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Aicardi syndrome: epilepsy surgery as a palliative treatment option for selected patients and pathological findings

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ABSTRACT – The optimal treatment for medically refractory epilepsy in Aicardi syndrome (AS) is still unclear. Palliative surgical treatment, including vagus nerve stimulation and corpus callosotomy, has therefore been used. There is limited data on the role of resective epilepsy surgery as a treatment choice in patients with AS. Here, we describe the seizures, anatomo-pathological findings, and neurodevelopmental outcome of palliative epilepsy surgery in two children with AS who had resective epilepsy surgery at the Cleveland Clinic. The related literature is also reviewed. Case 1 had a left functional hemispherectomy and was free of seizures and hypsarrhythmia for six months after surgery. Her gross motor skills improved after surgery. Outcome at 43 months was 1-3 isolated spasms per day. Case 2 had a right fronto-parietal lobectomy. Her seizures improved in frequency and severity, but remained daily after epilepsy surgery. Neurodevelopment changes included improved alertness and recognition of caregivers. This patient died 21 months after epilepsy surgery of unclear causes. Surgical pathology in both cases showed focal cortical dysplasia associated with other findings, such as nodular heterotopia and polymicrogyria. Epilepsy surgery could be an alternative palliative treatment choice in selective cases of AS, but studies on a larger patient cohort are needed to identify the possible role of surgery in children with AS. The complexity of the pathological findings may offer an explanation for the severity of seizures in AS.

Key words: Aicardi syndrome, resective epilepsy surgery, surgical pathology, palliative treatment, polymicrogyria, focal cortical dysplasia

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Aicardi syndrome (AS) is a severe neurodevelopmental disorder, characterized by the triad of seizures, total or partial agenesis of the corpus callosum (ACC), and chorioretinal lacunae, and almost exclusively affects females.

Seizures in AS are typically variable in semiology and frequency. Generally, the seizures are refractory to medical therapy. The prognosis of AS is related to a high rate of early mortality, considerable morbidity, and a generally poor developmental outcome. The optimal epilepsy treatment of AS is still unclear. Palliative surgical treatment, including vagus nerve stimulation (VNS) and corpus callosotomy (CC), has been previously used with variable outcome; from seizure improvement to worsening (Rosser *et al*., 2002; Saito *et al*., 2009; Kasasbeh *et al*., 2014). Additionally, improved seizure control was found following surgical resection of tumors in AS patients, such as chorioid plexus papillomas (Robinow *et al*., 1984; Donnenfeld *et al*., 1989; Taggard and Menezes, 2000).

There is limited data on the role of resective epilepsy surgery as a treatment choice in patients with AS (Rosser *et al*., 2002; Palmer *et al*., 2007; Saito *et al*., 2009). In addition, there is no information about the surgical neuropathological findings in AS. We report our experience with resective epilepsy surgery in two patients with AS and also describe the surgical pathology.

Case studies

After IRB approval, we identified eight patients with AS from the Cleveland Clinic epilepsy database. Two of them underwent resective epilepsy surgery. *Table 1* shows detailed clinical data, presurgical data, seizure outcome, and neurodevelopment changes after epilepsy surgery, as well as surgical pathology, for each case. The rest of the patients with AS who were not selected for resective epilepsy surgery continue to have daily to weekly seizures. One patient had a VNS implanted which changed the severity but not the frequency of seizures.

Case 1

Case 1 presented with seizures at 10 weeks old when she developed clusters of epileptic spams, occurring every 5-25 seconds, over 5-10 minutes; these occurred 3-10 times a day. They persisted daily after onset despite multiple AEDs and responded (50% improvement) transiently to ACTH. Her 72-hour video-EEG at the age of 14 months showed dominant epileptogenicity in the left hemisphere (90% left and 10% right interictal sharp waves) with epileptic spasms, showing a more pronounced evolution in the left hemisphere, lateralized by voltage (*figure 1C, D*). Video-EEG monitoring confirmed intractable epileptic spasms and axial tonic seizures with non-localizable ictal patterns, and her cognitive development was delayed significantly. Serial brain MRI and PET showed progressive worsening of left hemispheric atrophy and hypometabolism (*figure 1A*). Her right hemisphere had matured and become more normal. After serial presurgical evaluations, left hemispherectomy was deferred in favour of antiepileptic medication trials due to her diagnosis of AS and low confidence based on the benefit/risk ratio. Over the course of five years, she gained many developmental milestones despite daily spasms that did not respond to a variety of medical interventions. The right hemiparesis became more obvious. At age six and a half years, she had a left functional hemispherectomy.

After surgery she was seizure-free for six months. Her EEG showed resolution of hypsarrhythmia (*figure 1E*). Her development made remarkable progress. She had good eye contact, smiled, sat by herself, and learned to stand up with assistance. She practiced horse riding and enjoyed playing with toys. Her intellectual age developed to a level equivalent to a healthy child of around 12 months after the epilepsy surgery. Six months after the surgery, she had a recurrence of daily clusters of asymmetric epileptic spasms, 1-3 times per day, that led to developmental regression. Nevertheless, spasms were easier to control on combination therapy of valproate and clonazepam. Incomplete disconnection was considered a possibility as an explanation for seizure recurrence and hence anatomical hemispherectomy was discussed but placed on hold. Currently, this patient is 10 years of age. At the last follow-up visit, 42 months after the epilepsy surgery, she had 1-3 isolated spasms upon awakening only.

Case 2

Case 2 had a more severe disease course. She had global developmental delay since birth, left hemiparesis, and right microphthalmia. Initial seizures at four weeks of age were asymmetric flexor spasms with extension of the left arm and eye deviation to the right. She had about 10 clusters of spasms per day, lasting 5 to 15 minutes, with 50 to 100 spasms per cluster.

Her MRI (*figure 2*) showed bilateral diffuse brain malformation, with more severe focal malformation in the right fronto-parietal region, agenesis of the corpus callosum, and very delayed myelination of the deep structures and midbrain.

At age 17 months, during the video-EEG evaluation, sharp waves during wakefulness predominantly appeared from the right hemisphere, maximum in the right frontal region (>90% of discharges), and she also had right parietal sharp waves (10%).

Table 1. Clinical and presurgical data, seizure outcome, and neurodevelopment changes after epilepsy surgery, and surgical pathology in patients with AS who underwent epilepsy surgery.

	Case 1	**Case 2**
Clinical data:		
-Age at onset	10 weeks	4 weeks
-Initial seizures	Infantile spasms	Infantile spasms
-Seizure frequency at onset	7-12 spasms per cluster, each spasm 2-3 seconds, no isolated spasms	50-100 spasms per cluster, each spasm lasting a few seconds with random isolated spasms
-Development at seizure onset	Able to track and turn to sounds, lift her head, unable to roll	Severe global delay since birth
Examination:		
-Eye examination	Bilateral chorioretinal lacunae	Coloboma, micro-ophthalmia and right eye blindness
-Neurological examination	Right hemiparesis	Mild left hemiparesis
Presurgical evaluation:		
-Seizure type	Hypomotor seizure -> epileptic spasms/axial tonic seizures (in clusters)	Complex motor seizure -> automotor seizure -> right leg tonic seizure
-Seizure frequency	2-3 clusters per day lasting 2-3 minutes / 15-20 spasms per cluster No isolated spasms	10 clusters of spasms per day, lasting 5-15 minutes / 50-10 spasms per cluster Isolated spasms present during the day
-EEG	*See figure 1*	*See figure 2*
-Brain MRI		
-PET scan	Diffuse hypometabolism in left hemisphere sparing visual cortex	Severe hypometabolism in right frontal, parietal and temporal region and to a lesser degree in the left temporal lobe
-Ictal SPECT	Not done	Potential ictal zone in right posterior insula and adjacent frontal, parietal, and temporal operculum
Surgery:		
-Age	6 years 9 months	1 year 10 months
-Type of surgery	Left functional hemispherectomy	Right fronto-parietal lobectomy
Surgical outcome:		
-Seizure outcome	Seizure-free 6 months after surgery	50% seizure reduction after surgery
-Developmental outcome	Mental status and behaviour: improved alertness, affect, behaviour and growth Gross motor: able to grab toys with left hand, sits up and pulls to sit, stands up and stands for 2 hours, walks with walker Language: non-verbal	Mental status: recognizes parents and responds to noises Gross motor: does not hold objects, needs full support for sitting Language: non-verbal
Surgical pathology	Malformation of cortical development -Mild focal architectural disorganization -Neuronal cytomegaly Perivascular white matter atrophy Hyaline protoplasmic astrocytopathy Focal perivascular chronic inflammation Hippocampus hamartia	Malformation of cortical development; architectural disorganization Focal nodular heterotopia Perivascular white matter atrophy Benign choroid plexus cyst

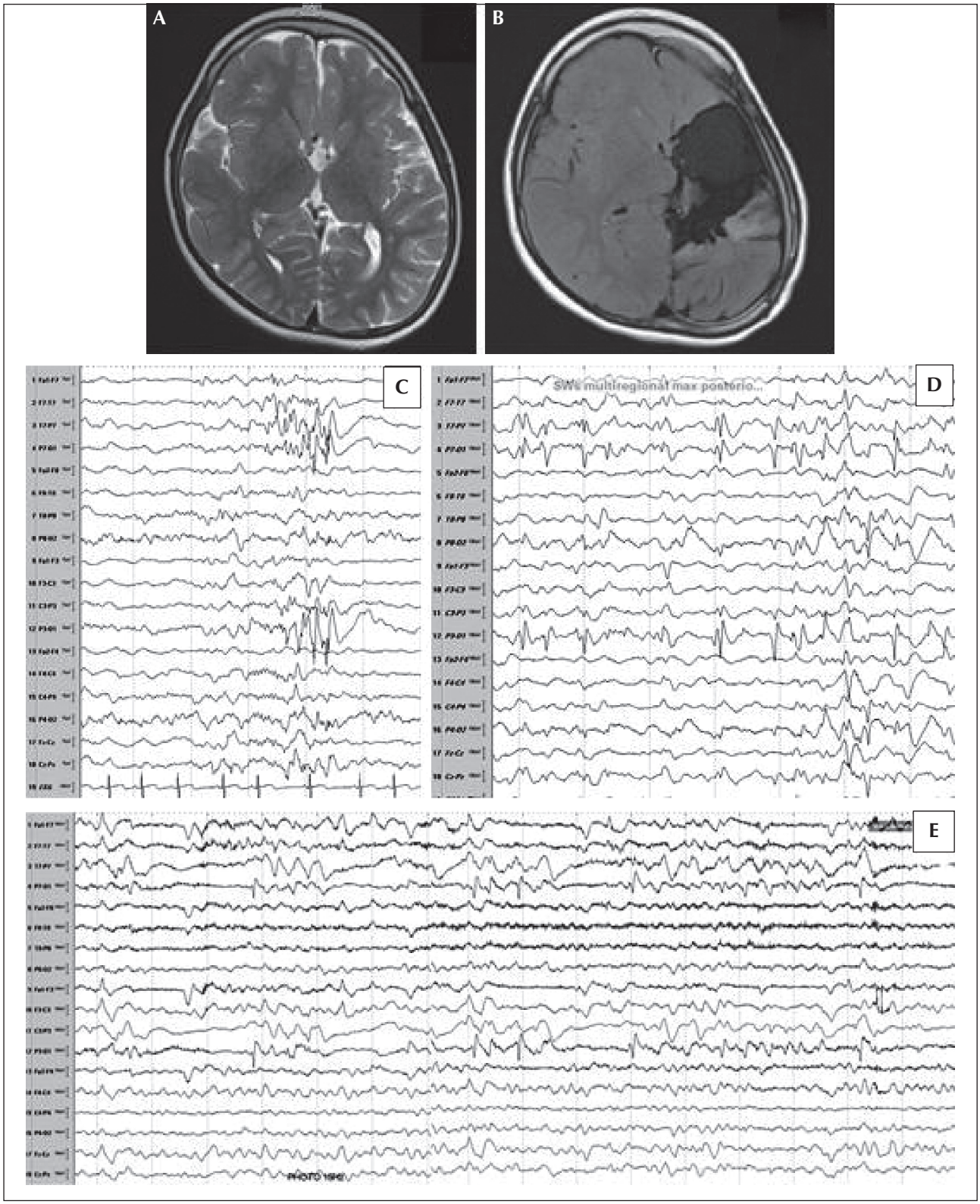

Figure 1. Case 1. (A) Pre-op MRI: partial agenesis of corpus callosum, with left frontal polymicrogyria. (B) Post-op MRI: left functional hemispherectomy. (C) EEG at seizure onset: left posterior spikes and reduced spindles in the left hemisphere. (D) EEG six months before surgery: multiregional spikes (hypsarrhythmia). (E) EEG six months after surgery: hypsarrhythmia was resolved.

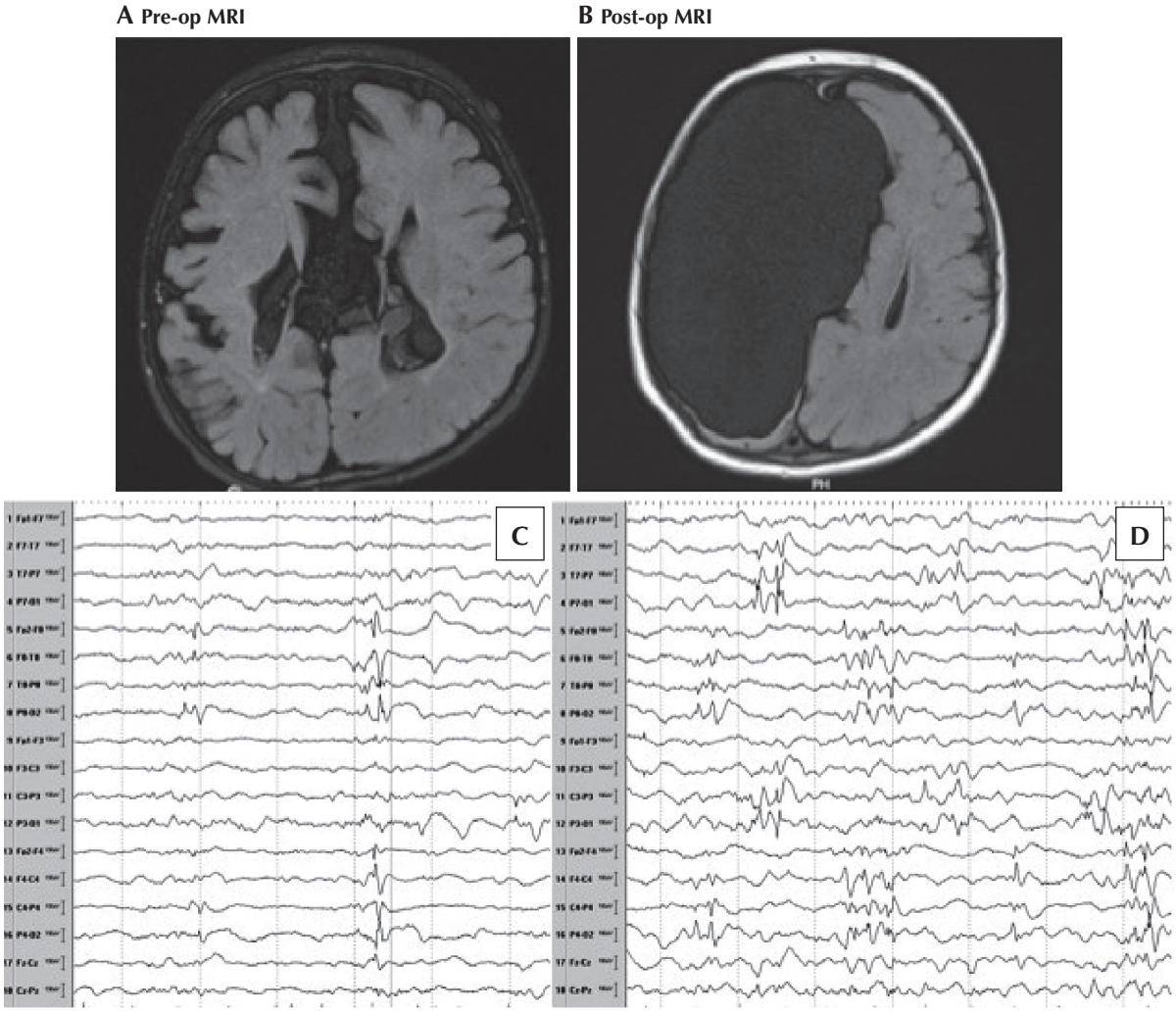

Figure 2. Case 2. (A) Pre-op MRI: callosal dysgenesis, interhemispheric and intraventricular cysts, and right frontal lobe malformation with gyral distortion. (B) Post-op MRI: right fronto-parietal lobectomy. (C) EEG four months before surgery, during wakefulness: 90% of discharges comprised right frontal sharp waves; about 10% of discharges comprised right parietal sharp waves. (D) EEG four months before surgery, during sleep: discontinuous, asynchronous "checkerboard" pattern with bursts of asynchronous left and right hemisphere spiking and intervals of relative cerebral quiescence.

However, during sleep, interictal EEG showed multifocal sharp waves bilaterally, appearing in a discontinuous, asynchronous "checkerboard" pattern, with bursts of asynchronous left and right hemisphere spiking and intervals of relative quiescence. EEG seizures during 15 complex motor seizures were non-localizable, with diffuse flattening and intermittent rhythmic alpha activity, maximum on the left hemisphere.

PET showed severe hypometabolism in the right frontal, parietal, and temporal regions. Ictal SPECT showed hypermetabolism in the right posterior insula and adjacent right frontal, parietal, and temporal operculum. The MRI and awake interictal EEG also supported that the right frontal, insular, and parietal region might be the predominant epileptogenic regions. Nevertheless, the prognosis of a favourable seizure-free outcome was guarded, in light of bilateral abnormalities on MRI and EEG.

Palliative surgery was offered with the understanding that resection of the severely malformed right fronto-parietal region may be of benefit. She had right fronto-parietal lobectomy at age 1 year and 10 months.

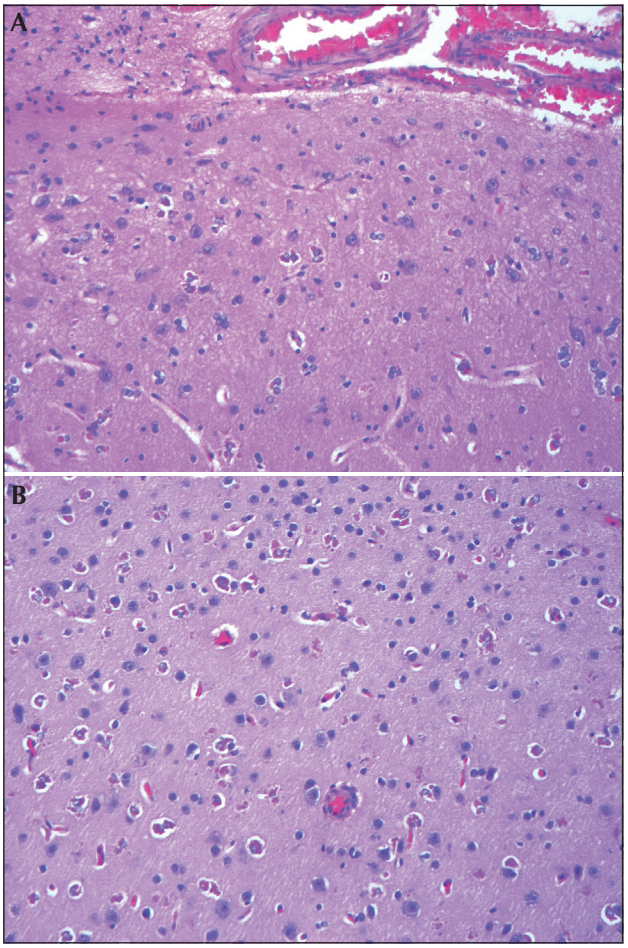

Figure 3. Pathological examination of Case 1. (A) Superficial left frontal cortex showing increased numbers of neurons in the molecular layer and an absence of layer 2 (haematoxylin and eosin; original magnification: x200). (B) A section from the left frontal lobe showing bright eosinophilic inclusions consistent with hyaline protoplasmic astrocytopathy (haematoxylin and eosin; original magnification: x200).

Postoperatively, she had EEG status epilepticus that lasted for about a week. Multiple electrographic seizures per day, lasting 4-12 minutes, were recorded when the patient was placed on continuous EEG monitoring. Ictal onset occurred from the left hemisphere and the remaining right parieto-occipital region, independently. An initial postoperative clinical seizure lasted 50 minutes. Most of the seizures were subclinical, but some of the left hemisphere seizures were associated with right arm clonic movements or asymmetric spasms. Status was treated with fosphenytoin, phenobarbital, intravenous lorazepam, and continuous infusion of midazolam. Treatment with lacosamide and ketogenic diet was added and the home AEDs were maximized. After surgery, her feeding seemed to worsen, and she was on nasogastric (NG) feed, but oral feed was resumed with the aid of speech and swallow

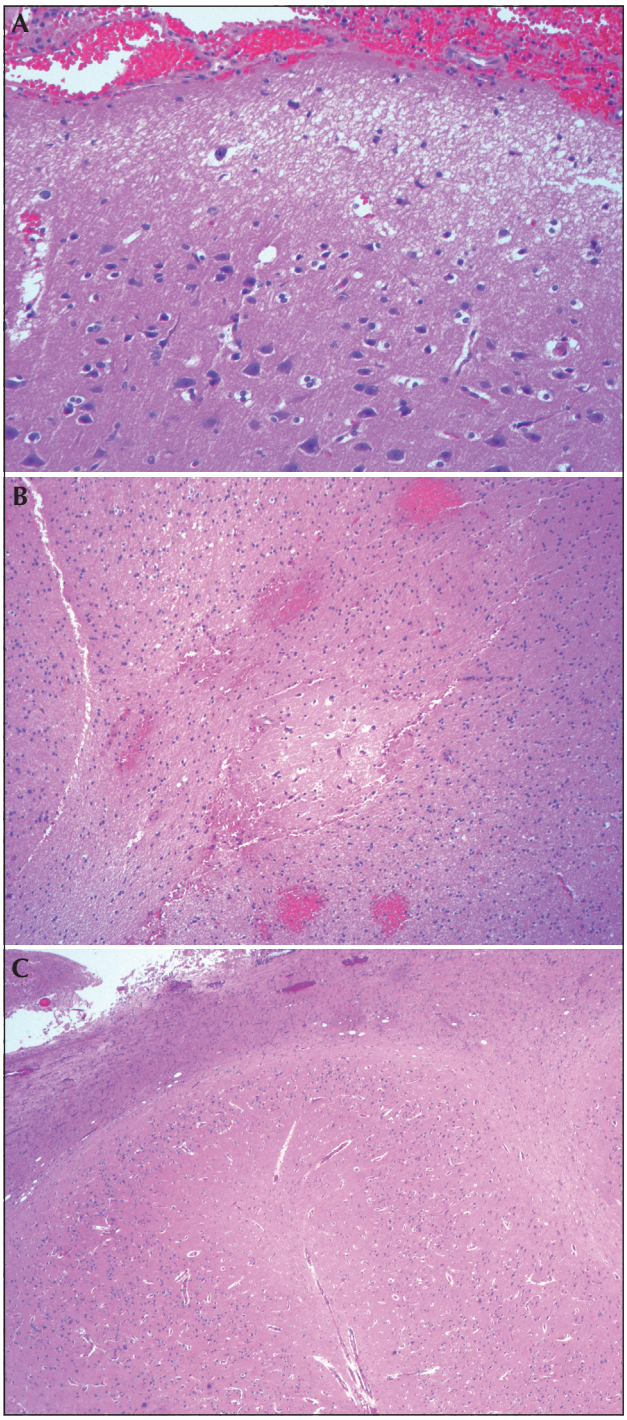

Figure 4. Pathological examination of Case 2. (A) A section from the right frontal lobe showing cortical architectural disorganization marked by a focal absence of cortical layer 2, consistent with focal cortical dysplasia (original magnification: x200). (B) A section from the right frontal lobe white matter showing a small nodule of grey matter situated in the white matter (nodular grey matter heterotopia) (haematoxylin and eosin; original magnification: x100). (C) Areas of the right frontal lobe showed an abnormally thin cortical layer devoid of the normal six-layer architectural pattern and consistent with polymicrogyria (haematoxylin and eosin; original magnification: x50).

Table 2. Cases reported in the literature, including the present case.

	Age at surgery	Surgery	Seizure outcome	Developmental outcome
Rosser *et al*. 2002	No data	Hemispherectomy	Seizure-free on one AED	Improved from a 2-month to a 9-month level
Palmer *et al*. 2007	11 years	Right parietal resection	Seizure-free for four years	Functional age of 7 years at 15 years of age; walks and runs
Saito *et al*. 2009	3 years?	Corpus callosotomy, then left functional hemispherectomy 5 months afterwards	Seizure-free for 7 months	No data
Case 1	6 years, 9 months	Left functional hemispherectomy	Seizure-free for 6 months	Improvement, walks a few steps with walker, more alert
Case 2	1 year, 10 months	Right fronto-parietal lobectomy	About 50% seizure reduction	Head and trunk control improved slightly

therapy once the status was controlled and treatment with phenobarbital and lacosamide was discontinued. After six months of surgical follow-up, she had some reduction in seizure frequency; about 50 seizures per cluster instead of up to 100 seizures per cluster, preoperatively. The duration and number of clusters per day have decreased slightly. With physical therapies after surgery, her head and trunk control improved somewhat. This patient died at age 3 years and 7 months (21 months after surgery) of unclear causes outside our hospital, thus no additional data related to her death are available.

Surgical pathology

Surgical pathology in both our patients showed architectural disorganization consistent with malformation of cortical development (focal cortical dysplasia) and perivascular white matter atrophy (*figures 3A, 4A*). The first patient also had changes consistent with hyaline protoplasmic astrocytopathy (*figure 3B*), focal perivascular chronic inflammation, and hamartia in the hippocampus. The second patient additionally had focal nodular heterotopia (*figure 4B*), polymicrogyria (*figure 4C*), white matter degenerative changes, and a benign right choroid plexus cyst.

Discussion

Seizures in AS are typically refractory to medical treatment. As refractory epilepsy continues, placement of VNS or brain surgery is often considered. The most common type of epilepsy surgery in these patients is corpus callosotomy. Most children with AS are not candidates for epilepsy surgery due to multifocal epileptogenicity. Brain surgery, such as hemispherectomy or cortical resection, has been performed in some children with AS, although virtually all continue to have seizures. To our knowledge, there are three reported cases of Aicardi syndrome treated by resective surgery, and surgical pathology has not previously been reported.

Table 2 presents a summary of reported resective epilepsy surgery cases of patients with AS. In a survey of 77 females with AS from the Aicardi Syndrome Foundation's family-based, self- reported questionnaires, six patients underwent epilepsy surgery, five received VNS, and one underwent hemispherectomy (Rosser *et al*., 2002). After hemispherectomy, the patient was seizure-free on one AED with developmental improvement, from a two-month level to a nine-month level (Rosser *et al*., 2002). In a nationwide survey in Sweden, Palmer and colleagues identified 18 cases of AS, one of whom had undergone epilepsy surgery (Palmer *et al*., 2007). This girl was unusually high functioning. After resection of a parietal epileptogenic zone at age 11 years, she was seizure-free for four years following her surgery, but developed postoperative left hemiparesis. At 15 years of age, the girl had very high motor function and she was able to walk and even run. Her functional age was seven years, and she had normal but monotonous speech.

In a study investigating treatment of epilepsy in severely disabled children with bilateral brain malformations, Saito and colleagues described one patient with AS and hypoplasia of the corpus callosum. Corpus callosotomy in this patient ameliorated the severity of tonic seizures. A left functional hemispherectomy performed five months later resulted in a seizure-free

period of seven months at the time of publication (Saito *et al*., 2009). Additionally, improved seizure control was found following surgical resection of tumors in AS patients, such as choroid plexus papillomas (Robinow *et al*., 1984; Donnenfeld *et al*., 1989; Taggard and Menezes, 2000). In our series, both patients showed focal features based on seizures semiology, EEG, neurological examination, and pre-operative imaging studies, which allowed us to consider resective epilepsy surgery as a treatment option. Case 1 significantly progressed developmentally during the seizure-free period. Case 2 had a more severe disease course since birth, and epilepsy surgery was offered as a palliative option to decrease the seizure burden. The second patient had a complicated post-operative disease course (status epilepticus and NG feeding), but she had an approximately 50% reduction of her seizures, with slight developmental improvement.

Our cases, as well as the cases reported in the literature, suggest that resective epilepsy surgery could be offered to selective cases of AS in which there is a clear predominance of focal epileptogenicity and some recovery of cognitive function could reasonably be expected. Palliative resective surgery can also be offered to ameliorate the seizure burden when other treatment choices have been exhausted. As demonstrated in Case 1, resective surgery allowed for a better or easier seizure management with antiepileptic drugs even when the seizures relapsed after the surgery.

Surgical pathology has not previously been reported. In our patients, focal cortical dysplasia was demonstrated. Case 2 also had focal nodular heterotopia and a benign right choroid plexus cyst. Several reports have documented these brain malformations in Aicardi syndrome based on image analysis or post-mortem pathological findings (Donnenfeld *et al*., 1989; Yamagata *et al*., 1990; Smith *et al*., 1996; Barkovich *et al*., 2001; Palmer *et al*., 2007; Hopkins *et al*., 2008). Periventricular nodular heterotopia and polymicrogyria were reported in 8-100% of patients in these cases series, and cerebral asymmetry in 20-100% of patients.

The first patient also had changes consistent with hyaline protoplasmic astrocytopathy. Cerebral hyaline astrocytic inclusions have been observed in patients with early-onset epilepsy, brain structural abnormalities, and developmental delay, and were initially described as a filaminopathy (Hazrati *et al.,* 2008). Subsequent studies have found that there are also other proteins in the inclusions, and the mix of proteins is different between patients (Hedley-Whyte *et al*., 2009; Visanji *et al.,* 2012). These inclusions may represent a unique clinicopathological entity. They can be seen outside the setting of Aicardi, and future studies are necessary to determine what their significance is and why they are observed in some patients and not others.

The number of pathological abnormalities found in our cases could explain the severity of their seizure burden and lack of neurodevelopment.

In summary, resective surgery may provide better seizure control or a temporary period of seizure freedom in AS patients with clear predominance of focal epileptogenicity, allowing progress in development and/or improved quality of life. Although studies on a larger patient cohort are needed to identify the possible role of surgery in the multidisciplinary treatment approach for children with AS, it is possible that concordance between focal EEG findings, especially early in the course of disease, and the region of predominant abnormality based on brain MRI could be variables to consider when referring children with AS for resective epilepsy surgery. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.

The authors have no personal, financial, or institutional interest in any of the drugs, materials or devices described in this article.

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TEST YOURSELF

(1) Aicardi syndrome is typically characterized by the following triad of features?
A. Seizures, agenesis of corpus callosum, and chorioretinal lacunae
B. Seizures, agenesis of corpus callosum, and polymicrogyria
C. Seizures, "burst suppression" pattern on EEG, and chorioretinal lacunae
D. Seizures, microcephaly, and chorioretinal lacunae

(2) Aicardi syndrome affects which of the following?
A. Mainly males
B. Mainly females
C. Both males and females

(3) Surgical treatment options for Aicardi syndrome include which of the following?
A. VNS
B. Hemispherectomy
C. Corpus callosotomy
D. Focal resection
E. All of the above
F. None of the above

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".