Reflex Seizures in Patients with Malformations of Cortical Development and Refractory Epilepsy

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Summary: *Purpose:* Malformations of cortical development (MCDs) are usually highly epileptogenic, and their hyperexcitability could facilitate the occurrence of reflex seizures. We sought to characterize reflex seizures in patients with MCDs and refractory epilepsy.

Methods: Clinical, electrographic, and neuroimaging data were reviewed in eight patients with MCDs who had reflex seizures reproduced during presurgical evaluation.

Results: All eight patients had both reflex and spontaneous seizures. In six, however, drop attacks or axial myoclonic seizures occurred only upon specific sensory stimulation. Reflex seizures were induced by more than one type of stimulus in most patients, but anatomofunctional correlations could usually be invoked. Six patients had significant intellectual impairment. Surgical resection controlled seizures in two patients.

Conclusions: Reflex seizures in patients with MCDs may be medically refractory and may often manifest as drop attacks or axial myoclonus. Surgical resection of focal lesions can bring reflex seizures under control. Putative mechanisms related to the relatively low frequency of reflex seizures in MCDs are discussed. **Key Words:** Reflex seizures—Malformations of cortical development—High degrees of epileptogenicity.

Reflex seizures most commonly occur in patients with genetically related epilepsy syndromes (1–6), in which triggering stimuli are related to photosensitivity or higher-order cognitive processing (7,8). Seizure provocation through other stimuli and in patients with symptomatic epilepsies is less common, although perirolandic lesions are known to induce reflex seizures.

A common assumption regarding reflex seizures is that hyperexcitable intracortical or corticosubcortical sensory circuits lead to fast and uninhibited recruiting and synchronization of neuronal pools (9–11). Converging clinical and experimental evidence suggests that malformations of cortical development (MCDs) are among the most hyperexcitable epileptogenic lesions (12,13). In addition, these malformations are often intrinsically epileptogenic

(14–16) and may establish abnormal connections with other cortical and subcortical structures (17,18). Thus, patients with MCDs are prone to respond with abnormally increased electrical volleys to modality-specific afferent stimuli, which would facilitate reflex provocation of seizures. Nonetheless, *series* of patients with MCDs and reflex seizures are not found in the literature. We report eight patients with reflex seizures associated with MCDs confirmed by imaging, histopathology, or both.

METHODS

Eight patients (four men) with spontaneous and reproducible reflex seizures and a MCD were studied. We defined specific reflex seizure precipitants as any sensory stimulus that precipitated the seizures in daily life and could be confirmed during evaluation. Self-precipitation was defined as recurrent intentional self-provocation of seizures through a specific type of sensory stimulation. Patients reported herein were recruited from a pool of 30 to 100 patients with MCDs evaluated in each of the

seven participating centers. Several other patients with MCDs and putative reflex seizures were excluded because the latter were not reproduced during video-EEG evaluation. Seizure onset ranged from 4 months to 11 years (mean, 4.6 years), and age at evaluation from 5 to 51 years (mean, 20.1 years). Chart review complemented by recent clinical assessment allowed collection of data regarding pregnancy and perinatal period, developmental milestones, history of status epilepticus, reflex and spontaneous seizure types, specific precipitants of reflex seizures, occurrence of self-precipitation, seizure frequency, and response to antiepileptic drugs (AEDs). Delayed development was rated as severe when acquisition of either walking independently or comprehensive language occurred after age 3 years, and moderate when after age 2 years. Mild developmental delay included any less significant delay in acquisition of motor or cognitive milestones. Because of the ascertainment of patients from six countries, their highly variable age range, and ability to cooperate with formal neuropsychological testing, we determined the presence and severity of intellectual disability according to schooling and independence in activities of daily living. Thus patients who were able to attend normal schools but could not complete elementary education were considered mildly impaired. Those who were not able to attend regular school but were independent in activities of daily living were considered moderately impaired, and those who could not function independently were regarded as severely impaired.

Multiple sessions of 16- to 32-channel video-EEG monitoring were performed for each patient, during which reflex seizures were documented. Scalp/sphenoidal electrodes were used for these recordings, except for one patient, who was studied with subdural grids and strips in the left frontocentroparietal regions. All patients underwent complete physical and neurologic examinations. High-resolution 1.5-Tesla magnetic resonance imaging (MRI) studies were available for all. Four patients underwent surgery: two had callosotomies, and two others localized cortical resections. Routine histopathology staining was done in excised surgical specimens. Postoperative follow-up ranged from 2.5 to 12 years.

RESULTS

Illustrative case reports

Patient 1

This 15-year-old Australian adolescent was the firstborn twin at 34 weeks' gestation. He was born in good condition after emergency cesarean section for breech presentation and premature labor. He had an episode of afebrile status epilepticus at age 3 years. One year later, self-induced drop attacks developed: staring at a white paper or a shiny surface would induce a tonic seizure with stiffening of the upper limbs and loss of awareness for ~10 s, occasionally associated with jerking, and followed by postictal confusion and drowsiness. These attacks increased in frequency as he grew older, with >10 per day. He succeeded persistently in evoking a seizure because of a sensation of well-being, "warm and fuzzy," as he stares. He has been instructed to sit down before provoking the episodes to prevent injuries, but unfortunately he has still sustained severe injuries because of drop attacks and prolonged generalized tonic–clonic seizures. He also has described episodes of shooting pain in the forehead with, sometimes, eye flickering for 10–15 s recurring every 5 min. Interestingly, he never had spontaneous myoclonic jerks, atonic drop attacks, or partial motor seizures.

Developmental milestones were significantly delayed. He has a moderate to severe intellectual handicap, no cutaneous or dysmorphic stigmata, but a mild generalized spasticity, with a right-sided predominance. In addition, he has cerebellar features characterized by intention tremor, dysdiadochokinesis, and ataxia. He also has tongue dyspraxia. Neurogenetic evaluation for fragile X syndrome was negative, karyotype was normal, and EEGs showed persistent focal epileptiform discharges in the right centroparietal region. MRI revealed subependymal heterotopia extending onto both temporal and occipital horns of the lateral ventricle, a right mesial occipital dysplasia, and a cerebellar hypoplasia (Fig. 1). An interictal fluorodeoxyglucose–positron emission tomography (FDG-PET) study showed a relatively decreased glucose
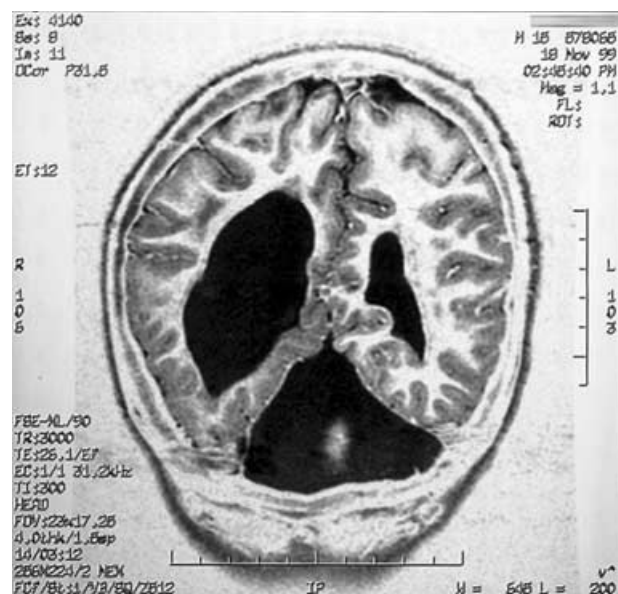
FIG. 1. Coronal inversion-recovery magnetic resonance imaging section of patient 1 shows a marked malformation in both posterior quadrants, with a right-side predominance. Note subcortical and periventricular heterotopic tissue (*arrows*), a right occipital dysplasia (*arrowhead*), dilatation of the posterior horns of the lateral ventricle, and cerebellar hypoplasia.

metabolism in right temporal, parietal, and occipital regions.

Patient 8

This 34-year-old woman had refractory seizures with onset at 8 years, which began with paresthesia and tonic extension of the right leg, and then dystonic posturing of all limbs and a high-pitched vocalization resembling a bird singing or loud laughter. Awareness was retained throughout the attacks. Seizures were spontaneous or consistently provoked by either rubbing the sole of the right foot or excessive bladder distention. Video-EEG evaluation showed interictal runs of pseudorhythmic sharp waves in the left parasagittal frontocentral region (Fig. 2A), and decremental fast activity in the same area during ictal events (Fig. 2B). MRI was normal. Intracranial evaluation with subdural strips covering the left dorsolateral superior and mesial frontocentral regions showed seizure onset in the mesial aspect of the postcentral gyrus (Fig. 2C). Extra-operative electrical cortical stimulation reproduced the seizures and confirmed that this region contained the sensory cortical representation of the right leg and foot. Resection of this region and the ipsilateral supplementary motor area, complemented by subpial transection of the mesial aspect of the motor cortex, has completely controlled seizures in the 3 years since surgery. A postoperative transient contralateral hemiparesis and expressive aphasia lasted for 1 week. A more prolonged weakness of the right foot resolved after some months with vigorous physical therapy. Postoperative MRI confirmed the extent of resection (Fig. 2D), and histopathology showed dysplastic neurons and balloon cells (Fig. 2E), indicative of a Taylor's type focal cortical dysplasia (19,20).

Clinical series of eight patients

Two patients had histories suggestive of pre- or perinatal distress, and one had status epilepticus. Five had developmental delay, and six were intellectually handicapped. Patient 2, with a deletion of the long arm of chromosome 11, had low-set ears. The other had normal physical examination. Only two patients, however, had a normal neurologic examination, with the others sharing diffuse hypotonia or spasticity, mild hemiparesis, and pseudobulbar signs. Further details can be obtained from Table 1.

Seizure characteristics

The findings are detailed in Table 2. All patients had reflex and spontaneous seizures, the latter always predominating. Seizure frequency varied from one per week to several per day. Two patients, both with severe mental retardation, had self-induced attacks.

In two patients, the semiology was identical whether attacks were spontaneous or provoked: one, with bilateral perisylvian polymicrogyria, had perioral myoclonus and drop attacks, and another, with focal cortical dysplasia in the medial frontoparietal region, had partial motor seizures and occasional secondary generalization (Tables 1 and 2). In the other six patients, the repertoire of reflex and spontaneous seizures differed in at least one seizure type. Four had spontaneous partial motor seizures and occasional secondary generalization, and recurrent drop attacks only upon specific stimulation: two with startle-induced drop attacks and two with seizures induced by visual stimulation or eye movement. A fifth patient with a centrotemporal focal dysplastic lesion had spontaneous and reflex partial motor and complex partial seizures, but perioral myoclonias only upon interoceptive stimulation of a full meal, and the last patient, with bilateral asymmetrical perisylvian polymicrogyria, had spontaneous and reflex partial motor seizures secondarily generalized, but myoclonus of the head and both arms on eating or eating-related cognitive activation.

Two patients had a single seizure-precipitating stimulus (patients 1 and 7). The others had reflex seizures induced by different types of stimuli, which nevertheless produced the same seizure manifestations. One had seizures precipitated by oculomotor and proprioceptive stimulation, two by eating or talking, two others by startle produced by sudden occurrence of a loud sound or a tactile stimulus (e.g., an unexpected stroke on the back), and one through sensory stimulation of the foot and by bladder fullness.

From clinical, interictal and ictal EEG, and imaging findings, it was possible to suggest a putative epileptogenic zone responsible for the reflex seizures in each patient. These data are detailed in Table 2. Four patients with diffuse or bilateral malformations had generalized, multifocal, or bilateral epileptiform interictal EEG spikes. All had bilateral or generalized reflex seizure patterns. Patient 2, however, with bilateral malformations in the posterior quadrants and a history of infantile spasms in the first year of life, had seizures starting in the right anterior quadrant. Three other patients had focal or unilateral spikes and localized epileptogenic zones. Patient 1 had focal EEG features associated with a gross malformation in the right posterior quadrant, although he also had bilateral periventricular nodular heterotopia. Finally, patient 7 had no interictal or unequivocal ictal epileptiform abnormalities on scalp EEGs. The autonomic features of his reflex attacks, coupled with a periinsular lesion, suggested a centroinsular epileptogenic zone.

Anatomic and histopathologic findings

MRI showed variable types of MCDs. Two patients had bilateral perisylvian polymicrogyia (Fig. 3), which was symmetrical in one and asymmetrical in the other. Both had reflex seizures provoked by eating, and one had recurrent reflex drop attacks, which were only partially responsive to anterior callosotomy. Two had extensive dysplastic features in the posterior quadrants, one with bilateral subependymal nodular heterotopia and a right occipital dysplastic cortex, and the other with grossly
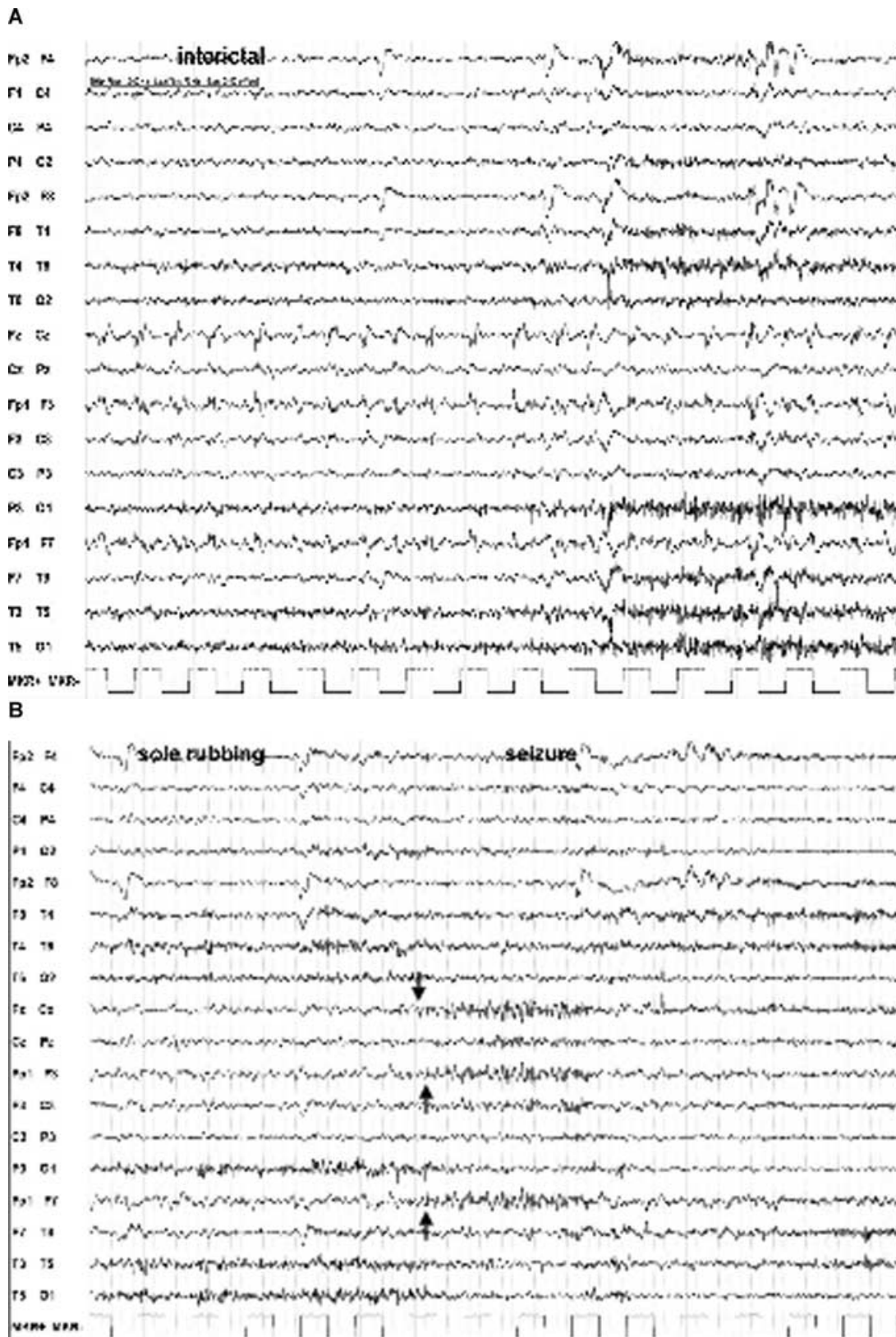
FIG. 2. EEG, magnetic resonance imaging (MRI), and histopathologic pictures of the evaluation and treatment findings of patient 8. **A:** Rhythmic interictal epileptiform discharges involving the left frontocentral (parasagittal) region. **B:** Reflex-induced seizure on scalp EEG, with onset in the same regions displaying rhythmic interictal discharges (*arrows*). **C:** Intracranial EEG with subdural electrodes (MRI insert) show a spontaneous seizure arising from the mesial primary sensory cortex, which was resected, in conjunction with the left supplementary motor area **(D)**. **E:** The dysplastic histopathologic features of the resected tissue.
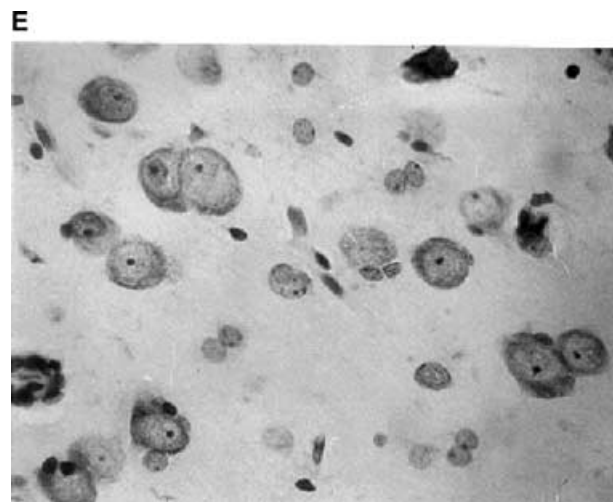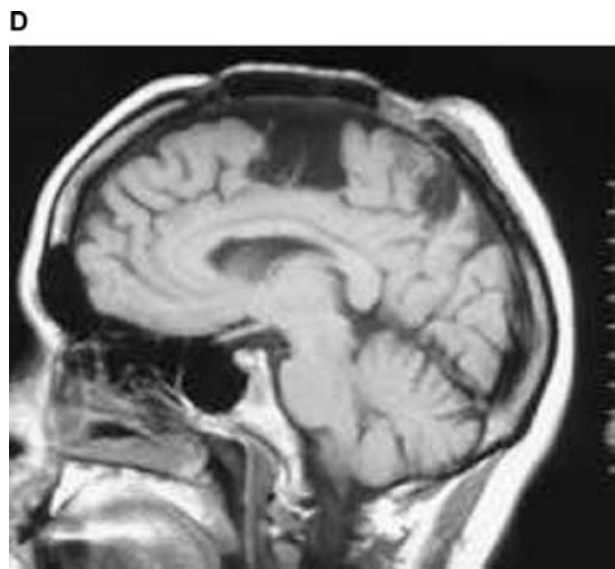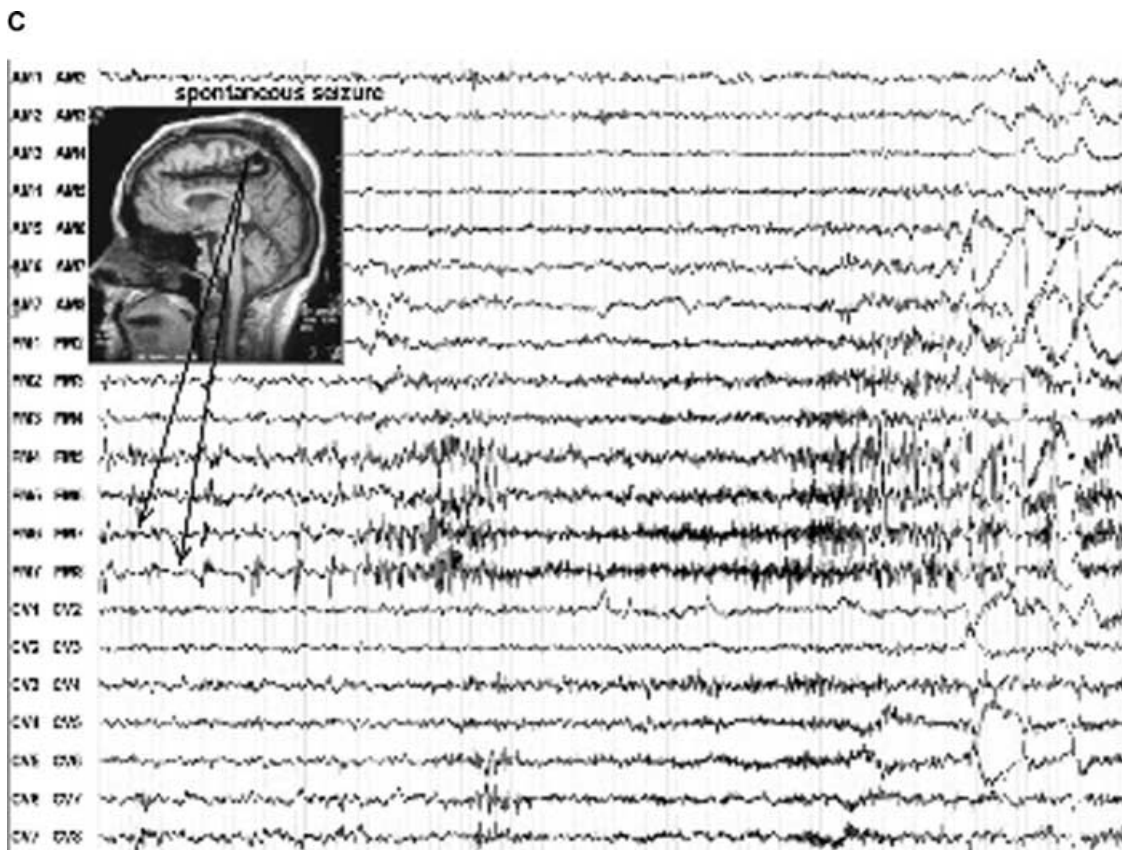
FIG. 2. Continued.

abnormal gyration in both parietooccipital regions. These patients had seizures precipitated by visual, oculomotor, or proprioceptive stimuli. A localized dysplastic abnormality was seen in two patients, in the centroinsular area in one (Fig. 4), with seizures triggered by a full stomach, and in the right frontal lobe in the other, who had startle-induced seizures. At operation, electrocorticography (ECoG) showed continuous spiking in the right frontal

lobe, and histopathology confirmed a Taylor-type focal cortical dysplasia (19,20). Postoperatively, seizures were fully controlled for 5 years, and he now has occasional simple partial seizures. One male patient had diffuse band heterotopia, or "double cortex," with startle seizures and frequent drop attacks, not helped by complete callosotomy. Finally, one patient with a normal MRI, but an EEG pattern suggestive of focal cortical dysplasia (patient 8;

TABLE 1. *Clinical, anatomical, and surgical findings*

| Patients	Age evaluation*	Age sz onset*	Perinatal injury	Development	Mental retardation	Abn physical exam	Abn neuro exam	MRI	Other evaluations	Surgery/ pathology	Surgical outcome
#1 Male	15	3	First twin 34 wks mild jaundice	Severely delayed	Severe	No	Gen spasticity bilat cerebellar signs	Cerebellar hypoplasia; bilat subepend heterotopia; rt occ dysp	PET: hypo-metab rt T-P-occ fragile-X excluded;	N/A	N/A
#2 Female	5	4 months	No	Severely delayed	Severe	Low implant both ears	Diffuse hypotonia	Abn gyration, both parieto-occ, rt pred	46,XX,del(11) (q22.2 q23.2)	N/A	N/A
#3 Male	7	3	No	Moderately delayed	Moderate	No	Mild lt hemiparesis	Diffuse bilat band heterotopia	N/A	Complete callosostomy	Died in status 7 years later; persisting reflex sz
#4 Male	7	3	No	Moderately delayed	Moderate	No	Diffuse hypotonia	Rt frontal blurring gray/white	N/A	Rt F lobectomy TTFCD	Free of reflex sz; mild simple partial sz persist
#5 Female	27	11	No	Mildly delayed	Mild	No	Severe pseudobulbar palsy	Bilat symm perysylvian polylicrogyria	N/A	Anterior callosostomy	Persisting reflex sz 12 years f-up
#6 Female	15	6	Bleeding first trim. gestation	Normal	No	No	Mild pseudo-bulbar palsy, oro-lingual dyspraxia	Bilateral perisylvian polymicrogyria, lt pred	N/A	N/A	N/A
#7 Male	51	3	No	Normal	Mild	No	No	Cortical thickening, increased signal inferior centro-insular	N/A	N/A	N/A
#8 Female	34	8	No	Normal	No	No	No	Normal	Subdural grid recordings left mesial central sz onset	Lt mesial F-C resection TTFCD	Sz free 30 mo f-up

*In years.

Abn, abnormal; bilat, bilateral; C, central; dysp, dysplasia; F, frontal; gen, generalized; hypometab, hypometabolism; hypsarrht, hypsarrhythmia; implant, implantation; lt, left; occ, occipital; P, parietal; PET, positron emission tomography; pred, predominant; rt, right; SBS, secondary bilateral synchrony; sz, seizure; symm, symmetrical; T, temporal.

TABLE 2. *Semilogical and neurophysiological features*

Patients	Specific precipitant	Precipitant seizure types	Interictal reflex EEG spikes	Ictal EEG	Reflex seizure putative epileptogenic zone	Seizure frequency	Self-precipitation	Spontaneous seizures	MRI
#1 Male	Staring at white paper or shiny surface	Tonic drop attacks	Rt C-P	Diffuse attenuation C-P-O pred	Rt posterior quadrant	> 10/day refractory	Yes	Eye flickering	Cerebellar hypoplasia; bilat subependymal heterotopia; rt mesial occ dysplasia
#2 Female	Forced eye dev to lt plus forced blinking	Tonic drop attacks	Gen hypsarht; later, rt F	Rt anterior quadrant	Rt anterior quadrant	Daily refractory to AED; some response to steroids	Yes	Partial motor	Abn gyration, both parieto-occ, rt pred
#3 Male	Startle touch and sound	Drop attacks	Multifocal SBS	Generalized irregular spike and attenuation	Generalized	Daily, refractory	No	Partial motor sec gen	Diffuse bilat band heterotopia
#4 Male	Startle touch and sound	Drop attacks	Rt F-C SBS	Rt F-C	Rt F	Daily to weekly, refractory	No	Partial motor sec gen	Rt frontal blurring gray/white
#5 Female	Eating talking over the phone	Peri-oral myoclonia drop attacks	Bilat C-T SBS	Generalized rhythmic alpha-like activity	Bilat perisylvian	Daily refractory	No	Peri-oral myoclonus, drop attacks	Bilat symm perysylvian polylicrogyria
#6 Female	Eating talking about eating	Myoclonus, head and arms; partial motor sec gen	Bilat C-T lt T pred SBS	Generalized irregular spike and attenuation	Bilat perisylvian	Weekly, refractory	No	Partial motor sec gen	Bilateral perisylvian polymicrogyria, lt pred
#7 Male	Gastric dilation after meals	Peri-oral myoclonia partial motor, sec gen	None	None	Lt centro-insular	Daily to weekly, refractory	No	Partial motor complex partial, sec gen	Cortical thickening, increased signal lt centro-insular
#8 Female	Rubbing sole rt foot bladder distension	Partial motor sec gen	Continuous lt F-C	Lt medial post-central gyrus	Lt medial post-central gyrus	Daily to weekly, refractory	No	Partial motor sec gen	normal

Bilat, bilateral; dev, deviation; lt, left; occ, occipital; pred, predominant; rt, right; sec gen, secondarily generalized; symm, symmetrical.
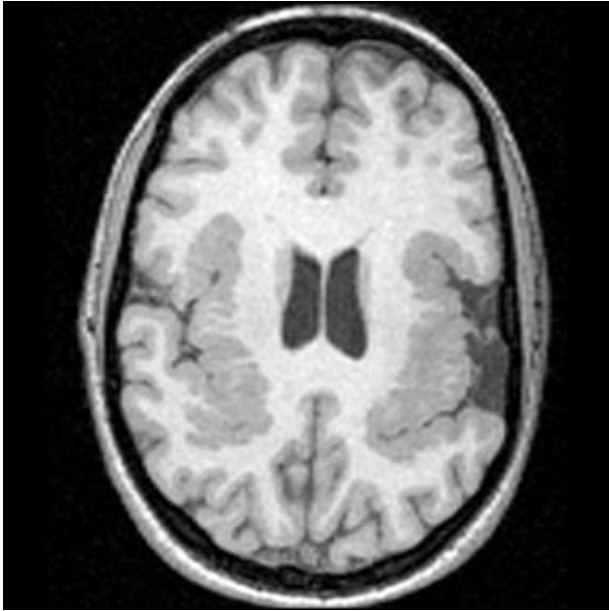
FIG. 3. Axial T_1-weighted magnetic resonance imaging section of patient 6 shows grossly malformed perisylvian regions bilaterally. Close analysis of the malformation suggests a polymicrogyric pattern.

Fig. 2A) (12,15) had seizures provoked either by stimulation of the sole of the right foot or by fullness of the bladder. Subdural electrodes showed an epileptogenic zone in the right medial central cortex, and resection of this area revealed a Taylor-type focal cortical dysplasia. Seizures are fully controlled after 30 months.

DISCUSSION

Reflex seizures result from neuronal circuits that are hyperexcitable to specific afferent stimuli (2,10,11). Ge-
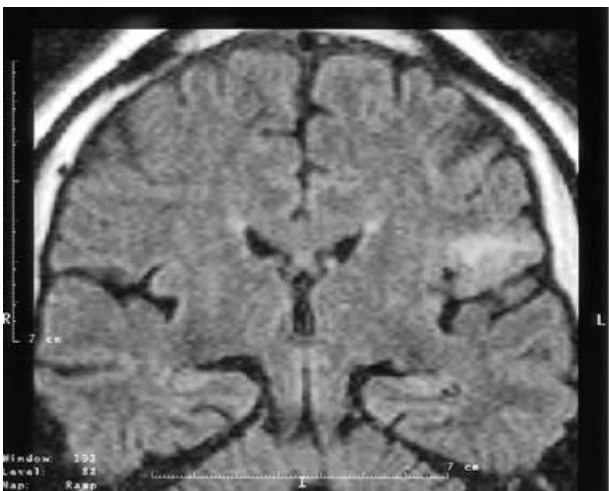
FIG. 4. Coronal fluid-attenuated inversion recovery magnetic resonance imaging acquisition of patient 7. Note focal area of increased corticosubcortical signal in the left anterior frontoinsular region, compatible with a dysplastic lesion.

netic and lesional mechanisms facilitating the recruitment and synchronization of larger neuronal pools by incoming sensory volleys are likely to be involved in this process (11,14,16).

We retained for inclusion in this report only those patients with MCDs who had reflex seizures reproduced during video-EEG evaluation. Other patients whose putative reflex attacks could not be verified were not included. Some of these reported attacks that were suggestive of a reflex mechanism, such as patients with rolandic MCD reporting clonic perioral movements associated with toothbrushing. Thus the very low prevalence of reflex seizures in patients with MCD, as inferred by the limited number of patients included in this report, may represent an underestimation.

All eight patients had both spontaneous and reflex seizures. This has been the case with many of the patients previously reported, irrespective of the underlying etiology (9,21). In contrast with most other reports, however, our patients had refractory seizures, and most had at least one type of seizure that was provoked only by specific stimulation and did not occur spontaneously.

Reflex seizures are often readily controlled with medication. This favorable response is to be expected in patients with idiopathic epilepsies, such as primary generalized epilepsies and reflex seizures related to photic stimuli, and also is seen in patients with partial cryptogenic epilepsies (1,3,5,6,8,22–24). Conversely, a few series and single-case reports of patients with symptomatic partial epilepsies and refractory reflex seizures have been published (9,25–28), and the present series would support the view that reflex seizures in the context of symptomatic epilepsies tend to be medically refractory.

Six of our eight patients had some types of seizures that occurred only upon specific stimulation, but not spontaneously. These were drop attacks or axial myoclonic seizures and were seen in patients with localized or more extensive MCDs. These seizure types usually result from rapid synchronization of ictal activity over both cerebral hemispheres, or from the activation of corticosubcortical circuits involved in the maintenance of axial tonus (29,30). It is possible that the enhanced epileptogenicity associated with MCDs may facilitate fast bilateral or subcortical propagation of ictal activity, leading to drop attacks or axial myoclonus upon sensory stimulation. With the exception of startle-induced seizures (26), severe seizures exclusively induced by sensory stimulation are rare, and it is thus possible that the dysplastic nature of the lesion in our patients facilitated their occurrence. [Indeed, a detailed report found that a significant number of patients with startle-induced drop attacks had variable forms of MCDs on evaluation with high-resolution imaging (26)].

A number of clinical and EEG findings suggest that MCDs are highly and intrinsically epileptogenic. These lesions often lead to medically refractory seizures (12,13), give rise to epilepsia partialis continua and other types of

status epilepticus (31–36), and produce continuous epileptogenic discharges recorded on the scalp EEG or directly over the lesion, on short- or long-term ECoG (15,16,37,38) (see Fig. 2A). Furthermore, these lesions are often localized around the rolandic regions (12,31,39), thus having the potential to lead to hyperexcitable sensorimotor synaptic loops.

The mechanisms associated with the intrinsic and enhanced epileptogenicity in MCDs are an active field of research. Morphologic studies point to persistent "epileptogenic" plasticity and abnormal connectivity, and it has been suggested that dysplastic neurons and balloon cells may escape programmed cell death through continuous expression of neurotrophins and *trk* receptor proteins (40). This would allow these cells to augment their synaptic network through retained active neurite plasticity. Neurophysiologic evidence for increased and intrinsic epileptogenicity of dysplastic tissue was recently obtained from in vitro studies of slices of tissue resected from patients with focal cortical dysplasia. In the presence of 4-aminopyridine, a K^+ channel blocker that increases transmitter release, spontaneous and prolonged epileptiform discharges resembling EEG seizures were recorded (41). These were blocked by the application of NMDA (*N*-methyl-D-aspartate) and AMPA (D-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonists, suggesting the participation of excitatory amino acid receptors in the process. Furthermore, immunocytochemical studies of malformed tissue have shown a reduced density of inhibitory γ-aminobutyric acid (GABA)ergic interneurons and an increase in the number of abnormally oriented pyramidal cells with immunostaining for excitatory amino acid receptors (42–44).

The basic mechanisms of epileptogenicity associated with other types of MCD—notably the heterotopias and polymicrogyria—have received less attention. Notably, however, it has been demonstrated that immature neurons in heterotopic positions can make reciprocal connections with the neocortex and other heterotopic aggregates (17,18), which could lead to networks of sustained hyperexcitability. In addition, basic research on animal models of polymicrogyria (45–48) has attested to the formation of hyperexcitable intracortical networks. Further studies on the neurochemical changes underlying both polymicrogyric and heterotopic malformations may clarify the epileptogenic tendency in these lesions.

The role of the different forms of MCDs in the generation of reflex seizures in our patients is additionally supported by functional anatomic correlation with the reflex seizure types (see Tables 1 and 2). Thus, patients with perisylvian lesions had seizures induced by eating or talking; those with posterior quadrant abnormalities had reflex attacks precipitated by visual, oculomotor or proprioceptive stimuli; one patient with a periinsular lesion had seizures related to interoceptive stimuli; and one of

the patients with startle-induced drop attacks had a diffuse band heterotopia (the other had a diffuse frontal lobe abnormality). Finally, one patient with seizures related to somatosensory stimulation of the sole of the right foot and to bladder fullness had a dysplastic lesion in the contralateral sensorimotor cortex.

Interestingly, in many instances, these malformations retain the usual function expressed by the region where they are located or where heterotopic neurons were bound to migrate. Although much is still to be learned in terms of MCDs and cortical function, some evidence from functional MRI suggests a gradient of functionality along the spectrum of MCDs. Thus polymicrogyric lesions are most often functional, followed by heterotopia. Focal cortical dysplasia and hemimegalencephaly, conversely, are the least functional (49,50). The potential inverse relation between functionality and degree of epileptogenicity is an attractive speculation, inasmuch as converging data show that epileptogenicity is highest in focal cortical dysplasias (51).

In patients with refractory reflex seizures associated with localized MCDs, resective surgery should be considered (27), and the favorable result achieved in patient 4 supports this approach. Likewise, if a dysplastic lesion is suspected on the basis of clinical and electrographic findings in patients with reflex seizures and normal MRI, further evaluation and surgery also should be considered, as shown by patient 8. The role of callosotomy to control reflex drop attacks in these patients is less clear.

It is intriguing that in most of our patients, different types of stimuli led to the same type of reflex seizures, suggesting that different types of stimuli can be channeled to the motor regions through the same sensory pathways. The two patients with eating seizures also had the same type of reflex seizures precipitated by talking. Seizures induced by talking can involve the same perisylvian regions responsible for eating-related attacks (9,25). Similarly, the patient with seizures independently provoked both by eye deviation to the left side and by blinking most likely has a trigger related to the cortical projection of proprioceptive afferents from the ocular muscles, which could be activated by either action. In the patient with seizures induced by rubbing the sole of the right foot and by urinary bladder distention, both stimuli would project to the medial aspect of the central region, where a focal cortical dysplasia was found at surgery. Finally, in two patients, sudden, unattended, presentation of either auditory or tactile stimuli led to startle-induced seizures (21,26,52).

The low frequency of reflex seizures reported in patients with MCDs might argue in favor of possible *protective* effects secondary to the malformation. Indirect evidence supporting this possibility is that in some patients operated on for an MCD, postoperative seizures originate in regions remote from the resection site or even in the contralateral hemisphere (53–55). It is possible that parts of the MCD

exerted tonic inhibitory effects on these regions, which became active only after removal of the major MCD. This hypothesis raises the issue of "distributed epileptogenesis" in MCDs (55). By this token, epileptogenicity associated with MCD would be distributed over a network interconnecting separate "foci" with variable epileptogenic thresholds. These foci could all be within the limits of the visible lesion or involve nonlesional adjacent or distant, synaptically interconnected regions. When outside the boundaries of the visible lesion, these foci could be associated with microscopic dysplastic abnormalities or simply represent low-threshold regions that developed as such through mechanisms of secondary epileptogenesis, particularly kindling (56). In such a network, ictal and interictal activity generated within slightly distinct time-frames at different "nodes" could have a net inhibitory effect over the whole network. Recent data derived from signal analysis of ictal stereo-EEG recordings in patients with partial seizures do suggest that an epileptogenic network, rather than a single focus, is operative immediately preceding seizure onset (57–59). Interestingly, however, this network conformation also can lead to scenarios in which ictal activity locally generated at a single node of a distributed network may be prevented from recruiting the whole network (and thus lead to a clinical seizure) if other nodes are displaying high-frequency, out-of-phase interictal spiking. This has been shown to occur experimentally (60) and is a theoretical model to suggest that out-of-phase hyperexcitability within a distributed network may indeed have a net inhibitory effect over the network. Such a model of distributed epileptogenesis could provide a mechanism through which a hyperexcitable response to an afferent sensory volley may not lead to reflex seizures. The fact that MCDs are highly epileptogenic and tend to generate a large number of interictal spikes may very well fit this model. As a corollary, clinical and basic science studies of MCDs may provide an opportunity for exploring both excitatory and inhibitory influences of high degrees of epileptogenicity on epileptogenic networks.

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