Epilepsy & Behavior Case Reports 8 (2017) 73–84

Contents lists available at ScienceDirect

Epilepsy & Behavior Case Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

Six adult patients with septo-optic dysplasia and drug-resistant epilepsy: Clinical findings and course☆,☆☆,★,★★,☆☆☆

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ARTICLE INFO

Article history:
Received 10 October 2016
Received in revised form 26 March 2017
Accepted 7 April 2017
Available online 19 April 2017

Keywords:
Septo-optic dysplasia
Seizures
Epilepsy
Drug-resistant
Cortical malformation
Seizure surgery

ABSTRACT

Septo-optic dysplasia (SOD) is a rare disorder associated with optic nerve hypoplasia, pituitary abnormalities and agenesis/dysgenesis of midline brain structures including the septum pellucidum and corpus callosum. Though sometimes associated with drug-resistant epilepsy, this association has not been well studied. We report six SOD patients with associated malformation of cortical development (MCD) and drug-resistant epilepsy who underwent video-EEG telemetry at our centre between 1998 and 2016 for drug-resistant epilepsy. Three then underwent surgery; right temporal neocortical resection, right functional hemispherectomy and placement of a vagus nerve stimulator. Clinical findings and the patients' ultimate courses are discussed.

1. Introduction

Septo-optic dysplasia (SOD) is an uncommon developmental anomaly, initially described in 1941 [1] and again in 1956 [2], that has an estimated incidence of roughly one per 10,000 live births [3]. Occurring in both males and females, it is classically characterized by the triad of optic nerve hypoplasia; midline brain abnormalities that include the absence of the corpus callosum and septum pellucidum; and hypothalamic-pituitary endocrine deficiencies [4–6]. However, it also appears in conjunction with a wide variety of cerebral anomalies, albeit most consistently with schizencephaly [7–13], such that the term SOD-Plus was recently proposed to describe SOD associated with cortical dysplasia [8]. The clinical presentation of SOD can range from mild to no symptoms [14,15] to severe developmental delay and incompatibility with life. It also can be associated with mild to severe visual impairment, sensorineural hearing loss, and a range of other symptoms and signs that include a variety of endocrine disorders including precocious puberty, dwarfism and diabetes insipidus; other skeletal abnormalities; anosmia; and a range of cardiac anomalies, among others [5,7,8,10,16–22]. Seizures have also been described, which range from infantile spasms [23–25] to a variety of drug-resistant epilepsies presenting either during childhood or adulthood [4,5,9,11,13,19,20,26–31]. However, most published reports on patients with seizures and SOD are limited to a single case report or at most series that include a few patients. (See Table.)

In this report, we review the clinical features associated with SOD in six adult epilepsy patients. Ages ranged from 18-58 years. All had drug-resistant seizures and were seen between 1998 and 2016 for video-EEG telemetry in the Epilepsy Monitoring Unit (EMU) at the University Hospital at the London Health Sciences Centre (LHSC). These cases are first summarized individually and then analyzed collectively.

☆ Statistical analysis conducted by: Kevin, MD, PhD, Western university.
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★ Author contributions: McLachlan; Patient recruitment. Diosy: Patient recruitment. Burneo: Patient recruitment. Mirsattari: Manuscript revision and study design.
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☆☆☆ Author disclosures: All authors report no disclosures.

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http://dx.doi.org/10.1016/j.ebcr.2017.04.001

Table
Radiological Features (MRI)-Surgery and seizure outcomes.

Case	MRI brain	Hypothalamic-pituitary axis/ MRI	Seizures	Surgery	Seizure outcome
1	Bilateral frontal lobe schizencephaly and pachygyria	Normal	Refractory	No	Unchanged on ASDs
2	Bilateral perisylvian cortical dysplasia and polymicrogyria	Normal	Refractory	VNS	The outcomes should be listed as "Class 5" etc. The classification system used should be referenced at the end of the table. Class 5 ILAE Less than 50% reduction of baseline seizure days.
3	Multiple congenital abnormalities including cortical dysplasia, heterotopic grey matter and agenesis of corpus callosum.	Normal	Refractory	Right functional hemispherectomy	Class 3 ILAE One to three seizure days per year, with and without aura
4	Multiple congenital abnormalities including cortical dysplasia, bilateral closed lip schizencephaly, cortical heterotopia, absence of the septum pellucidum, small optic nerves bilaterally, a small optic chiasm and hypoplastic pituitary gland.	Hypoplastic anterior pituitary	Refractory	Right temporal neocortical resection	Class 4 ILAE Four seizure days per year to 50% reduction of baseline seizure days, with and without auras.
5	Multiple congenital abnormalities including, absence of the septum pellucidum, hypoplasia of chiasm and optic nerves, agenesis of corpus callosum and heterotopia.	Normal	Refractory	No	Unchanged on ASDs
6	Partial agenesis of the corpus callosum, hypogenesis of the anterior commissure and the optic chiasm,heterotopia and white matter changes.	Normal	Refractory	No	Unchanged on ASDs

2. Cases

Case 1: A 57-year-old female and presented to the EMU with intractable seizures. Neuro-ophthalmic examination revealed absent visual fixation, pendular nystagmus and bilateral disc pallor, as well as fundoscopically-confirmed hypoplasia of both optic discs with visual impairment from age 6 months. Magnetic resonance imaging (MRI) of the brain revealed SOD, as well as open-lipped schizencephaly affecting both frontal lobes and pachygyria (Fig. 1a). Video-EEG monitoring revealed both epileptic and non-epileptic seizures, with the interictal EEG showing abundant multifocal slow waves “from several different areas of the brain”, and left temporal spikes during sleep. Thirteen non-epileptic spells were captured, characterized by either the sensation of shaking, right-sided weakness, and irregular shaking and grunting, all associated with preserved alpha rhythms and semiology of non-epileptic behavioral events. Five epileptic seizures occurred. These were characterized by generalized stiffening followed by asymmetric right arm tonic posturing, followed by symmetric tonic then clonic seizure activity with diffuse muscle and movement artifact, the onset non–localizable on EEG. However, the interictal EEG revealed abundant multifocal slow waves and left temporal spikes during sleep (Fig. 1b). The patient's seizures were resistant to three different antiseizure medications.

Case 2: A 33-year-old male presented to the EMU with drug-resistant seizures. In addition to SOD, MRI of the brain showed bilateral perisylvian cortical dysplasia and polymicrogyria involving the frontal and parietal lobes, in addition to right-sided band heterotopia. (Fig. 2a). Prolonged EEG recording displayed independent bi-temporal spikes, particularly in the area of the perisylvian polymicrogyria, and were more frequent in the right hemisphere, than the left as well as independent bi-temporal slowing (Fig. 2b). The ictal EEG revealed seizures originating in the right cerebral hemisphere. The patient underwent subdural EEG recording, which demonstrated principal spike activity in the right temporal region, though regional spikes were also noted elsewhere within the right henisphere. He subsequently underwent placement of a vagus nerve stimulator, which was unsuccessful at controlling his seizures.

Case 3: An 18-year-old female with psoriatic arthritis presented with drug-resistant seizures in 1998, with all of her seizures originating within the right hemisphere. Her initial MRI brain showed multiple congenital abnormalities including SOD, cortical dysplasia, bilateral occipital heterotopia, right frontal cortical dysplasia, heterotopic gray matter, and agenesis of the corpus callosum. At that time, she underwent partial right functional hemispherectomy, but experienced no improvement in

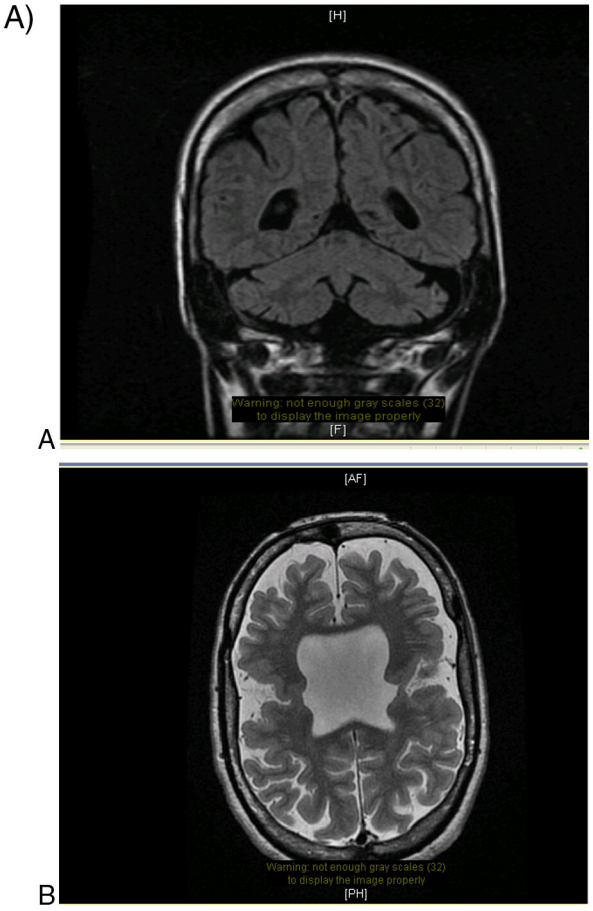

Figure 1A & B. a: Axial FSE T2 and Coronal FLAIR images: In the frontal lobes, bilaterally there is open-lipped schizencephaly. The lip extends anterior from the precentral gyrus into the lateral ventricles bilaterally. No heterotopia was present. Pachygyria is noted anterior and posterior to the clefts bilaterally. b: EEG of the patient in Case 1 with bipolar montage demonstrates: The posterior background activity contains a 11-Hz alpha rhythm. Intermixed medium to medium-high amplitude 5-6 Hz bitemporal and intermittent bursts of theta were present. Occasional semi-rhythmic 2 Hz bifrontally predominant diffuse 1-5 second runs of delta were present. A-Spikes: Principally during drowsiness and wakefulness, broad involving the F7-M1-T3 derivations. C-Seizure: Sudden muscle artifact, then rhythmic 3 Hz, later obscured by muscle artifact ending abruptly approximately 83 s after electrographic onset. Clinical onset preceded electrographic onset. Reword: Semiology involved the patient grabbing both knees first and then the hand rails, prior to elevating his right arm/flexed at the elbow prior to evolution to a generalized motor seizure with post-ictal somnolence. Patient grabs knees with hands, holds hand rail, then elevates right arm, flexed at elbow, then tonically slumps off bed with a secondary generalized seizure; sleeps postictally.