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The Congenital Bilateral Perisylvian Syndrome: Imaging Findings in a Multicenter Study

Ruben Kuzniecky, Frederick Andermann, and the CBPS Study Group

PURPOSE: To describe the neuroimaging findings and the clinical features in patients with the congenital bilateral perisylvian syndrome. **PATIENTS AND METHODS:** Evaluation including history, general and neurologic examinations, electroencephalogram, chromosomal studies, and imaging data were reviewed in 31 patients. Pathologic material was available in two patients. **RESULTS:** All patients had similar neurologic dysfunction, primarily pseudobulbar paresis. Dysarthria and severe restriction of tongue movements were present in all. Motor milestones were delayed in 75% of the patients and language milestones in all. Mild to moderate intellectual deficits were documented in 75% of patients (full-scale IQ = 70). Pyramidal signs were observed in 70%. Seizures were present in 87% and were intractable to medical therapy in half of this group. MR revealed bilateral perisylvian and perirolandic malformations with exposure of the insula. The malformations were symmetrical in 80% of cases. Pathologic correlation revealed four layered polymicrogyria in the affected areas. **CONCLUSION:** The congenital bilateral perisylvian syndrome is a homogeneous clinical-radiologic entity. The underlying abnormality is probably polymicrogyria.

Index terms: Brain, growth and development; Brain, abnormalities and anomalies; Brain, magnetic resonance

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Advances in diagnostic imaging techniques, particularly magnetic resonance (MR) imaging, have permitted the recognition of developmental malformations of the central nervous system with a high degree of accuracy (1-4). Recent clinical-radiologic correlative studies have demonstrated the broad spectrum of these malformations and have contributed to the recognition that some of these disorders have common pathogenetic mechanisms (2, 5-8).

Kuzniecky et al (9) described four patients with congenital faciopharyngomasticatory diplegia, epilepsy, and cognitive deficits. On imaging studies, all had bilateral perisylvian structural abnormalities best characterized as dysplastic in nature.

It has been discovered that similar patients had been seen in several countries, but their conditions had not been recognized as a distinct entity. In this report, we present the clinical and imaging findings in 31 patients with this condition, which we have named the *congenital bilateral perisylvian syndrome*.

Patients and Methods

Thirty-one patients, including the four previously reported (9), were entered in this study. Ten international centers participated. Patient enrollment was based on clinical features alone or by the presence of clinical and imaging findings; in no case were patients recruited on the basis of the imaging findings alone. Recruitment from the participating investigators was carried out through a standardized protocol. All patients underwent physical and neurologic examinations. A standardized detailed questionnaire emphasizing pregnancy, development, associated malformations, and family history was used to acquire information. The histories were substantiated by medical records whenever possible. Particular attention to seizure history, seizure type, frequency, response to treatment, and course of treatment was also given.

Investigations included routine electroencephalographic studies, chromosomal high-resolution banding, metabolic

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Investigators and institutions that participated in this study are listed in the appendix.

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screening (six patients), and neuropsychologic testing when possible (10–12).

All patients had imaging studies including computed tomographic (CT) scans, and 28 had MR examinations. Because of the international collaborative nature of the study, patients were imaged with different MR units. Imaging studies included a variety of T1- and T2-weighted pulse sequences. Coronal, axial, and sagittal images, with section thickness varying from 3 to 8 mm, were obtained in the majority of patients. More recently some patients underwent studies using inversion-recovery sequences in the coronal and axial planes (1200/20/1 [repetition time/echo time/excitations], inversion time = 300, field strength = 1.5 T). The configuration of the sylvian and opercular regions were particularly studied. In addition, the antero-posterior extensions of the dysplastic malformations were evaluated using axial images. Cortical thickness was measured using a previously reported technique (2).

Neuropathologic material was available in two patients. Macroscopic examination and histologic sections were obtained using routine techniques.

Results

Clinical Features

Twenty of the 31 patients were girls or women. Their ages at the time of study ranged from 1 month to 41 years (mean 18 years). No particular prevalence of ethnic or racial origin was observed, but the study group included only European and North American centers.

Family histories revealed no instance of known consanguinity. A positive family history of epilepsy was present in one sibling, and in another family, an older brother who died at birth was reported to have had multiple congenital malformations. The occurrence of the syndrome was documented in two families; in one family, identical monozygotic male twins affected with the syndrome were studied. In the other family, an affected sister and brother with a deceased maternal uncle possibly affected with the syndrome were documented. Chromosomal and metabolic studies were normal in all those tested (17 of 31).

Pregnancies were normal in all but six patients. One was born prematurely (36 weeks), and three reported vaginal bleeding during the first trimester. Polyhydramnios was documented at 28 weeks gestation in one, and another patient's mother underwent abdominal surgery during the 10th week of pregnancy. Deliveries were normal in 20 patients, but 11 patients were born by breech presentation. Perinatal asphyxia was reported in three patients. Associated malformations were present in 30% of patients. Table 1

TABLE 1: Main clinical features in 31 patients with the congenital bilateral perisylvian syndrome

Feature	No of Patients Affected	%
Abnormal tongue movements	31	100
Dysarthria	30 ^a	97
Mental retardation	26	85
Dysphagia	25	81
Absent gag reflex	23	75
Drooling	22	71
Pyramidal signs	22	70
Club feet	6	20
Arthrogryposis multiplex	4	13
Micrognathia	2	6
Syndactily	1	3
Hip dysplasia	1	3

^a Dysarthria could not be evaluated in a 1-month-old child.

depicts the incidence and types of abnormalities present in the 31 patients. Motor milestones were mildly delayed in 75% of patients, with most of them achieving independent ambulation at approximately 17 to 20 months of age. Language milestones were delayed in all. Deglutatory problems were evident in all patients when solid food was introduced in the diet.

Neurologic manifestations common to all patients consisted of severe dysarthria and nasal speech. Two patients were mute with normal comprehension. The degree of dysarthria varied from moderate to severe. Tongue movements were consistently restricted with very limited protrusion and lateral movements. Intellectual assessment showed that 75% of patients had mild to moderate cognitive deficits, with an average full-scale IQ in those tested of 70 (range 52–77). Five patients exhibited low average intelligence (full-scale IQ 82–91). Language testing revealed normal comprehension in those tested.

Seizures were documented in 27 of the 31 patients (87%). Epileptic attacks began between the ages of 6 and 12 years in the majority. The seizures in the majority of cases consisted of atypical absence and rare generalized tonic-clonic attacks. In addition, atonic and tonic drop attacks were also documented. Five patients (19%) had partial seizures with or without secondary generalization, and three patients had bilateral clonic contractions of the lips or perioral seizures with secondary generalization. The frequency of seizures varied between individuals, but 55% of patients had seizures almost daily. Electroencephalograms showed generalized or bilateral spike and wave discharges in 50% of patients.

Imaging Studies

CT scan revealed symmetrical bilateral perisylvian cortical thickening. The abnormal cortex appeared thick and smooth, and the sylvian fissures were slightly enlarged in all patients. On CT, the malformations extended into the centroparietal regions with minor asymmetries (Fig 1A). Calcifications were not observed. MR confirmed the bilateral perisylvian involvement but, with higher resolution, demonstrated some variability in the extent of the abnormalities among patients. In the sagittal plane, the malformations were centered in the insular region with variable extension into the pars opercularis. The subcentral gyrus was invariably involved with limited extension into the transverse temporal gyrus (Fig 1B). Using axial and coronal images, the insula and in particular the long insular gyrus were studied. The insula appeared exposed, and the long insular gyrus was invariably thick. Posterior extension with involvement of the supramarginal gyrus and associated atrophy of the angular gyrus was prevalent. In some cases, the malformations involved the opercular and perisylvian regions alone, whereas in others the malformations extended into the parietal and superior temporal regions. The cortex had a thick appearance in some regions, intermixed with shallow sulci and broad gyri. Cortical thickness in the abnormal regions ranged from 8 to 10 mm (Fig 2). At the most posterior aspect of the malformations, increased subarachnoid space was common. Using inversion-recovery sequences, the abnormal cortex showed increased interdigitations between white and gray matter overlaid by small fused gyri, suggesting polymicrogyria (Fig 3). Nodular heterotopias or other abnormalities were not present

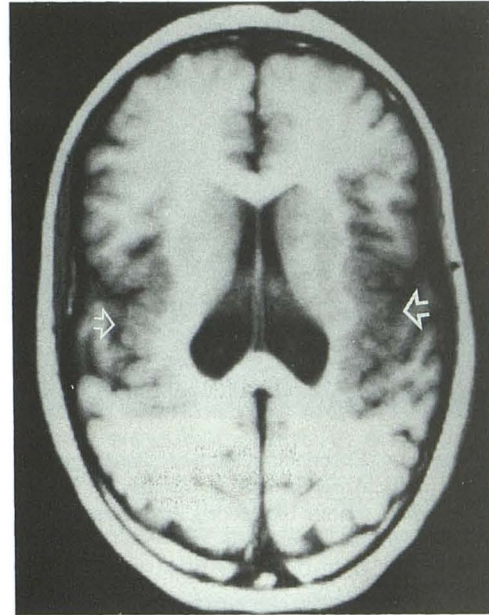


Fig. 2. Patient F-14. Axial image (400/20/2) shows symmetric bilateral malformations involving the insular region. Note small gyri and shallow sulci (arrows).

on MR. An absent septum pellucidum was observed in one patient.

Of the 28 patients with MR examinations, 20 had primary involvement of the insular-opercular region. In three others, the abnormal thick cortex was restricted to the insular region. In the remaining five, extension into the superior temporal and parietal regions was observed. Detailed evaluation of the MR using axial images revealed that the extent of the malformations was symmetrical in 80% of patients. In 20%, the MRs demonstrated minor asymmetry in the anteroposterior extension of the malformations (Fig 4). Clinical-imaging correlations revealed a relationship between the

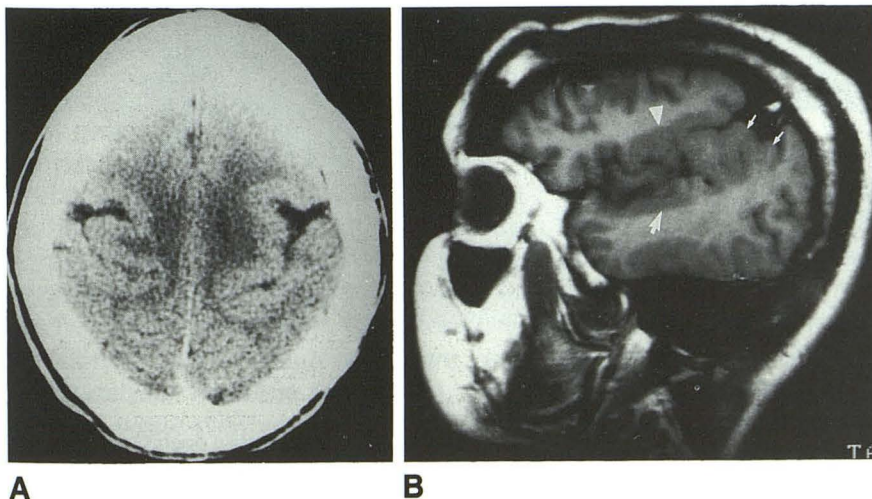


Fig. 1. Patient B-6.

A, CT scan section demonstrating bilateral centroparietal cortical malformations. Note slight asymmetric distribution posteriorly.

B, Sagittal image (500/15/2 [repetition time/echo time/excitations]) shows abnormal cortex involving the insula and sylvian fissure and extending posteriorly into the parietal lobe. The malformation involves the superior temporal gyrus (arrow), subcentral gyrus (arrowhead), and supramarginal gyrus (small arrows).

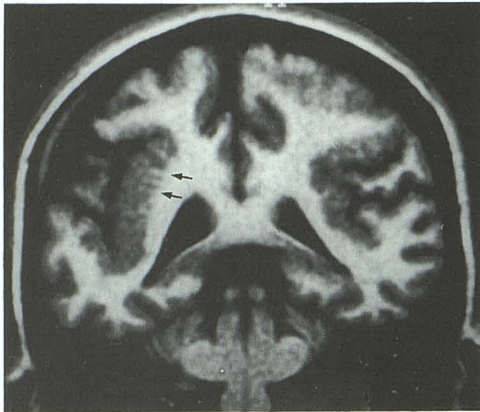


Fig. 3. Patient I-4. Coronal inversion-recovery sequence demonstrates asymmetrical malformations. Densely packed small gyri with thin gray-white matter digitations are observed within the malformations (arrows).

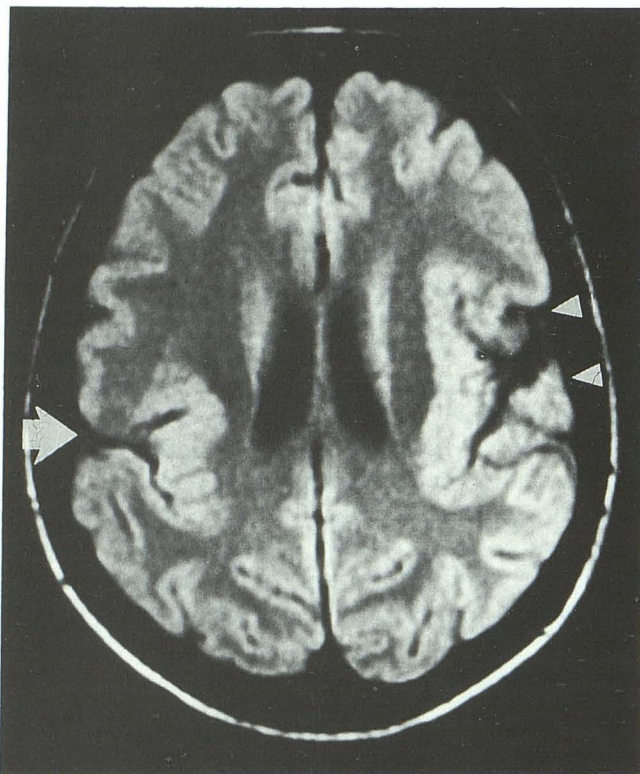


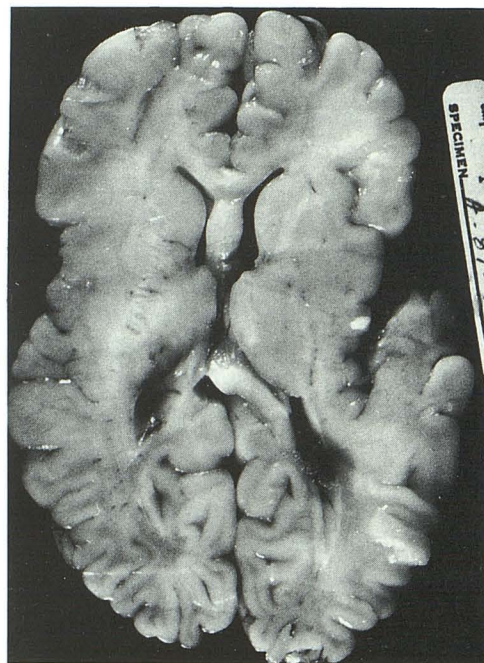
Fig. 4. Patient I-10. Axial image (2000/30) revealing asymmetric malformations. On the right, the defect is located posteriorly with almost normal insular closure and no involvement of the opercular region (arrow). On the left the insula and operculum are involved. Note exposure of insula (arrowheads).

degree of oromotor dysfunction and the bilateral symmetry of the malformations; those with asymmetrical lesions tended to have milder forms of dysarthria. Pyramidal dysfunction correlated with malformations extending into the prefrontal and central regions. Severe pyramidal dysfunction

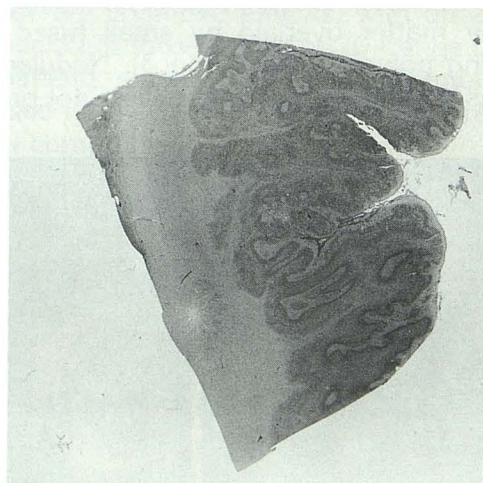
correlated with extensive malformations in three patients.

Neuropathologic Findings

Two patients died. In one, the death was attributed to aspiration; in the other no clear cause was found. Macroscopic examination of the brain revealed asymmetrical opercularization in one and symmetrical bilateral opercular hypoplasia resulting in exposure of the insula in the other (Fig 5A). No periventricular heterotopias were



A



B

Fig. 5. Patient M-31. A, Macroscopic view showing asymmetric opercularization. B, Histologic section through the right operculum showing polymicrogyric cortex (magnification 2X).

found, and the rest of the brain was normal in both. Histologic sections revealed four layered polymicrogyria in the insular and opercular region extending into the inferior frontal and parietal regions (Fig 5B).

Discussion

The 31 patients described in this study share a congenital syndrome with remarkable similarities. The syndrome includes developmental delay, variable cognitive deficits, prominent cortical pseudobulbar symptoms, and variable pyramidal signs. Seizures were common, and all patients shared the presence of bilateral perisylvian cortical malformations on imaging studies. These clinical and imaging features are sufficiently consistent to suggest a homogeneous entity.

These patients have prominent cortical pseudobulbar symptoms, especially variable dysarthria, orofacial paresis, and, most strikingly, the inability to protrude or move the tongue from side to side. In addition, they demonstrate a dissociation between voluntary and emotional facial movements. Similar acquired symptoms have been described in adults as the Foix-Chavany-Marie syndrome because of bilateral anterior opercular infarctions (13, 14). It is clear that the prominent pseudobulbar symptoms are the direct result of involvement of the insular and opercular regions. The degree of oromotor dysfunction, however, did not correlate with the extension of the malformations on MR, but depended on their symmetrical distribution; those with asymmetrical opercular and insular abnormalities tended to have milder forms of dysarthria. Conversely, those with pyramidal limb motor dysfunction had evidence on MR of extended malformations into the prefrontal and central regions when compared with those patients with no or mild pyramidal signs.

Imaging studies revealed the presence of bilateral perisylvian and perirolandic abnormalities in all patients. The lesions for the most part tended to be symmetric, but in 20% the bilateral distribution was asymmetrical. CT scans demonstrated thick smooth cortex in the opercular region, but MR revealed that some cortical areas had multiple small gyri. Furthermore, using inversion-recovery sequences, we were able to demonstrate multiple small gyri and absence of normal white-matter digitations within the lesions in some patients. Therefore, contrary to the early suggestion that the lesions represent pachygyria

or macrogyria, we believe that the imaging features are representative of polymicrogyria in the opercular and perisylvian regions (9). The insular distribution and the well-known predilection of the parasylvian region for polymicrogyria support our impression (15–16).

In a recent report, Barkovich et al described 12 patients with what the authors termed bilateral focal cortical dysplasia (2). Six had frontal involvement; in five the malformations were in the parietal lobes; the remaining patient had bilateral occipital lesions. Seizures and developmental delay were common, but details regarding oromotor dysfunction were not given. In addition, autistic behavior and dystonia were observed. As in our population, Barkovich et al noted that those with posterior frontal-lobe involvement had major motor dysfunction when compared with those who had more restricted and posterior malformations. Notwithstanding the clinical differences, we believe that at least some of their patients are probably examples of the syndrome described in this report.

The exact mechanism and timing for the development of these malformations remain controversial. The insula is first apparent at 18 weeks gestation. At 30 weeks, the opercula override the insulas, resulting in the normal adult brain configuration (17). The presence of an open operculum indicates opercular developmental arrest presumably by an insult occurring before 30 weeks gestation. Histologic studies in two of our patients revealed polymicrogyria in the abnormal cortex involving the opercular regions bilaterally, with variable extension into the frontal lobes (Figs 5A and 5B). The etiology of polymicrogyria is variable (1, 15–18). Ischemia has been postulated as a possible mechanism. Bilateral porencephalic cysts surrounded by microgyria have been reported and represent a severe ischemic insult caused by perfusion failure (15–18). Histopathologic studies have suggested that polymicrogyria may be the result of a postmigration insult (20–24 weeks gestation) (15–19). Conversely, experimental work in rodents (20–21) and case studies on fetal diseases (22) have suggested that accidents caused by early migration (12–16 weeks gestation) may be responsible for the microgyric cortex, and therefore polymicrogyria represents a disorder of neuronal migration. On the basis of these data, Barth (1) has suggested that early migration polymicrogyria is of the unlayered type, and that postmigration insults give rise to four-layered microgyria. The presence of periventric-

ular nodular heterotopias associated with unlayered type polymicrogyria may support his theory. Irrespective of the exact timing of the injury, and considering that both early and late ischemic injuries may induce similar macroscopic perisylvian malformations (open operculum), it is likely that in our patients the lesions are the result of a restricted ischemic injury during development.

The condition in many of these patients is presently unrecognized. It is our experience that many children with this syndrome are not diagnosed, because the combination of spastic cerebral palsy, mental retardation, and epilepsy are common among children with bilateral cerebral injuries. Appropriate evaluation of speech abnormality and identification of the prominent pseudobulbar signs should be sufficient to make a tentative diagnosis. This can be confirmed with CT or MR.

The clinical and imaging features of these patients suggest a congenital developmental syndrome. Although Barkovich et al intentionally used the term *bilateral cortical dysplasia* to describe these malformations, they correctly suggested that the underlying histologic abnormality in some of these patients may be polymicrogyria (2). Our study confirms with pathologic data their suggestion and illustrates the clinical and imaging spectra of this syndrome.

Appendix

The following investigators and institutions participated in this study: *Investigators*: Ruben Kuzniecky, Study Chairman (University of Alabama at Birmingham Epilepsy Center); Frederick Andermann, Study Cochairman (Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada); Renzo Guerrini (INPE-IRCCS, Stella Maris, Pisa, Italy); Donnatela Tampieri, Eva Andermann, Andre Palmi, and Michael Shevell (Montreal Neurological Institute and Montreal Children's Hospital, McGill University); Lucia Fusco and Federico Vigevano (Hospedale Bambino Gesù, Rome, Italy); Neill Graff-Radford (University of Iowa, Iowa City, Iowa); Suzanne Christie, Peter Humphreys, and Sharon Whiting (University of Ottawa, Ottawa, Ontario, Canada); Jean Aicardi (Hopital des Enfants Malades, Paris, France); G. Ambrosetto and Carlo A. Tassinari (Università di Bologna, Bologna, Italy); Bernardo Dalla Bernardina and Vito Colamaria (Università di Verona, Verona, Italy); Edward Faught and Richard Morawetz (University of Alabama at Birmingham); and Charlotte Dravet (Centre St Paul, Marseille, France).

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