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CASE REPORT

COL4A1 mutations should not be a contraindication for epilepsy surgery

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Abstract
Purpose We describe the first case in the literature of complication-free epilepsy surgery in a paediatric patient with collagen type IV alpha 1 (COL4A1) mutation.
Methods This is a case report.
Results COL4A1 mutations disrupt the integrity of vascular basement membranes, so predisposing to a broad spectrum of disorders including periventricular leucomalacia, haemorrhagic stroke, aneurysm formation, epilepsy and developmental delay. Intracranial haemorrhage is reported and may be recurrent or associated with trauma and anticoagulant therapy. Children have an increased risk of stroke with general anaesthesia. A 6-year-old girl, COL4A1 mutation positive, had drug-resistant epilepsy, cerebral palsy and developmental delay. Following presurgical evaluation, she was a candidate for corpus callosotomy. Previous general anaesthesia had been uncomplicated. Preoperative full blood count and coagulation studies were normal. Perioperatively, normotension was maintained, and anticoagulation was avoided. A complete corpus callosotomy was performed with no intracranial haemorrhage or other perioperative complications.
Conclusion Although there is an increased risk of intracranial haemorrhages in COL4A1 patients, this is not clearly quantifiable. There are minimal data in the literature on the subject. COL4A1 mutations should not be a contraindication for presurgical evaluation. Each patient should be individually evaluated and assessed, risks and benefits were carefully weighed, and informed decisions were reached after thorough discussions with patients and families.

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Introduction

Collagen type IV alpha 1 (COL4A1) mutations cause abnormalities in the integrity of vascular basement membranes [1] and predispose to a broad spectrum of systemic and intracranial disorders including white matter changes, periventricular leucomalacia, haemorrhagic stroke, aneurysm formation, epilepsy, developmental delay and ocular and renal abnormalities [2]. There is a documented but not clearly quantifiable risk of intracranial haemorrhages which are often recurrent. While spontaneous haemorrhage and asymptomatic bleeds have been described, trauma, physical exercise and anticoagulant use have been suggested as risk factors in affected individuals [2]. Inheritance is autosomal dominant, but de novo cases have also been described [3]. We describe the first case in the literature of epilepsy surgery in a paediatric patient with COL4A1 mutation, with no adverse consequences.

Case report

A 6-year-old female who had had structural focal epilepsy and developmental delay since early childhood was referred for consideration of epilepsy surgery. She was one of di-chorionic di-amniotic twins and was born at 36 weeks, weighing 2.52 kg, by elective caesarean section for intrauterine growth retardation of the other foetus. She was in good condition at birth, and the postnatal period was unremarkable. Her twin sister had a facial haemangioma. Family history was otherwise non-contributory.

Strabismus was noted at 6 months and right-sided motor neglect at 9 months of life. Her gross motor skills were delayed, and she eventually developed bilateral spastic/dystonic cerebral palsy (GMFCS levels I and II) with right side weaker than left, and legs were more affected than arms. She also showed mild learning difficulties and behavioural difficulties.

She experienced her first epileptic seizures around 2 years of age. These were initially described as vacant spells with vomits on occasion, quickly evolving in weeks to episodes of right arm and leg stiffening with eye flickering to the right side. Episodes were short (5 s) but escalated rapidly to occur 20 times a day. Sodium valproate was initiated, and she remained seizure-free for 6 months. Seizures returned and were characterised by tonic posturing involving the right more than the left side of the body, followed by or intermixed with epileptic spasms, in isolation or in clusters, flexor or extensor in nature, often with a right hand lead. She never experienced generalised tonic-clonic episodes or required PICU admissions for prolonged seizures. She had failed multiple anti-epileptic drugs: sodium valproate, carbamazepine, levetiracetam, clobazam, topiramate, oral prednisolone, phenytoin and lamotrigine. The ketogenic diet had also been trialled with partial benefit, but intolerable side effects of irritability and aggression. At the time of presurgical evaluation, she was on oxcarbazepine (27 mg/kg/day) and vigabatrin 82 mg/kg/day).

The interictal EEG background was slow, with multifocal discharges independently involving the midline and right frontal region. At ictal onset, the EEG showed a discharge followed by a broad slow wave with attenuation, followed by runs of spike activity, mainly over the midline and right frontal region. Despite the asymmetric clinical semiology, the EEG did not demonstrate consistent lateralisation or localisation.

Magnetic resonance imaging (MRI) at 3 years of life showed bilateral signal abnormality and atrophy of the periventricular white matter, more severe on the left, and extending to involve the posterior limb of the left internal capsule, with signs of previous germinal matrix haemorrhage. The corpus callosum was thinned, and the overall features were consistent with periventricular leucomalacia (Fig. 1). A follow-up scan at 6 years of life showed no progression of disease. Extensive neurogenetic workup revealed a positive COL4A1 mutation.

The patient was discussed at multi-disciplinary epilepsy surgery conference, and in the context of multi-focal, bilateral MRI and EEG abnormalities, a decision was made to offer a corpus callosotomy with a view to reduce the tonic seizures and, possibly, to allow for emergence of localisation. The risks and benefits of the procedure were discussed extensively with the patient's family. In favour of surgery, the epilepsy was drug-resistant and had had a major negative impact on the patient's quality of life. Conversely, the COL4A1 mutation implied additional risks associated with epilepsy surgery. The degree of excess risk was unclear, and there was minimal literature on which to base the risk benefit analysis. On balance, the decision to offer surgery was based on the severity of the epilepsy, and following the consenting process, the parents were keen to proceed with the operation.

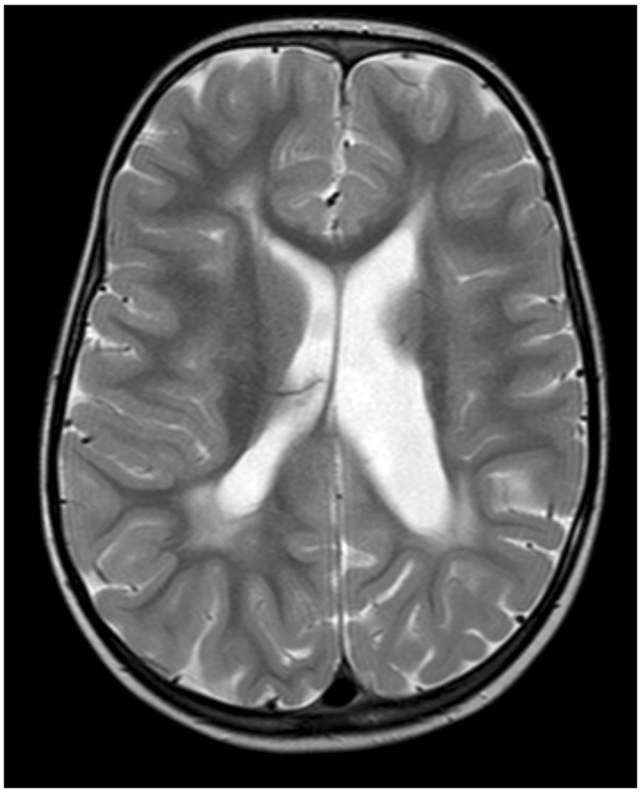

Fig. 1 MRI brain at the age of 5 years and 11 months. Axial T2-weighted image at the level of the lateral ventricles showing the asymmetrical brain atrophy, worse on the *left*, with periventricular scarring and presence of corpus callosum

Previous general anaesthesia had been uncomplicated. Preoperative full blood count and coagulation studies were normal. Routine anaesthetic technique (including propofol for induction and fentanyl and atracurium bolus followed by infusion of remifentanyl at 3 mg/kg/min) was utilised, maintaining normotension.

Complete corpus callosotomy was performed in a standard manner. The patient was positioned in supine with the head in a pin fixation device. Neuronavigation registration (Medtronic Stealth) to a preoperative MRI data set was performed. Prophylactic amikacin and flucloxacillin antibiotics were administered. A linear transverse skin incision was made at the level of the coronal suture, and craniotomy was performed across the midline. Due to the pre-existing right-sided weakness, the dura was opened to the left of the midline. The interhemisheric fissure was identified, and dissection to the corpus callosum was performed. A complete corpus callosotomy from the rostrum to the splenium was performed using micro-

dissectors, and the extent of disconnection was checked with neuronavigation. The ventricular system was not breached. A watertight dural closure was performed, and the craniotomy flap was fixed with absorbable sutures. The wound was closed in layers. The operative course was uneventful with no significant intracranial haemorrhage. The patient made an uncomplicated recovery and was discharged to home on day 5 postoperatively. She remained seizure-free and without any complications at 4 months after the operation.

Discussion

This is the first report in the literature of epilepsy surgery in a patient with COL4A1 mutation. The apparent increase risk of intracranial haemorrhage related to neurosurgical procedures has, therefore, not been quantified.

The increased perioperative risk is likely to be multifactorial. Abnormalities in the structural integrity of vascular basement membrane predispose to haemorrhage, and in addition, there is an increased incidence of cerebral aneurysm formation in patients with COL4A1 mutations which further increases the risk of perioperative intracranial haemorrhage. In the case reported here, preoperative MRI angiography was not performed. Increased risk of stroke following general anaesthesia has also been suggested [4]; however, our patient had undergone previous general anaesthesia with no complications. No specific haematological abnormalities have been associated with COL4A1 mutations. The only COL4A1-associated blood test abnormalities reported in the literature are a mild decrease in glomerular filtration rate and increased creatine kinase levels in patients with HANAC (hereditary angiopathy, nephropathy, aneurysms and cramps) syndrome. This syndrome has a different clinical presentation with usually asymptomatic small vessel brain disease and is caused by mutations localised within the CB3[IV] fragment of COL4A1, which encompasses major integrin binding sites [5].

As part of the presurgical evaluation, the individual risks and benefits should be carefully weighed, and informed decisions were reached after thorough and frank discussions with patients and their families. If surgical options are pursued, we suggest that routine preoperative full blood count and coagulation studies are performed in order to identify any additional haemorrhagic risk. No specific anaesthetic or surgical techniques have been suggested to reduce perioperative risk. In the case reported here, it was felt that the epilepsy was so severe and disabling that we could justify offering surgical treatment. COL4A1 mutation has only recently been identified, and it is therefore likely that patients with undiagnosed COL4A1 mutations have undergone epilepsy surgery in the past. In our opinion, COL4A1 mutation should not be an absolute contraindication for epilepsy surgery. Our case demonstrates that epilepsy surgery may be a viable management option for patients with COL4A1 mutation and medically refractory epilepsy.

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