

Surgical Resection for Intractable Epilepsy in “Double Cortex” Syndrome Yields Inadequate Results

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Summary: *Purpose:* To analyze the results of surgical treatment of intractable epilepsy in patients with subcortical band heterotopia, or double cortex syndrome, a diffuse neuronal migration disorder.

Methods: We studied eight patients (five women) with double cortex syndrome and intractable epilepsy. All had a comprehensive presurgical evaluation including prolonged video-EEG recordings and magnetic resonance imaging (MRI).

Results: All patients had partial seizures, with secondary generalization in six of them. Neurologic examination was normal in all. Three were of normal intelligence, and five were mildly retarded. Six patients underwent invasive EEG recordings, three of them with subdural grids and three with stereotactic implanted depth electrodes (SEEG). Although EEG recordings showed multilobar epileptic abnormalities in most

patients, regional or focal seizure onset was recorded in all. MRI showed bilateral subcortical band heterotopia, asymmetric in thickness in three. An additional area of cortical thickening in the left frontal lobe was found in one patient. Surgical procedures included multiple subpial transections in two patients, frontal lesionectomy in one, temporal lobectomy with amygdalohippocampectomy in five, and an additional anterior callosotomy in one. Five patients had no significant improvement, two had some improvement, and one was greatly improved.

Conclusion: Our results do not support focal surgical removal of epileptogenic tissue in patients with double cortex syndrome, even in the presence of a relatively localized epileptogenic area. **Key Words:** Subcortical band heterotopia—Double cortex—Surgery—Intractable epilepsy—MRI.

Subcortical band heterotopia, or double cortex syndrome, is a rare neuronal migration disorder deriving from mutations in the doublecortin (DCX) gene located on chromosome Xq22.3–q23 (1–3) in most patients, and is usually associated with medically intractable epilepsy. There is a marked female preponderance, but a few men have been described to date (4,5), and we are currently aware of 18 patients. Delayed acquisition of developmental milestones is frequent, and mental retardation is usually mild or moderate, but also can be severe (6–9).

On magnetic resonance imaging (MRI), double cortex is characterized by a band of subcortical heterotopic gray matter separated from the overlying cortex by a layer of white matter. The heterotopic band is sometimes asymmetrical and of variable thickness, and is generally most obvious in frontocentroparietal regions (5,6,9,10). It is found anteriorly only in patients with doublecortin mutation (11). The appearance of the overlying cortical mantle on MRI can be normal or may vary from a simplified gyral pattern to true pachygyria (9). The subcortical band consists of clusters of unlaminated ganglion cells with variable degree of columnar organization (6,12).

About one third of patients with double cortex syndrome have an association of tonic–clonic and myoclonic seizures with atypical absences and drop attacks (6–8,13). However, focal clinical signs such as head

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deviation or clonic movements of one limb at seizure onset observed in some individuals suggest the diagnosis of focal partial epilepsy (4–9). Infantile spasms and Lennox–Gastaut syndrome also have been reported (4,6,7,9). About 60% of the patients have focal lobar or multifocal epileptic abnormalities (6,7,9), but EEG findings are usually characterized by generalized slow spike-and-wave or polyspike and wave, and multifocal spiking (7, 8,13).

The presence of a certain degree of focal electroclinical and neuroimaging features in double cortex syndrome raises the possibility of surgical treatment. Raymond et al. (5) reported a 29-year-old woman with double cortex syndrome and temporal lobe seizures, who underwent a right temporal resection and was free of disabling seizures after surgery.

Here we report eight patients with double cortex syndrome who underwent surgical treatment for intractable seizures. They were studied at the Montreal Neurological Hospital and Institute, at the Hospital Sao Lucas in Porto Alegre, the Chonbuk National University Medical School in Chonju, the Austin & Repatriation Medical Centre in Melbourne, at the Rush-Presbyterian–St. Luke's Medical Center in Chicago, and at King's College Hospital in London.

CASE REPORTS

Demographic, clinical, electrophysiologic, and neuroimaging data of the eight patients are summarized in Table 1.

Patient 1

A 14-year-old girl had a cluster of six generalized tonic–clonic seizures in <24 h at age 15 months. Three months later she had an episode of convulsive status epilepticus, and then daily tonic drop attacks developed. At age 4 years, she also had partial complex seizures with motor automatisms and secondary generalization followed by prolonged right hemiparesis. Seizures were sometimes ushered in by headache or stomach pain lasting for many hours, and by fear. The mean seizure frequency was ~30 per week. Her global IQ was 50. Epileptiform interictal abnormalities recorded during video-EEG telemetry were bilateral, with a clear left-hemispheric predominance. They were characterized by intermittent fast activity at 10 Hz from the left centroparietal area and by frequent spiking over the left hemisphere, with predominance in the midtemporal area. Ictal activity consisted of 5-Hz rhythmic activity with onset in the left centrottemporal area, with maximal amplitude at electrodes P3, T3, and T5. High-resolution MRI showed an asymmetrical double cortex, with a thicker subcortical band and pachygyria of the overlying cortex in the left hemisphere (Fig. 1A). In May 1996, the patient under-

went an anterior callosotomy. Seizures frequency and patterns remained unchanged [Engel's classification (14) IVb].

Two years later, she underwent intracranial EEG recordings using two stereotactic implanted depth electrodes with seven contacts each placed orthogonally through the left second temporal gyrus, aiming at the anterior hippocampus and the amygdala. Eleven epidural electrodes were inserted, aiming at frontocentroparietal areas and the superior temporal gyrus. Despite the multifocal interictal epileptiform abnormality, a more active generator was found in the left mesial temporal lobe. Other independent, but less active, generators were seen in the superficial temporal contacts, the posterior temporal lobe, and the second frontal gyrus.

Two months later she had a left anterior temporal resection with removal of the mesial structures (Fig. 1B). Eighteen months after operation she had no reduction in partial motor attacks, and little change in her minor attacks and atypical absences. Episodes of secondary generalization with right-sided hemiparesis occurred at times, but seizures were no longer ushered in by fear.

Patient 2

A 16-year-old girl had staring episodes with oral automatisms, dysphasia, dystonia of the right arm, and giggling at age 5 years. Daily seizures were preceded by stomachache or epigastric sensation, and were at times secondarily generalized. On video-EEG telemetry, interictal epileptiform abnormalities were recorded from both frontotemporal areas, sometimes in the form of intermittent sharp waves at 6–10 Hz with phase reversals at F3 and F4. Seizures had bifrontal onset or were recorded from the left temporal lobe. Several attacks also originated in the right frontoparietal region with rapid spread to the contralateral frontal lobe. She had rare seizures with tonic stiffening of extremities and falling associated with generalized EEG background attenuation. An MRI was reported to be normal. At age 15 years, she underwent a left anterior temporal lobectomy with resection of mesial structures. She continued to have drop attacks and clusters of gelastic episodes [Engel's classification (14) IVb] and was reevaluated. A high-resolution MRI revealed a thin asymmetric subcortical heterotopic band, better seen in the right frontocentral area.

Patient 3

In a 34-year-old normally intelligent man, tonic drop attacks developed, preceded by left-arm clonic or myoclonic movements at age 4 years. These occurred 5 to 10 times a day. He had multiple minor scalp and head injuries. Prolonged video-EEG telemetry recordings showed bifrontal interictal slowing and generalized spiking with right frontal predominance. Seizure onset was at times bifrontal, and at other times, right frontocentral.

TABLE 1. Clinical, electrophysiologic, neuroradiologic, and surgical data of eight patients with subcortical band heterotopia treated surgically

Patient/ sex/age (yr)	Age at seizure onset (yr)	Neurologic examination; psychology	Clinical seizure pattern	EEG	MRI	Surgery/outcome ^a
1/F/14	11/4	Normal; MR	Epigastric aura, fear, CPS with motor automatisms; postictal hemiparesis, R; tonic drop attacks; SG	I: generalized, temporal > centroparietal and frontal, L >> R II: L parietotemporal and mesiotemporal	Asymmetric SBH, thicker in the left hemisphere; pachygyria	1. anterior callosotomy/IV 2. L temporal lobectomy with amygdalohippocampectomy/IV
2/F/16	5	Normal; MR	Epigastric aura, CPS with oral automatisms, dysphasia, dystonia arm, R; SG	I: frontotemporal, L + R II: bifrontal; L temporal; R frontoparietal	Asymmetric, thin SBH, thicker in the right hemisphere	L temporal lobectomy with amygdalohippocampectomy/IV
3/M/34	4	Normal; normal	Clonic arm movements, L; tonic drop attacks	I: generalized with R frontocentral predominance II: bifrontal, frontocentral, R	Symmetric SBH thicker in the right frontal lobe	MST, R frontocentroparietal/I
4/F/21	10	Normal; MR	Visual aura, somatosensory aura and hand clonus, R; head turning, R with tonic posturing of the arms; SG	I: spikes and sharp waves, frontal, L > R II: L occipitotemporal with spread frontal; L frontal	Symmetric SBH and pachygyria, frontal, L	L frontal/III
5/M/20	16	Normal; normal	CPS with staring and oral automatisms	I: bitemporal R >> L II: bitemporal R > L	Asymmetric SBH, thicker in the right hemisphere	R temporal resection with amygdalohippocampectomy/III
6/F/15	4	Normal; MR	CPS with bilateral asymmetrical clonic jerking, tonic posturing, head turning, R; staring, oral automatisms; SG	I: temporal, L + R; generalized II: bitemporal; L temporal	Symmetric, SBH; pachygyria	L temporal lobectomy with amygdalohippocampectomy/IV
7/F/11	5	Normal; MR	CPS with fence posture, head and eyes turning, R; SG	I: multifocal with R frontoparietal predominance II: R postcentral gyrus	Symmetric, SBH; pachygyria	MST, R centroparietal/IV
8/M/20	NA	Normal; normal	CPS with SG	I: temporal R II: temporal R	Symmetric, SBH	R temporal lobectomy with amygdalohippocampectomy/IV

CPS, complex partial seizures; F, female; I, EEG interictal epileptic abnormalities; II, EEG ictal seizure onset; L, left; M, male; MR, mild or moderate mental retardation; MST, multiple subpial transections; R, right; SBH, subcortical band heterotopia; SG, secondary generalization.

^aEngel's classification.

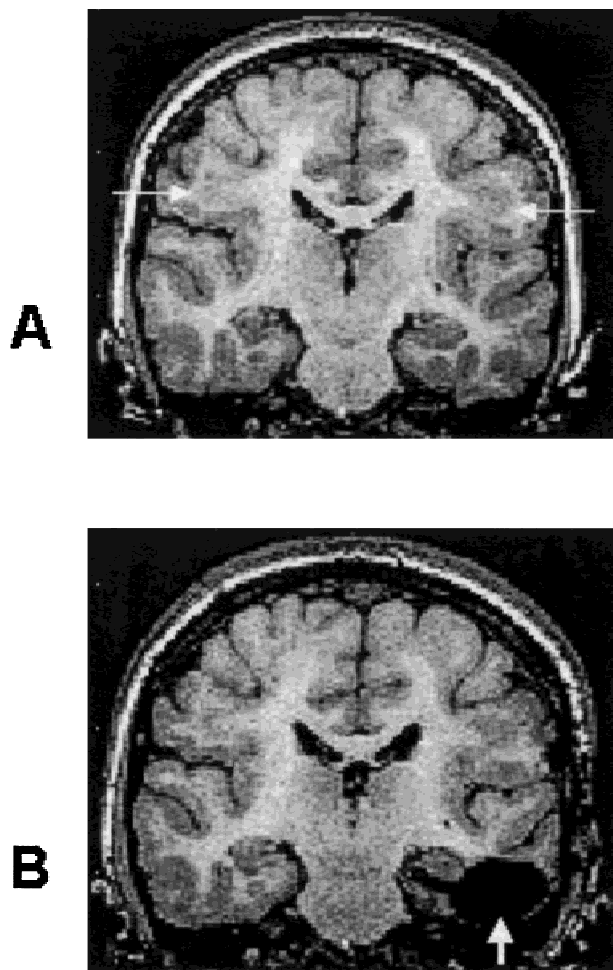


FIG. 1. A: Coronal high-resolution T₁-weighted magnetic resonance imaging (MRI) showing a thin asymmetric subcortical heterotopic band, better seen in the right frontocentral area (right is left on the images). B: Coronal MRI section showing a left anterior temporal resection with removal of the mesial structures.

High-resolution MRI showed subcortical band heterotopia, thicker in the right frontal lobe. The overlying cortex appeared normal. The better to identify the area of seizure origin, we placed two subdural grids over the right hemisphere with 64 contacts over frontal, central, and parietal areas. A single depth electrode with four contacts 1 cm apart was placed orthogonally in the postcentral gyrus. Interictal abnormalities consisted of frequent stereotyped spikes recorded mostly over the pre- and postcentral gyrus, but also the premotor area. No interictal epileptiform activity or seizure activity originated in the subcortical heterotopic band sampled by the depth electrode. Multiple subpial transections (15) were carried out in the frontal, central, and superior parietal areas. One year after surgery, he had no further drop attacks, but continued to have persistent infrequent focal myoclonic jerks of the left hand [Engel's classification (14) IIb].

Patient 4

A 21-year-old woman with mild mental retardation developed seizures at age 10 years. She had two distinct patterns. In the first, attacks were ushered in by a light blinking in the left visual field followed by an electric sensation, clonic movements of the right hand, and head version to the right, occasionally leading to secondary generalization. The second pattern consisted of rapid head turning to the right followed by asymmetric tonic posturing of the arms and secondary generalization. Neurologic examination was normal. Scalp EEG showed continuous diffuse slow-wave activity in the delta frequency band associated with bursts of spikes and sharp waves in frontal regions, predominantly on the left. The MRI showed continuous bilateral subcortical heterotopic band in the frontal, parietal, and occipital lobes, and a region of pachygyria in the left frontal region. Because seizure onset could not be established on the basis of surface recording during prolonged video-EEG telemetry, a 32-contact grid was placed over the left frontal lobe and strips over mesial temporal and temporooccipital regions. Seizure onset was recorded from the temporooccipital strip contacts, with rapid spread to the left frontal region, but also from the left frontal area sampled by the grid. It was decided to perform resection of this area in the left frontal lobe. Intraoperative EEG was performed with simultaneous recording from the dysplastic lesion, the adjacent cortex, and from the subcortical heterotopic band with cortical and depth electrodes. Non-epileptic, monomorphic, synchronous, rhythmic waves at 5–9 Hz (250–450 μ V) were recorded from the subcortical band.

One year after surgery she continues to have occipital seizures [Engel's classification (14), III].

Patient 5

A 20-year-old gardener with a normal intellect had a minor head injury at age 15 years. Complex partial seizures developed without secondary generalization from age 16 years. On video-EEG telemetry, seizures were stereotyped and were characterized by staring and oral automatisms, but without focal motor features. On scalp EEG recordings, seizures had right posterior temporal onset with rapid bilateral spread to frontotemporal regions. Intracranial recordings with grids showed frequent interictal slow and sharp slow activity over the right temporal lobe and infrequent left temporal discharges. Seizures had bisynchronous temporal onset with right side-predominant polyspike activity. Neuropsychological examination revealed a full-scale IQ of 89 and a slight impairment of nonverbal memory. An MRI was reported to be normal.

In July 1986, he underwent a right temporal lobectomy with amygdalohippocampectomy. Seizures recurred within 3 months of surgery. Later he experienced a

seizure-free period of >2 years [Engel's classification (14) IIIb]. A postoperative MRI showed a bilateral asymmetric subcortical band heterotopia involving frontotemporooccipital regions, thicker in the right hemisphere.

Patient 6

In this 15-year-old mildly intellectually disabled girl, at age 4 years, complex partial seizures with clinical features developed, including bilateral asymmetric clonic jerking, tonic posturing, staring, and oral automatisms. During video-EEG telemetry, clonic head movements or version to the right characterized most of the seizures, and some attacks rapidly generalized. Interictal epileptiform activity consisted of independent bilateral and generalized polyspike and slow-wave discharges. On scalp EEG, seizures had bitemporal onset. One year later, she underwent reassessment with SEEG, which demonstrated a predominantly left temporal seizure onset with rapid spread to the right temporal region. An MRI was reported as normal. She had an anterior left temporal lobectomy with resection of mesial structures. Seizures recurred within 2 months of operation [Engel's classification (14) IVb].

She was admitted for reassessment 5 years later. Repeated MRI showed a symmetric diffuse heterotopic band with slight pachygyria of the overlying cortex.

Patient 7

This 11-year-old left-handed girl had onset of generalized tonic-clonic seizures, atypical absences, and focal motor seizures at age 5 years. At age 7 years, pharmacologically intractable epilepsy developed, with an average of 15 seizures each week. Clinically the seizures were characterized by a tonic fencer posture involving deviation of head and eyes to the right with elevation of the left arm. She had borderline intelligence. The MRI showed a continuous, bilateral symmetric subcortical band heterotopia. During prolonged video-EEG monitoring, surface EEG recordings showed multifocal epileptic discharges mainly in the left parietal and bilateral frontal, with less frequent bitemporal independent spikes. She underwent SEEG with electrodes implanted bilaterally in frontoparietal and temporal areas. Active spike activity was recorded from the left parietal region. Twenty seizures were recorded, and originated in the left postcentral gyrus with spread to the supplementary motor cortex. Because the patient had no focal neurologic deficit, she underwent subpial multiple transections (15) of the parietal area. Intraoperative electrocorticography (ECoG) was done by using a specially designed depth-electrode recording from six contacts in the heterotopic band immediately beneath six contacts within the normally migrated cortex. The heterotopic cells generated high-voltage spikes followed by regularly recurring slow waves and electrographic seizures independent of those arising in immediately overlying normally migrated cor-

tical layers. Seizures arising in the normally migrated cortex resulted in clinically observed movements when the anesthetic levels were reduced. Conversely, electrical activity arising in and confined to the heterotopic cortex never yielded clinical seizures at any anesthetic level. Multiple subpial transections (15) of the normal migrated cortex, overlying the heterotopia, did not eliminate discharges within the heterotopic neurons.

Seven years after surgery, the patient had no appreciable change in seizure pattern and frequency [Engel's classification (14) IVb].

Patient 8

A 20-year-old man was investigated because of intractable complex partial seizures with frequent secondary generalization. The EEG showed seizure onset in the right temporal lobe, and the MRI showed a continuous band heterotopia. The patient underwent a right temporal lobectomy. Seizures continued after operation [Engel's classification (14) IVb], and the patient had a psychotic episode 6 weeks after surgery.

DISCUSSION

In patients with double cortex syndrome, the subcortical heterotopic band tends to be diffuse, and the epileptic activity, multifocal. However, in many of these patients, there is a propensity to focalization, from both clinical and electrographic points of view. It is in such patients that consideration was given to surgical treatment. All patients presented here had ictal clinical features, consisting of simple partial seizures with somatosensory or autonomic symptoms (patients 1, 2, and 4) or tonic-clonic movements of one limb (patients 3 and 7), and complex partial seizures with automatisms and secondary generalization (patients 1, 2, and 5-8). Although interictal epileptic abnormalities were clearly generalized or multifocal in patients 1, 2, 4, and 7 on scalp EEG, there was a degree of lobar abnormality in all, and a focal seizure onset was demonstrated in those patients who had invasive recordings (patients 1, 3, 6, and 7). However, only patient 3 had a satisfactory postoperative seizure outcome. Whether this was primarily due to the multilobar extent of the transected cortex or to the relative high degree of focality of the epileptic focus remains unclear. Some improvement also was achieved in patient 1, in whom only simple partial seizures were eliminated, and in patient 4, in whom priority was given to resection of the highly epileptogenic area of pachygyria in the left frontal lobe. In this last patient, the presence of another active occipitotemporal focus may explain the unfavorable surgical outcome. In patient 1, the callosotomy did not modify the epileptic attacks including the drop attacks, and the second resective surgery, which could not include the large multifocal epileptogenic zone, also was insufficient to make the patient seizure

free. In this patient, it is possible that the restricted callosal section may have had limited the therapeutic success, because this palliative procedure has led to considerable and long-standing reduction of falling attacks in four of the six previously reported patients with double cortex syndrome (6,16–18).

Because of widespread structural abnormality, surgical planning in double cortex syndrome is difficult. Even when the authors were aware of the diffuse nature of the process, evidence for some degree of focality in the electroclinical and neuroimaging features justified a localized cortical resection in the patients presented here. However, despite some reduction in attacks in a few of the patients, resection did not lead to sufficient decrease in seizure frequency and severity, and should therefore not be considered the treatment of choice.

In five of the seven patients, a temporal resection was carried out based on clinical and electrical evidence of greater involvement of the temporal lobe. In all these four patients, results were poor. In three of them, the band heterotopia was recognized only when the patients were restudied because surgical results were inadequate. One may conclude that the temporal features were non-specific, perhaps the result of spread or of a multifocal generator, thus representing a misleading pseudotemporal localization similar to that found in patients with hypothalamic hamartoma or periventricular nodular heterotopia. In these conditions also, temporal resection is fruitless despite interictal and ictal EEG evidence suggestive of seizure onset in the temporal lobe (19,20). In patients with electrographic temporal foci and particularly without obvious mesiotemporal atrophy, the possibility of double cortex should be considered because this represents a warning of poor outcome.

In conclusion, our results do not encourage consideration of focal resection of epileptogenic tissue in double cortex syndrome, even considering the intractability of the epilepsy. Conversely, anterior callosotomy may offer hope of improvement in patients with drop attacks. However, as expected, this palliative procedure never resulted in complete cessation of attacks. The efficacy of multiple subpial transections requires assessment in a larger group of patients to confirm its role in the surgical treatment of intractable epilepsy in patients with double cortex syndrome whose clinical seizure pattern is consistently localized.

DEDICATION

This communication is dedicated to the memory of Frank Morrell, epileptologist, neurophysiologist, husband, and friend, who first attempted to clarify the origin of epileptic generators in patients with double cortex.

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