Neuropathology 2006; **26**, 236–242 doi:10.1111/j.1440-1789.2006.00659.x

East Asia Friendship Workshop

Bilateral perisylvian ulegyria: Clinicopathological study of patients presenting with pseudobulbar palsy and epilepsy

Hyoung-Ihl Kim,[1] Min-Cheol Lee,[2,3] Ji-Shin Lee,[2] Hyung-Seok Kim,[2] Myeong-Kyu Kim,[3] Young-Jong Woo,[3] Jae-Hyoo Kim,[3] Shin Jung,[3] Andre Palmini[4] and Seung U. Kim[5,6]

[1]Department of Neurosurgery, Presbyterian Medical Center, Chonju, [2]Department of Pathology and [3]Epilepsy Clinic, Chonnam National University Medical School, Gwangju, Korea and [5]Brain Disease Research Center, Ajou University, Suwon, Korea; [4]Porto Alegre Epilepsy Surgery Program, Hospital Sao Lucas da PUCRS, Porto Alegre, Brazil; and [6]Department of Neurology, University of British Columbia, Vancouver, BC, Canada

Structural abnormalities related with pseudobulbar palsy have been gaining attention because of their characteristic symptoms and unique pathogenesis. We present five cases of bilateral perisylvian ulegyria (BPU) presenting epilepsy and pseudobulbar palsy with pathogenesis different from previously reported syndromes. All patients showed medically intractable seizures, complex partial seizures with secondary generalization and clinical symptoms of pseudobulbar palsy, including dysarthria, limitation of tongue movement and drooling. MRI revealed BPU in all patients, and BPU associated with hippocampal sclerosis in four patients. Intracranial EEG recording with subdural grip and stripe was helpful for localizing the area of ictal generation. Resective surgeries, including the temporal lobe, central area and parietal lobe, were performed depending on the localizing information. The surgical outcome was favorable after 9.8 years of follow-up. Characteristic features of ulegyria were confirmed on pathological examination. Ulegyria is considered to be another important perinatal or postnatal structural abnormality which can explain the etiological heterogeneity for pseudobulbar palsy, which results from bilateral perisylvian lesions. Awareness of this disorder can provide a useful strategy for evaluation and treatment which differs from that in perisylvian polymicrogyria.

Key words: atrophy, complex partial, epilepsy, gliosis, pathogenesis, pseudobulbar palsy.

Correspondence: Min-Cheol Lee, MD, PhD, Department of Pathology, Chonnam National University Medical School and Hospital, 5 Hakdong, Dongku, Gwangju 501-190, Korea. Email: mclee@jnu.ac.kr

Received 13 June 2005; revised and accepted 29 July 2005.

INTRODUCTION

Recent advances in brain imaging technology and the availability of surgical specimens obtained from epilepsy surgery have broadened our understanding of structural abnormalities associated with intractable epilepsy.[1,2] Structural lesions involving the bilateral perisylvian region have gained close attention as they present characteristic clinical symptoms.[3–5] Clinical manifestations stemming from bilateral perisylvian structural abnormalities include pseudobulbar palsy characterized by dysarthria with poor lingual and labial consonant dysarthria, limited tongue movement, drooling and dysphasia. Such manifestations are often accompanied by mental retardation and epileptic seizures.[6–8] Of these symptoms, speech abnormalities were particularly emphasized by Worster-Drought.[3,4,9,10] However, Graff-Radford et al. first described characteristic MRI findings for perisylvian polymicrogyria in patients with pseudobulbar palsy.[11] The latter findings were later analyzed by Kuzniecky to propose a new syndrome, congenital bilateral perisylvian syndrome (CBPS).[6]

Ulegyria shows shrunken groups of gyri with gliosis, especially in the depths of the sulci, but relatively well-preserved gyral surfaces, which are consistent with the late effects of perinatal hypoxic brain damage.[3,8,12–14] Ulegyria tends to occur in a symmetrical fashion and often involves the perisylvian region. Accordingly, patients with ulegyria show similar symptoms to those of CBPS. However, ulegyria was seldom reported to explain pseudobulbar palsy resulting from structural abnormalities in the bilateral perisylvian region. Bilateral perisylvian polymicrogyria has been predominantly cited to explain these characteristic symptoms in patients whose MRI show similar structural lesions despite the possibility of etiological heterogeneity

explain the pseudobulbar palsy.[15] We herein describe a new syndrome characterized by pseudobulbar palsy and epilepsy resulting from bilateral perisylvian ulegyria (BPU).

MATERIALS AND METHODS

Patients

We retrospectively analyzed seven patients who underwent surgical resections between 1993 and 1998 because of medically intractable seizures, pseudobulbar palsy and MRI findings suggesting ulegyria. Surgical specimens from these patients were re-evaluated to confirm typical histological findings of ulegyria. Histological criteria to diagnose ulegyria include groups of atrophic gyri, loss of the cortical tissue in the depths of the sulci and destruction and gliosis of subcortical white matter.

Patients consisted of four men and one woman, who had medically intractable seizures. Patients were underwent surgery at a mean age of 32 years (range, 21–42) after 20–30 years of recurrent seizures (mean 25). Postoperative follow up for these patients ranged from 7 to 12 years (mean 9.8).

Clinical features

All patients were evaluated according to preoperative investigation protocols, including clinical history, thorough neurological examination, MRI, video-EEG monitoring, and intracranial EEG recordings. Specifically, the severity of pseudobulbar signs was classified as mild, moderate or severe, depending on the degree of dysarthria and the restriction in tongue movement. To correctly detect the abnormal findings on MRI, we paid close attention to the extent and location of the ulegyric abnormalities on T1-weighted coronal and axial images. In addition, we noted the presence and the extent of increased subcortical signals indicative of gliosis on T2-weighted, proton density or fluid-attenuated inversion recovery (FLAIR) images. Associated hippocampal sclerosis was also observed. All patients were investigated with a video-EEG monitoring system to analyze the seizure types and ictal EEG patterns (Stellate, Canada). All patients were additionally investigated with subdural grids and strips (Ad-Tech, Inc, USA).

Operative procedures and outcome

Resective surgery was performed in all patients, supplemented by multiple subpial transections in one. All surgical specimens were submitted for pathological evaluation. Tissues were serially dissected into 3 mm thicknesses and were examined grossly and microscopically. Microscopic slides were prepared from formalin-fixed, paraffin-embedded tissue. Sections were cut 4 μm thick and were stained with hematoxylin-eosin (HE). The number of slides examined in each case ranged from six to 14 (mean, nine slides). Luxol fast blue-PAS (periodic acid-Schiff) stain, and immunohistochemical stains for glial fibrillary acidic protein (GFAP) and neurofilament protein (M/H) were used in selected cases. Surgical outcome was categorized by the classification system described by Engel.[16]

RESULTS

Clinical characteristics and seizure analysis

Table 1 summarizes the clinical characteristics. One patient had a history of hypoxia at birth and one patient had traumatic delivery. Five patients showed pseudobulbar signs to a moderate ($n = 3$) or mild degree ($n = 2$). The seizure type at the time of surgery was complex partial progressing to generalized tonic clonic in all patients. Standard EEG showed unilateral temporal spikes in one, yet multilobar spikes were observed unilaterally in six patients. However, six patients who underwent intracranial EEG recordings showed single lobar seizure onset in four and unilateral multilobar seizure onset in two. The seizure onset area grossly matched the area of cortical ulegyric abnormality.

MRI findings

MRI revealed ulegyric characteristic features of ulegyric cortical abnormalities, which include thin gyri in the depth of sulci and subcortical gliosis (Fig. 1). Ulegyric abnormalities in the bilateral perisylvian region were observed in five patients. One patient had a bilateral ulegyric abnormality in the parieto-occipital region. Only one patient showed a unilateral ulegyric abnormality in the left centroparietal region. Bilateral abnormalities involved the perisylvian region in a symmetrical fashion in all patients. In addition, four had associated hippocampal sclerosis.

Surgery and pathological findings and surgical outcome

Temporal lobectomies were performed in four patients: one had only a temporal lobectomy, two had additional resections of the central area and one had supplementary multiple subpial transections in the central area (Fig. 2). One other patient had a cortical resection of the ulegyric cortex and adjacent area under the guidance of electrocorticography after electrical stimulation mapping of central area. Postoperatively, two patients showed worsening of dysarthria, which was gradually relieved. One patient showed an infection of the bone flap. Excised ulegyric specimens showed marked atrophy of both gray matter along sulci and white matter. Thus, the cortex showed

Table 1 Clinical features of patients with bilateral perisylvian ulegyria

Patient No.	Age	Sex	Duration epilepsy (years)	Perinatal insults	Pseudobulbar signs	Magnetic resonance imaging	Seizure types	Spikes instandard EEG	Invasive recording	Operation	Pathological feature	Final outcome
1	21	M	20	Hypoxia at birth	++	BPU + Lt HS	CPS GEN	Lt T	no	Lt TL	HS	IB
2	29	F	25	Not assessed	+	BPU + Rt HS	CPS GEN	Rt C-T-P	Rt, T-C	Rt TL + C Rec	U + HS	II
3	42	M	30	Not assessed	++	BPU + Rt HS	CPS GEN	Rt C-T-P	Rt C	Rt TL + C Rec	U + HS	II
4	38	M	30	Traumatic birth	+	BPU + Lt HS	CPS GEN	Both C-T	Lt T	Rt TL + Rt C MST	U + HS	IV
5	30	M	20	Not assessed	++	BPU F-C-P	CPS GEN	Both F-T	Rt C	Rt C Rec	U	II

+, Mild degree; ++, moderate degree; BPU, bilateral perisylvian ulegyria; C, central; CPS, complex partial seizures; F, frontal; GEN, secondary generalization; HS, hippocampal sclerosis; Lt, left; MST, multiple subpial transection; P, parietal; Rec, resection; Rt, right; T, temporal; TL, temporal lobectomy; U, ulegyria.

mushroom-like shapes in the superficial gyri in gross examination. Calcification and cystic changes were observed in two patients. Microscopically, variable degrees of irregular subpial and subcortical gliosis, laminar cortical necrosis and formation of neuronal islands were observed in the gray matter. In addition, many amyloid bodies were present in subpial cortex and gray-white matter junctions. White matter showed reactive gliosis, focal calcifications and fibrosis, pseudocystic change, and secondary demyelination (Fig. 3). Four patients with MRI pictures suggestive of hippocampal sclerosis had neuronal loss and gliosis in the hippocampus and in the subiculum, predominating on subfields CA1 and CA3.

One patient was seizure free (Engel's class I) and two had rare seizures (Class II) and did not improve significantly (Class IV) with a mean follow up of 9.8 years.

DISCUSSION

Our study showed that ulegyria can be an important pathologic abnormality that explains pseudobulbar palsy and epileptic seizures. Pathologic examination of ulegyria was not feasible in one patient out of five, because surgical resection of the patient was limited to the temporal lobe where abnormal spikes developed during invasive EEG recording covering the temporocentral area. However, it is certain that MRI findings are very compatible with perisylvian ulegyria.

Ulegyria is caused by perinatal and postnatal injury in the cortical neurons.[14] However, it is not possible to obtain positive histories to pursue the causes of perinatal events, for they are minor or overlooked by mothers. Only two of our patients were witnessed by their family to have perinatal events related with pathogenesis of ulegyria. Damage to neurons may be limited to border regions between the arterial distributions of major blood vessels. Etiology is not yet clear, circulatory collapse and a consequent decrease in perfusion of tissues supplied by the end branches of major blood vessels may result in cortical gyral damage.[17]

In the late phase, after severe cortical neuronal necrosis, damaged gyri are narrowed, sclerotic, cystic and/or white to a greater extent than adjacent intact cortex.[18] Subcortical deep white matter is reduced in volume and is sclerotic or cystic. Damaged gyri may have a mushroom-like appearance.[19,20] This gyral damage may be focal, bilateral, symmetrical or diffusive. Interestingly, these changes may involve abnormalities of perisylvian regions resembling the morphology and clinical characteristics of congenital bilateral perisylvian syndrome.[2,11,21,22] In fact, these similarities often make it difficult to make a correct diagnosis, consequently, the appropriate treatment option can often be missed. Ulegyria is different from CBPS in several respects: CBPS demonstrates bilateral polymicrogyric

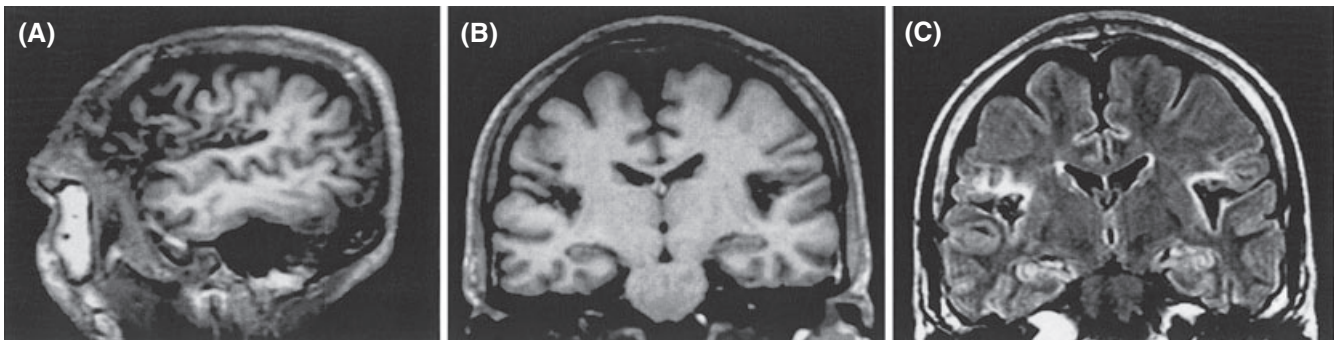

Fig. 1 MRI of patient with ulegyria (Case 5): (A) T1 weighted sagittal image demonstrates the ulegyria in perisylvian region; (B) T1 weighted coronal image demonstrating bilateral involvement of ulegyric abnormality in perisylvian region; (C) flair imaging showing subcortical gliosis extending deep into sylvian fissure.

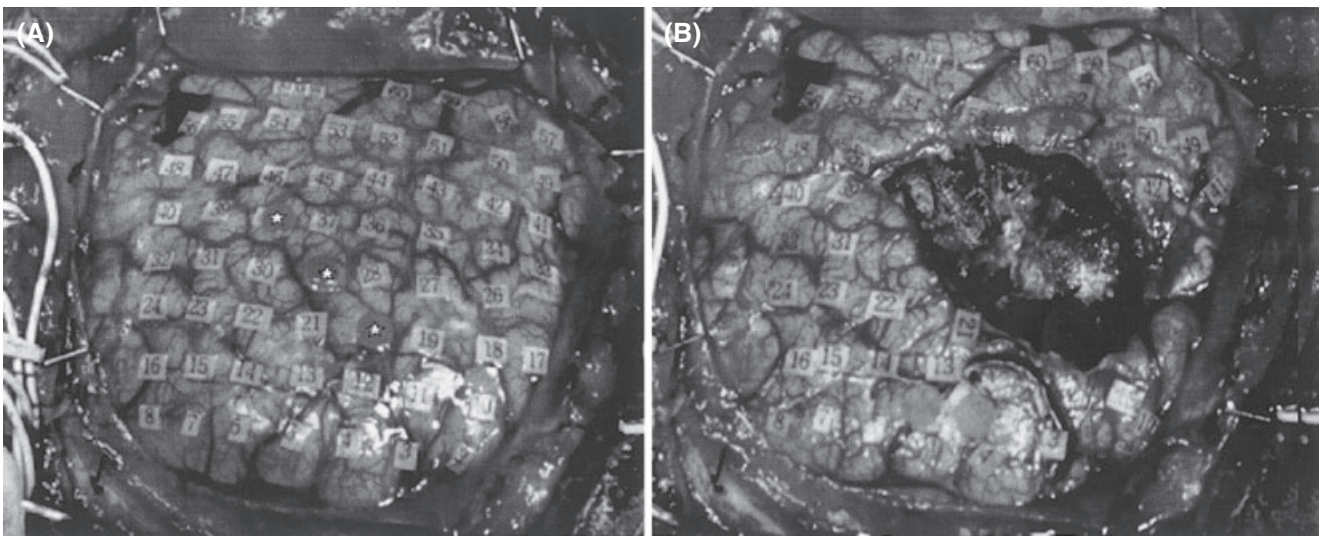

Fig. 2 Operative photography in patients with ulegyria: (A) exposed cortex with markers, white stars indicate the motor cortex, note the narrowed cortices behind motor cortex; (B) post-operative photography shows the resection of the lower central area including motor and sensory cortex.

abnormalities, which result from disturbances of neuronal migration in the embryonic stage and it often shows genetic inheritance.[6,23] Awareness of the differences between ulegyria and polymicrogyria can help early diagnosis by MRI, although clinical and epileptic manifestations are very similar.[13,24]

Epileptic seizure is an important problem that is presented in both ulegyric and CBPS patients. Seizures may be medically intractable, from which surgical methods are sought. However, surgical resection has been abandoned in CBPS because of bilaterality of lesions. Only callosotomy was considered if patients showed drop attacks.[25] Ulegyria has diffusive subcortical gliosis, which may be related with epileptogenicity, and therefore these lesions are amenable to surgical resection. Recently, resective surgeries in the presence of bilateral lesions have been reported in the literature with variable results.[26–28] Likewise, we performed resective surgeries in our patients with favorable outcomes. It is not clear why unilateral ulegyria is related to seizure generation despite the presence of bilateral ulegyria. It may be related to the fact that unilateral hippocampal sclerosis is mostly responsible for seizure generation in the presence of bilateral hippocampal atrophy/sclerosis.[9] Another reason why we decided to perform resective surgery was the presence of associated hippocampal sclerosis. Hippocampal sclerosis supported by electrographic evidence is likely to be considered for resective surgery despite the presence of bilateral structural abnormalities. We assume that pathogenesis of hippocampal sclerosis in this setting is different from the conventional one. Hippocampal sclerosis is thought to be produced by perinatal or postnatal hypotension, which also causes cortical neuronal

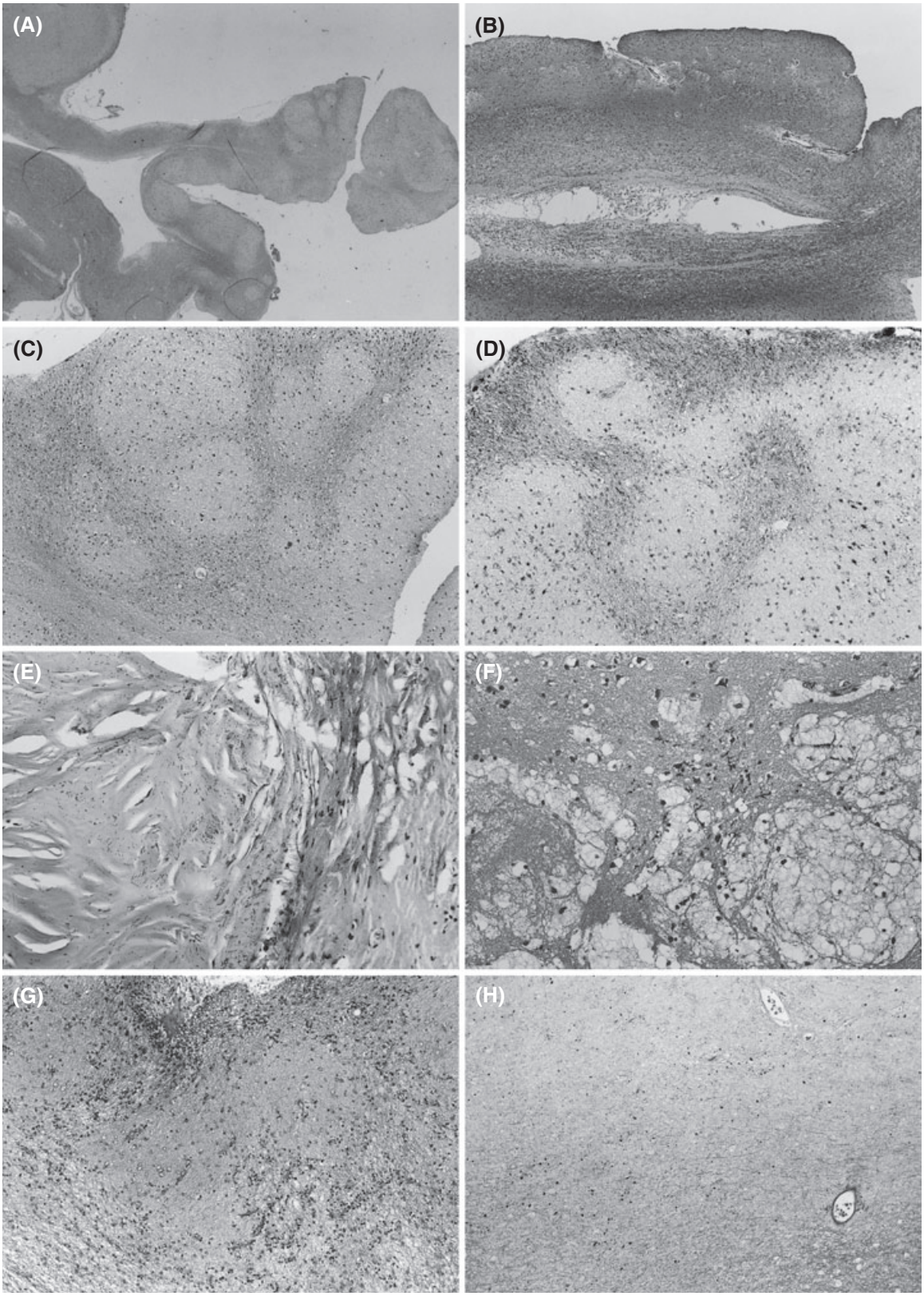

Fig. 3 Histopathologic examinations of the epileptogenic lesion exhibit perisylvian ulegyria. (A, B) Cerebral cortex discloses a mushroom-shaped gyrus formed by severe atrophy of deep gyrus with less severe atrophy of superficial gyrus (H&E, ×4), and laminar necrosis and thinning of the gray matter associated with reactive gliosis and pseudocystic change (H&E, ×25). (C, D) Neuronal islands are sequestrated by irregular, lobular gliosis in the gray matter (H&E, ×60), which features are supported by an immunohistochemical stain (GFAP, ×60). (E, F) Gliofibrotic nodule (H&E, ×100) and microcystic change (H&E, ×80) are shown. (G, H) Many amyloid bodies are present throughout the gray and white matter (Luxol fast blue-PAS, ×35), and the white matter revealed decreased stainability for myelin (Luxol fast blue-PAS, ×40).

loss, rather than initial febrile convulsions or recurrent early childhood seizures.[29]

Worster–Drought syndrome (WDS) is another syndrome presenting pseudobulbar palsy. It is not clear how this disorder is related to CBPS or bilateral perisylvian ulegyria because most of these cases were diagnosed before MRI was invented. Although there are minor differences between CBPS and WDS, they are regarded as a continuum.[30] However, we think some patients with WDS may have bilateral perisylvian ulegyria presenting with pseudobulbar palsies. Two of our patients had no mental retardation as in WDS. It is more reasonable to conclude WDS may be caused by prenatal defect of embryogenesis-bilateral perisylvian polymicrogyria or ulegyria.

In summary, based on our experiences, we would conclude that bilateral perisylvian ulegyria is a unique syndrome that presents with pseudobulbar palsy and epilepsy, similar to CBPS. However, the basic pathogenesis of bilateral perisylvian ulegyria is very different, and consequently, neuropathologic features are contrasted with those of CBPS. If patients with bilateral perisylvian ulegyria have intractable epilepsy, surgical resection can be considered in selected cases. The promising results of resective surgery in our patients support this notion. Although the basic mechanism of epileptogenesis needs further refinement, subcortical gliosis and associated hippocampal sclerosis may be contributing to provoking recurrent seizures.

ACKNOWLEDGMENTS

This work was supported by a research grant of KOSEF through the Medical Research Center (R13-2002-013-00000-0) at Chonnam National University.

REFERENCES

1. Palmini A, Andermann F, Olivier A *et al.* Neuronal migration disorders: a contribution of modern neuroimaging to the etiologic diagnosis of epilepsy. *Can J Neurol Sci* 1991; **18**: 580–587.
2. Sener RN. Bilateral, perisylvian and rolandic cortical dysplasia in trisomy 13 syndrome. *J Neuroradiol* 1996; **23**: 231–233.
3. Guerreiro MM, Andermann E, Guerrini R *et al.* Familial perisylvian polymicrogyria: a new familial syndrome of cortical maldevelopment. *Ann Neurol* 2000; **48**: 39–48.
4. Clark M, Carr L, Reilly S, Neville BG. Worster–Drought syndrome, a mild tetraplegic perisylvian cerebral palsy: review of 47 cases. *Brain* 2000; **123**: 2160–2170.
5. Kuzniecky R, Andermann F, Guerrini R. Congenital bilateral perisylvian syndrome: study of 31 patients. The CBPS Multicenter Collaborative Study. *Lancet* 1993; **341**: 608–612.
6. Kuzniecky R, Andermann F, Guerrini R. The epileptic spectrum in the congenital bilateral perisylvian syndrome. CBPS Multicenter Collaborative Study. *Neurology* 1994; **44**: 379–385.
7. Kim HI, Palmini A, Choi HY, Kim YH, Lee JC. Congenital bilateral perisylvian syndrome: analysis of the first four reported Korean patients. *J Korean Med Sci* 1994; **9**: 335–340.
8. Gordon N. Worster-Drought and congenital bilateral perisylvian syndromes. *Dev Med Child Neurol* 2002; **44**: 201–204.
9. Christen HJ, Hanefeld F, Kruse E, Imhauser S, Ernst JP, Finkenstaedt M. Foix-Chavany-Marie (anterior operculum) syndrome in childhood: a reappraisal of Worster–Drought syndrome. *Dev Med Child Neurol* 2000; **42**: 122–132.
10. Arbelaez A, Castillo M, Tennison M. MRI in a patient with the Worster–Drought syndrome. *Neuroradiology* 2000; **42**: 403–405.
11. Graff-Radford NR, Bosch EP, Stears JC, Tranel D. Developmental Foix–Chavany–Marie syndrome in identical twins. *Ann Neurol* 1986; **20**: 632–635.
12. Barkovich AJ, Hevner R, Guerrini R. Syndromes of bilateral symmetrical polymicrogyria. *AJNR Am J Neuroradiol* 1999; **20**: 1814–1821.
13. Olive M, Ferrer I, Arbizu T, Calopa M, Ferrer X, Peres J. [Polymicrogyria and ulegyria: diagnosis by magnetic resonance.] *Neurologia* 1992; **7**: 117–119. (In Spanish with English abstract.)

14. Kinney HC, Armstrong DD. Perinatal neuropathology. In: Graham DI, Lantos PL (eds). *Grienfield's Neuropathology*, **Vol. 1**, 7th edn. London: Arnold, 2002; 519–606.
15. Engel J, Van Ness P, Rasmussen T. Outcome with respect to epileptic seizures. In: Engel J (ed.) *Surgical Treatment of the Epilepsies*. New York: Raven Press, 1993; 609–621.
16. Azzarelli B, Meade P, Muller J. Hypoxic lesions in areas of primary myelination: a distinct pattern in cerebral palsy. *Child Brain* 1980; **7**: 132–145.
17. Morys J, Narkiewicz O, Wisniewski HM. Neuronal loss in the human claustrum following ulegyria. *Brain Res* 1993; **616**: 176–180.
18. Borit A, Herndon RM. The fine structure of plaques fibromyeliniques in ulegyria and in status marmoratus. *Acta Neuropathol* 1970; **14**: 304–311.
19. Gropman AL, Barkovich AJ, Vezina LG, Conry JA, Dubovsky EC, Packer RJ. Pediatric congenital bilateral perisylvian syndrome: clinical and MRI features in 12 patients. *Neuropediatrics* 1997; **28**: 198–203.
20. Guerrini R, Barkovich AJ, Sztriha L, Dobyns WB. Bilateral frontal polymicrogyria: a newly recognized brain malformation syndrome. *Neurology* 2000; **54**: 909–913.
21. Van Bogaert P, Donner C, David P, Rodesch F, Avni EF, Szliwowski HB. Congenital bilateral perisylvian syndrome in a monozygotic twin with intra-uterine death of the co-twin. *Dev Med Child Neurol* 1996; **38**: 166–170.
22. Borgatti R, Triulzi F, Zucca C *et al.* Bilateral perisylvian polymicrogyria in three generations. *Neurology* 1999; **52**: 1910–1913.
23. Ambrosetto G, Antonini L. Anterior corpus callosotomy: effects in a patient with congenital bilateral perisylvian syndrome and oromotor seizures. *Ital J Neurol Sci* 1995; **16**: 311–314.
24. Villani F, D'Incerti L, Granata T *et al.* Epileptic and imaging findings in perinatal hypoxic-ischemic encephalopathy with ulegyria. *Epilepsy Res* 2003; **55**: 235–243.
25. Tuxhorn IE, Pannek HW. Epilepsy surgery in bilateral Sturge–Weber syndrome. *Pediatr Neurol* 2002; **26**: 394–397.
26. Abou-Khalil B, Andermann E, Andermann F, Olivier A, Quesney LF. Temporal lobe epilepsy after prolonged febrile convulsions: excellent outcome after surgical treatment. *Epilepsia* 1993; **34**: 878–883.
27. Andermann F. Why study mesial temporal atrophy in patients with intractable temporal lobe epilepsy? *J Neurol Neurosurg Psychiatry* 2003; **74**: 1606–1607.
28. Babb TL. Bilateral pathological damage in temporal lobe epilepsy. *Can J Neurol Sci* 1991; **18**: 645–648.
29. Teixeira RA, Li LM, Santos SL *et al.* Early developmental destructive brain lesions and their relationship to epilepsy and hippocampal damage. *Brain Dev* 2003; **25**: 560–570.
30. Nevo Y, Segev Y, Gelman Y, Rieder-Grosswasser I, Harel S. Worster-Drought and congenital perisylvian syndromes-a continuum? *Pediatr Neurol* 2001; **24**: 153–155.