the right rolandic sulcus towards the homolateral ventricle lined with grey matter in favour of a right schizencephaly without other associated abnormalities. The electroencephalogram (EEG) (Fig. 3) had concluded that the midazolam refractory partial epileptic-evil condition necessitated deep sedation with thiopental 5 mg/kg/h.

The evolution was marked by the clinical resolution of the seizures in 48 hours. However, the control EEG revealed the persistence of the state of sub-clinical evil, hence the need to increase the dose of thiopental to 4 g/day. The electroencephalographic control confirmed the therapeutic efficacy. The development was characterised by the occurrence on the fourth day of a successfully treated pneumatically acquired pneumonitis (VAP). In the eighth day, and after improvement of the ventilatory and infectious parameters, sedation was stopped and the patient successfully severed with phenobarbital relay associated with clobazam and lamotrigine orally.

The patient then went out on bitherapy (clobazam and lamotrigine) with close follow-up marked by an absence of epileptic seizures and a normal course of pregnancy, which was completed at term and gave birth to a healthy female child.

3. Discussion

The status of refractory epilepticus (SRE) is defined as a state of epileptic evil resistant to antiepileptic drugs of first line (benzodiazepines) and second line (phenytoin, phenobarbital etc.) [5].

There are "super-refractory" or malignant SREs that are therefore resistant to a first anaesthetic. Often these are patients with aetiology of the state of epileptic evil likely to be responsible for its resistance to treatment [5,6]. Numerous causes are suspected: vascular, inflammatory, tumorous, metabolic, and malformative such as cortical dysplasia and schizencephaly [7]. The latter is defined by the presence of a transcerebral cleft passing through the cortex of the lateral ventricle at the periphery with separated or fused lips by an ependymo-piale suture. The cleft is bordered by cortex covered with pia matter and vessels. It is a rare disorder of cerebral cortical development that is part of anomalies of sulcation and neuronal migration [3,8].

Two anatomical types of schizencephaly are described; Type I schizencephaly or closed-lip form, the cerebral cleft is fused by superimposing the grey matter that extends from the ventricular surface to the cortex. Outside, the clogged slit is always centred by

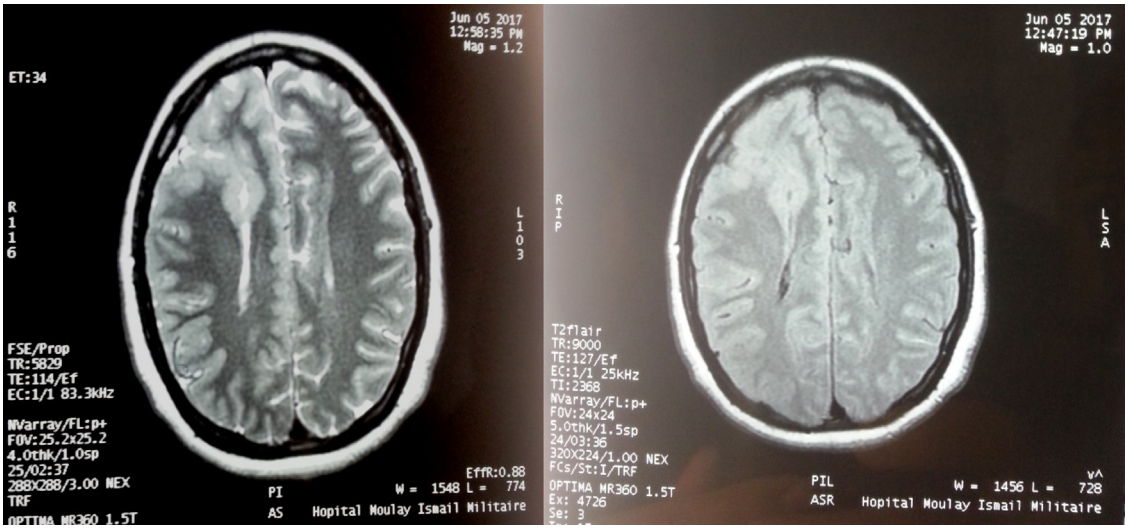

Fig. 2. MRI images showing unilateral right schizencephaly.

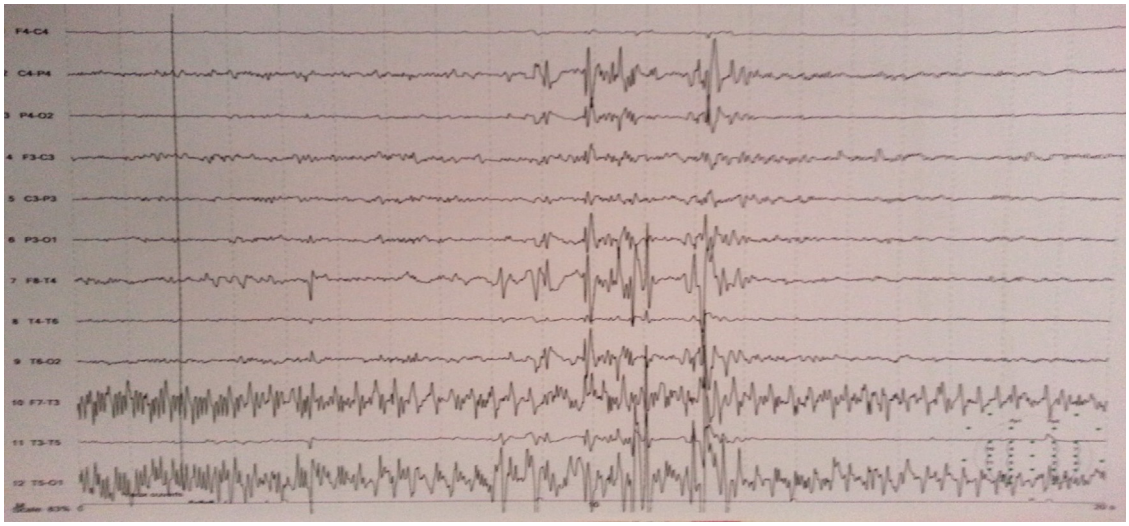

Fig. 3. EEG showing a right fronto-temporal paroxysmal activities diffusing on the contralateral side.

a localised enlargement of the sub-arachnoid spaces. In type II schizencephaly or open- lip form, the walls of the slit are well separated from each other. The polymicrogyric cortex is visible along this cerebral cleft, and often presents a very hypertrophic aspect expressing the exuberance character of the process of neuronal repair [9]. Numerous abnormalities can be associated such as absence of septum pellucidum, callous dysgenesis, controlateral cortical dysplasia of the split, calcifications, ectromelia or heterotypes of the white matter [3].

The aetiology of schizencephaly remains uncertain. It may be ischemia (especially in the middle cerebral artery), foetal distress due to maternal trauma, foetal cytomegalovirus infection, or even prenatal exposure to toxic substances such as cocaine or other alpha-stimulants, or carbon monoxide poisoning [10]. It results from a lack of cerebral perfusion at a critical period of neuronal migration towards the 7th week of gestation. At this time, the less vascularised areas, and therefore the most sensitive to ischaemia, are the ventricular walls [8]. In addition to this exogenous hypothesis linked to foetal aggression during pregnancy, familial cases of schizencephaly linked to a mutation on the *EMX2* gene have been published in the literature, supporting the implication of a genetic mechanism, at least for a part, In the pathogenesis of schizencephaly [9,11].

This gene, located on chromosome 10q26, would be involved in brain development. The mode of transmission would be autosomal recessive [10,12]. The existence of deletions of these genes, in certain open forms of schizencephaly, has recently been demonstrated. The study of these genes must be carried out in the perspective of genetic counselling [3].

The clinical expression of schizencephaly depends on the bilaterality of the slit, its size and its seat. Type I, revealed later, is manifested by hemiparesis or contralateral monoparesis and partial drug resistant seizures or motor deficit. In type II, clinical alterations occur in the neonatal period and are dominated by microcephaly, psychomotor retardation and convulsions [2–4]. During pregnancy, several factors may have a role in the epileptic crisis's upsurge. This is the case of hormonal changes including hyper-estrogenism, metabolic changes, sleep disorders, poor adherence to antiepileptic therapy for fear of teratogenicity, changes in plasma levels of AEs due to pregnancy vomiting, drug interactions, Expansion of plasma volume, increased cardiac output with increased hepatic and renal blood flow, which accelerates the elimination of AE [13,14]. If pregnant physiological changes are likely to induce epileptic crisis, in approximately 55% of parturient, the EC frequency remains unchanged, and the frequency is decreased in 10% of cases [13]. In addition, women free of EC several months before conception, for about 9 months, have 84 to 92% chance of not having seizures throughout pregnancy [15,16].

This case report is very particular cause of the late appearance of epileptic seizures in this pregnant woman who has never done so. The diagnosis of eclampsia was excluded because of the absence of arterial hypertension and proteinuria. The coincidence of these manifestations with a pregnancy raises the probability of a mechanism triggering seizures although our patient has already had two previous pregnancies that occurred without incident but this remains to be demonstrated.

The diagnostic strategy of schizencephaly in the ante- and postnatal period has been revolutionised by MR imaging [4]. In this case, the diagnosis is based on the highlighting of an extended horizontal cerebral cleft of the lateral ventricle wall to the cerebral cortex. The grey matter covering the gap is abnormal, thick and irregular. The highlighting of a localized dilatation of the lateral ventricle, in the form of a dimple at the sidewall, is a valuable sign for the diagnosis of closed-lip schizencephaly. It also helps to search other malformations in the central nervous system [2]. Between 1988 and 1996, 33 children with schizencephaly were examined. Two cases of type II schizencephaly were the subject of an antenatal diagnosis in foetal magnetic resonance imaging (MRI) leading to a therapeutic termination of pregnancy. Diagnosis was retained in all cases on imaging data: MRI and CT scans [3]. However, the latter is not sufficient in type I, whereas in type II, when the slit is wide, diagnosis by imaging is easier [17].

Antenatal ultrasound diagnosis is possible and essential. The ultrasonic evidence of an anechoic slit and the associated parenchymal loss became possible in antenatal ultrasound [2]. Besides antiepileptic drugs, surgery has an important role in the treatment of drug-resistant partial epilepsies, and to benefit from a better recovery potential when it is achieved early. It can be considered in several contexts: refractory seizures, or treated with excessive doses of drugs; partial seizures always identical, or constant EEG focus, suggesting a localised and stable origin; epilepsy for which a more or less localized lesion is observed on the MRI [11,18]. This has been described in a patient with unilateral schizencephalitis and poorly controlled complex partial seizures that have been observed to be focal on the temporal lobes. The anterior temporal lobectomy allowed almost complete control of convulsions. Despite the extensive malformation, a relatively restricted resection was very advantageous [19].

Surgical treatment may then be discussed, but preliminary data from SEEG explorations are in favour of complex epileptic networks, far exceeding the extent of structural abnormalities [20] making surgical cure often impossible because of the central topography of lesions and of the presence of extensive epileptogenic zones [2].

Ethical statement

I testify, on behalf of all co-authors, that our article submitted to anesthesia critical care and pain medicine has not been published in whole, or in part, elsewhere; the manuscript is not currently considered for publication in another journal; all authors have been personally and actively involved in substantive work leading to the manuscript and will hold themselves jointly and individually responsible for its content.

Disclosure of interest

The authors declare that they have no competing interest.

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Available online 31 July 2018