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Case Report

Neurosurgery for intractable epilepsy in pregnancy: A case report

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ABSTRACT

We describe the management of a 39-year-old woman with intractable focal epilepsy whose condition deteriorated during pregnancy and who required emergency neurosurgery. A literature search did not identify any previous reports of epilepsy surgery in pregnancy. To our knowledge, this is the first time surgery was planned and executed in rapid order with a successful outcome, without obstetrical or surgical complications and seizure freedom achieved. The value of rapid communication between established women's health advanced nurse practitioner clinics, the multidisciplinary Epilepsy Surgery Group and specialist Obstetrical Epilepsy service is highlighted. A care cycle for pregnant women with refractory epilepsy is proposed.

Introduction

Epilepsy is a chronic neurological disorder affecting approximately 40,000 people in Ireland and 50 million worldwide. It is characterised by a predisposition to recurring seizures, which result from abnormally synchronous firing of neurons in the brain [1]. Globally, around 15 million women with epilepsy are of childbearing age (12–51 years). Pregnant women with epilepsy account for 0.3% and 0.5% of all pregnancies worldwide, some 600,000 annually [2]. Anti-Seizure medication (ASM) is used during pregnancy to avoid maternal and foetal complications associated with seizures despite the risks, such as major congenital malformations and neurodevelopmental delays [3]. Tonic-clonic seizures are associated with risks to the foetus and the pregnant woman [2]. Other seizures are thought to be less harmful but may be associated with injury, intrauterine growth retardation and premature delivery [2]. Uncontrolled seizures are associated with a tenfold increase in maternal mortality. Deaths are predominantly seizure related, and most are due to sudden unexpected death in epilepsy (SUDEP) [4]. Sveberg [5] explored the impact of seizures on the developing foetus and found that focal aware seizures are relatively innocuous to the foetus, but focal seizures with impaired awareness carry the risk of trauma. In two case reports, Nei [6] and Sahoo and Klein [7] describe a drop in foetal heart rate during focal seizures with impaired awareness. Hypoxia and lactic acidosis are associated with tonic-clonic seizures, including focal to bilateral tonic-clonic seizures, which, during pregnancy, may be transferred through the placenta to the foetus and result in asphyxia [8]. An association with the occurrence of all types of seizures and small foetal size for gestation as well as pre-term delivery and low birth weight was also found [9].

Despite newly emerging diagnostic and therapeutic techniques, intracranial pathologies requiring urgent neurosurgical treatment in the obstetric setting still pose a challenge for clinicians in the absence of clinical guidelines. An individualised, interdisciplinary treatment approach, with the shared primary concern of the mother's health and safety, is necessary to develop an effective treatment strategy for both the expectant woman and her offspring [10].

Case

A 39-year-old right-handed woman with known focal epilepsy reported an 500-fold increase in daily seizures and a change in seizure semiology after becoming pregnant, G3P2ab1. The patient was diagnosed with epilepsy aged 7. Her most typical seizure was focal aware non-motor onset event with behavioural arrest.

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There were no epilepsy risk factors apart from an underlying structural abnormality. Four therapeutic trials of appropriate ASMs had failed, and the patient was therefore diagnosed with pharmacoresistant epilepsy. An epilepsy surgery evaluation referral was advised previously but declined by the patient as she did not feel that the burden of seizures warranted neurosurgery. The patient was a stay-at-home mother.

Pre-pregnancy seizure burden did not significantly affect the patient's family life, and while not seizure-free, she had reached the balance of seizure frequency versus side effects of ASMs. On reporting her pregnancy to the epilepsy service, she was referred to the Epilepsy Women's Health Advanced Nurse Practitioner Clinic. Epilepsy and pregnancy education, caring for herself, seizure triggers, SUDEP and baby care post-partum were provided. At the initial review at ten weeks gestation, the patient reported a minor increase in the frequency of previously behaviourally bland focal aware seizures she had experienced throughout life, from 1/week to 1–3/week. Pre-pregnancy ASMs were Lamotrigine 175 mg BD and Levetiracetam 1500 mg BD. During this consult, the patient was advised to titrate Lamotrigine to 250 mg BD.

Early in the second trimester, seizures evolved to hyperkinetic events occurring 3 – 4 times per night. Daytime events began to emerge with associated falls and injury risk. These seizures were unresponsive to an increase in ASMs. At the follow-up review, 16 weeks gestation, 44 events were reported in 4 weeks from August- September 2020. She described two distinct seizure events: one occurring from sleep and consisting of thrashing of all limbs, too brief to video. The second started with a strange feeling, plucking at clothes, vocalisation and being unable to respond but with retained awareness of surroundings and ability to hear those around. Her medication regime at this time was Lamotrigine 250 mg BID and Levetiracetam 2000 mg BID; ASM levels were therapeutic.

A prior routine electroencephalogram (EEG) in February 2018 captured the awake and drowsy states. No interictal epileptiform activity was reported. A 24-hour ambulatory EEG (Dec 2019) showed no definite EEG cortical change associated with captured stereotypical events. A lack of video and poor diary keeping limited the study. MRI Brain 1.5 T (Jul 2014) showed high signal abnormality within the subcortical white matter, and grey matter of the right frontal lobe appeared unchanged when compared to the report of MRI 2003 and likely representing a focus of gliosis or cortical dysplasia (Fig. 1A).

The patient's case was discussed at the weekly multidisciplinary team meeting. She was subsequently referred to the National Epilepsy Surgery Service in Beaumont Hospital, located in the same city, for video EEG monitoring to provide diagnostic clarification of her epilepsy, locate the focus (foci) of activity, and quantify the burden of seizures. An advanced nurse practitioner, with a special interest in patients with medically refractory epilepsy, coordinated care between centres. The national epilepsy care programme uses a bespoke shared electronic record to ensure continuity of care between epilepsy centres [11]. Continuous video EEG monitoring was performed in Beaumont Hospital from 02/10/20 until 08/10/20 at 19 weeks gestation. EEG samples were reviewed daily. Interim reports were generated as required.

A well-formed background rhythm was documented during the hospitalisation, with occasional right anterior quadrant, F8, F4 maximal sharp waves, which were also seen at Fp2, T4 and C4. Nineteen electroclinical seizures were recorded without drug withdrawal. The seizure were of two types, one with a characteristic behavioural arrest but with apparent loss of awareness and, most notably, a second where this progressed to a hyperkinetic event with thrashing limbs and side-to-side movements. The latter would mainly arise from sleep. The EEG signature in each case showed a right anterior quadrant onset, suggestive of a right frontal signature (Fig. 2). ASMs were increased and weighted toward nocturnal dosing, administering levetiracetam, 1000 mg mane, 3500 mg nocte, and lamotrigine, 200 mg mane, 500 mg nocte. This dose change pushed events out until approximately 5 am but, but on each occasion, failed to control her seizures fully.

The case was discussed at the National Epilepsy Surgical Review Meeting (ESRM) on October 9, 2020. Representatives from neurosurgery, neurophysiology, neuropsychology, neurology and epilepsy nursing agreed that the lesion seen on her MRI in 2014 was suggestive of cortical dysplasia and represented a good candidate for lesion removal. The patient was diagnosed with pharmacoresistant frontal lobe epilepsy, with predominantly sleep-related focal to bilateral tonic-clonic seizures with occasional focal onset impaired awareness daytime events. It was acknowledged that this condition is notoriously drug-resistant, and she had a 500-fold seizure increase during her pregnancy.

The risks to the mother and the baby for the duration of the pregnancy were discussed at the ESRM with the input of The Obstetrical Epilepsy Service and anaesthesia. Consensus to proceed with urgent resection was reached given the high seizure frequency, seizure severity, high doses of ASMs required and particularly the increased risk of SUDEP in pregnancy with nocturnal seizures. The patient was duly counselled, including the potential for mood lability following both this type of surgery and birth and she chose to proceed.

On the 19th of October 2020, the patient underwent a successful focal frontal lobe resection; at 24 weeks pregnant. No cortical EEGs (phase II) or cortical mapping were performed during the resective surgery. Two auras were experienced six weeks post-op, but otherwise, she reported seizure freedom. A foetal scan showed growth appropriate for age. She successfully reduced her medication and was maintained on lamotrigine 100 mg mane 300 mg nocte and levetiracetam 500 mg mane and 2000 mg nocte for the rest of her pregnancy. Post-op imaging shows complete

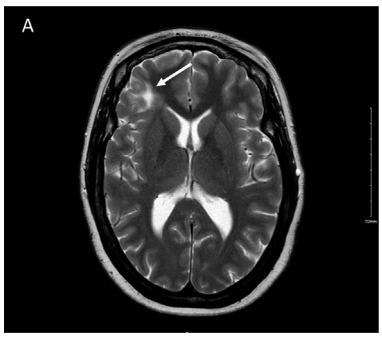


Fig. 1A. Pre-Op MRI (Axial FSE T2W) Right Fronto -lateral dysplasia(arrow).

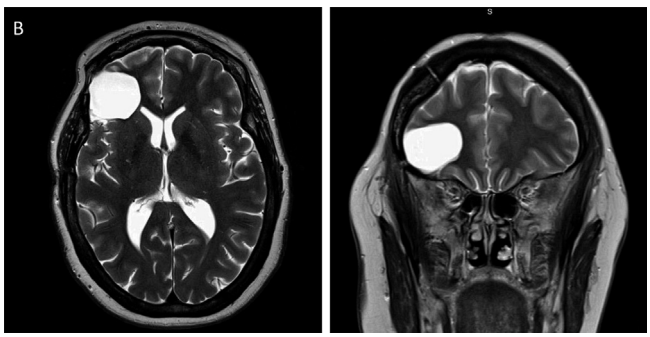


Fig. 1B. Post-Op MRI (A)Axial and Coronal FSE T2 W).

lesion removal (Fig. 1B). Histopathology analysis reported the resected specimen with architectural abnormalities, dysmorphic neurones and balloon cells representing those of a Cortical Dysplasia Palmini Type 2B (Fig. 3).

In February 2021, a baby girl was born at full term by vaginal birth with no complications. The patient remains seizure free at 28 months. Baby is two years old, growth centiles are within expected parameters, and she has achieved all developmental milestones.

Discussion

This case posed many challenges for the healthcare team. There is a dearth of information in the literature on epilepsy surgery in pregnant women. The urgency of the case, given the safety risks for this pregnant woman and her foetus from uncontrolled convulsive seizures. No precedent to guide care was identified. This was the first woman to be discussed at the epilepsy surgical meeting with a view to urgent surgical intervention during pregnancy.

The patient was on high-dose ASM polytherapy, increasing the risks of teratogenicity and neurocognitive/developmental delay. Pregnancy increases mortality risk in women with epilepsy tenfold, predominately due to sudden unexpected death in epilepsy [4]. Worsening seizure control in pregnancy, medication adherence, altered drug bioavailability, sleep deprivation, exhaustion, and psychological stress are all contributing factors. Chen et al. [9] found an association between seizures of all types during pregnancy and small foetal size for gestational age. Moreover, seizures during pregnancy were more likely to be associated with preterm delivery and lower birth weight.

The effects of antiepileptic drugs on intrauterine growth were discussed by Tomson [2]. They noted that treatment with certain ASMs is associated with an increased risk of intrauterine growth restriction, concluding that Valproate is associated with the highest risk of inducing MCMs, phenobarbital and topiramate with intermediate risks. ASM polytherapy has traditionally been thought to mean a higher risk of MCMs than monotherapy [1], but more recent data suggests that the type of ASM rather than the number of ASMs is more important. Over the past 50 years, research has shown that ASMs increase the risk of foetal anomalies. In a systematic review, lamotrigine or levetiracetam posed no additional potential to cause major congenital malformations (MCMs) [12] and is supported by others [13]. Findings from three major registries, the NAAPR, UK and Ireland Register and EURAP, confirm a lower risk with lamotrigine and levetiracetam compared to other ASMs. The lowest risk was associated with lamotrigine at < 325 mg/day at conception. The inclusion of valproate or topiramate appears to increase the prevalence of MCMs [14].

Focal cortical dysplasias (FCDs) are common causes of medically refractory epilepsy and are highly epileptogenic [15]. Both

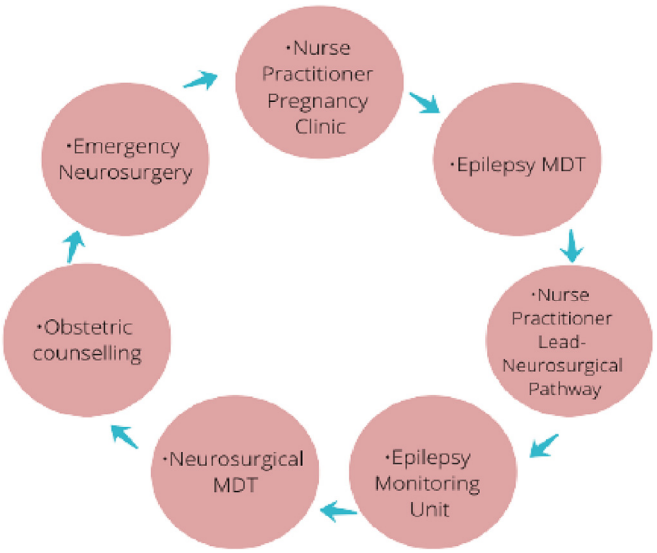
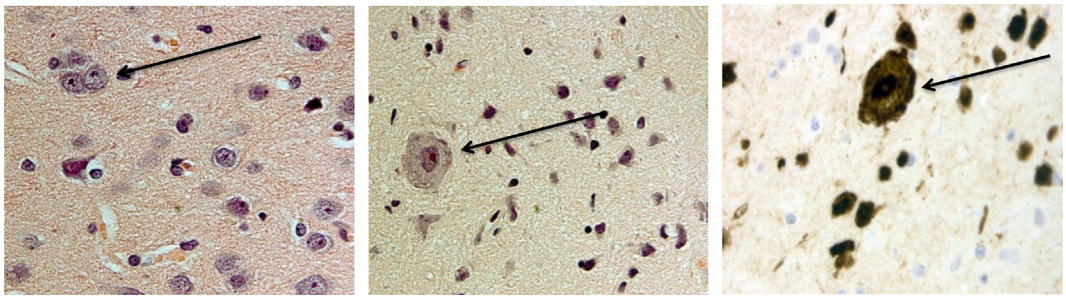
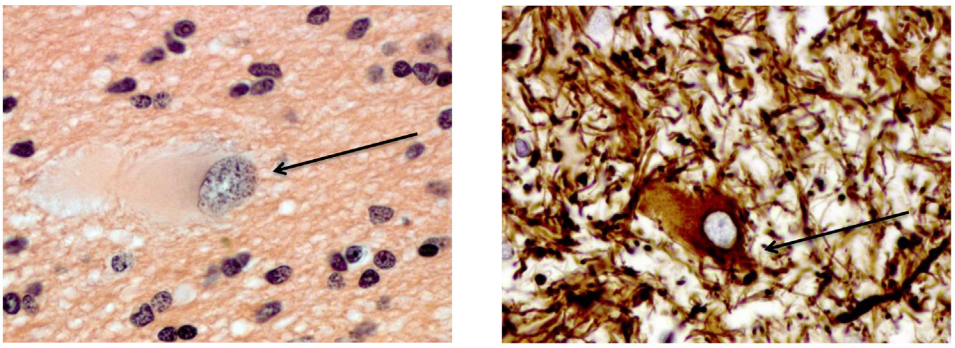


Fig. 3. Care cycle for pregnant women with epilepsy and increased seizures.



Dysplastic Neurones H+E X 40 | Dysplastic Neurones H+E x 40 | Dysplastic Neurones CD34 x 60



Balloon cells H+E X 60 | GFAP X 60

Fig. 2. All seizures showed a stereotypical right anterior onset, with first visible change being irregular slowing in the right frontotemporal region (highlighted) before evolving rhythmically over the same areas.

12-month and long-term seizure freedom outcomes were found to be very good in resective epilepsy surgery patients with FCD II [16,17]. Regarding the risks of the surgery, the main concern was the use of anaesthesia. Regional anaesthesia is considered safer in pregnancy than general anaesthesia due to the possibility of laryngeal oedema and changes in maternal posture during pregnancy, but the mode of anaesthesia was chosen with the best surgical outcome in mind.

The foetus is often exposed through placental transport to the same drugs as the mother during anaesthesia. Still, no serious adverse outcomes in the foetus have been associated with either general or regional anaesthesia [18]. Changes in maternal physiology, such as profound hypotension from blood loss etc., during surgery, can have consequences for the developing foetus, so careful balancing of risks and benefits of the surgery needs to be undertaken. In 2016 the Food and Drug Administration issued a warning of the potential risks of prolonged (greater that 3 h) anaesthetic exposure on brain development in young children and fetuses [19]. This warning has been criticised, The American College of Obstetricians and Gynecologists has supported these criticisms and emphasised that it should not discourage the performance of any indicated surgical procedure [20].

Women with epilepsy, prior to pregnancy, require preconceptual advice related to optimise pregnancy outcomes. The majority of women with epilepsy will remain stable when pregnant but data suggests for pregnancies with seizures occurring in the first trimester and those exposed to lamotrigine and proactive approach to adjusting doses of ASMs should be taken [21]. In this case, despite significant increases to ASMs, seizure control could not be achieved. Nevertheless, the established pathway of care (Fig. 3) between the ANP-run women's health clinic, the epilepsy surgery service, and the obstetrical epilepsy service ensured rapid response and an overall favourable outcome. In short, balancing the foetal and maternal risks associated with seizures against the teratogenic risks associated with exposure to increasing doses of ASMs during pregnancy and the potential risks of anaesthesia favoured proceeding with emergent neurosurgical resection.

Ethical statement

Hereby, I /insert author name/ consciously assure that for the manuscript /insert title/ the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors and co-researchers.
5) The results are appropriately placed in the context of prior and existing research.
6) All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference.
7) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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