Bilateral Focal Polymicrogyria in Ehlers-Danlos Syndrome

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Background: Ehlers-Danlos syndrome (EDS) is a heterogeneous group of generalized connective tissue disorders that has been described in association with epilepsy and cerebral cortical dysplasia, mostly gray matter heterotopias, in 3 reports. However, to our knowledge, association of EDS with another type of cortical cerebral dysplasia, bilateral focal polymicrogyria, has never previously been described.

Setting: Two research-oriented hospitals.

Patients: We describe 2 patients with EDS and bilateral polymicrogyria. The first, a 29-year-old black man, presented with EDS of unspecified type, seizures, and bilateral frontocentral and frontoposterior polymicrogyria with hypoplasia of the inferior part of the cerebellar vermis. The second, a 20-year-old woman, had type III EDS, seizures and congenital bilateral perisylvian syndrome with polymicrogyria.

Conclusions: The association of bilateral focal polymicrogyria and EDS in these 2 patients suggests that extracellular matrix proteins implicated in the pathogenesis of EDS, such as collagen and tenascin, may play an important role in cerebral cortical formation and organization. In a clinical setting, the association of EDS with these cortical structural lesions has implications for diagnosis and management.

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Ehlers-Danlos syndrome (EDS) represents a group of connective tissue disorders that are characterized by excessive skin elasticity and ligamentary hyperlaxity. It has variable clinical, genetic, and biochemical features,1,2 and more than 10 subtypes are currently recognized. The clinical heterogeneity is a result, in part, of mutations in several different genes. Type I and type III collagen genes, as well as procollagen N-protease, copper transport gene, and fibronectin, have been implicated in different forms of EDS.1,2 Cerebral cortical dysplasia and epilepsy have been described in 3 patients with EDS.3-5 Two of these patients had an association of EDS of unspecified type, seizures, periventricular subependymal heterotopias, and other anomalies, such as aneurysms of the siphons of Valsalva.3,5 The third patient presented with type I EDS, seizures, and computed tomographic evidence of an abnormally shaped sylvian fissure, probably also representing polymicrogyria, and heterotopic gray matter.3 We describe 2 patients with EDS and seizures related to focal bilateral polymicrogyria.
ate sodium, and were controlled when carbamazepine (800 mg/d) was added to the regimen when the patient was 25 years old.

Fragility and hyperelasticity of the skin and hypermobility of the joints led to a diagnosis of EDS. The patient’s skin was smooth, dry, and hyperextensible (Figure 1, left). He had papyraceous and keloid scars over his knees and elbows. Hypermobility predominated in his small joints (Figure 1, right). He had a funnel-shaped thorax, thick lips, bilateral ptosis, retrognathia, and a short stature (1.5 m). He looked prematurely aged, and his physician described him as looking like “an old pleated dwarf.” These last findings did not fit the general classification scheme of EDS; therefore, the diagnosis of EDS of unspecified type was retained. The results of the neurological examination were normal, and the neuropsychological examination showed moderate mental retardation.

The patient’s karyotype was normal. Molecular testing was negative for the fragile X chromosome. Light microscopy of a skin biopsy specimen revealed no abnormalities. The results of coagulation tests, ophthalmological examination, chest radiography, and thoracic computed tomography were normal. Two-dimensional echocardiograms and MRI scans of the heart revealed grade 2 aortic regurgitation and a mild dilatation of the posterior sinus of Valsalva. A cerebral computed tomographic scan demonstrated bilateral frontal cortical atrophy. Cerebral MRI scans showed bilateral frontotemporal and frontoposterior polymicrogyria and hypoplasia of the inferior part of the cerebellar vermis (Figure 2).

The patient is presently asymptomatic and undergoes 2-dimensional echocardiography twice a year.

CASE 2

A 22-year-old white woman presented with intractable seizures. She was born after 39 weeks’ gestation, and forceps delivery was used because of fetal distress. She had minimal delay in motor milestones but a striking retardation of speech development. She was unable to speak but could generate vowel sounds. She had infantile spasms in the first year of life, and later a generalized seizure pattern emerged with frequent drop attacks.

Figure 1. Clinical features of Ehlers-Danlos syndrome in patient 1. Hyperextensibility of skin (left) and joints (right).

Figure 2. Patient 1. Left, T1-weighted transverse magnetic resonance imaging scan showing bilateral frontotemporal and frontoposterior polymicrogyria. Right, T1-weighted sagittal magnetic resonance imaging scan showing frontotemporal and frontoposterior polymicrogyria and hypoplasia of the inferior part of the cerebellar vermis.
The physical examination revealed facial diplegia with pronounced difficulties in both mouth opening and lip pursing. Her tongue movements were severely restricted, and she could not pronounce any consonants. She had some distal limb weakness and poor rapid alternating finger movements. Some sensory abnormalities were also noted. Her posture was stooped, and she had difficulty with tandem walking. Neuropsychological examination revealed mild mental retardation. She had marked joint hypermobility and minimal skin hyperextensibility. Her skin was soft and there was abnormal scarring. Examination of the patient’s mother and sister revealed similar skin and joint findings. Dermatological consultation confirmed a diagnosis of type III EDS.

Cerebral MRI scans demonstrated abnormal gyration of the gray matter in both sylvian and perisylvian regions extending superiorly from frontoparietal areas (Figure 3). Curvilinear reconstruction in the coronal plane revealed polymicrogyric cortex along the banks of the widened sylvian fissures. The patient’s mother and sister had normal findings on MRI.

The clinical and imaging findings were characteristic of a congenital bilateral perisylvian syndrome. Despite optimal antiepileptic treatment, seizures recurred, and an anterior callosotomy, sparing the splenium, was performed when the patient was 20 years old. At present, she is still having seizures, although they are less frequent and less severe than before the callosotomy.

**COMMENT**

The clinical findings in both patients were compatible with EDS, and both presented with neurological abnormalities and seizures, which were related to bilateral focal polymicrogyria. The patient described by Pretorius and Butler had similar findings on computed tomographic scans, suggesting the presence of heterotopic gray matter and perisylvian polymicrogyria. The other 2 patients with EDS presented with extensive periventricular subependymal heterotopias, and one of them also had partial agenesis of the corpus callosum and mega cisterna magna.

Polymicrogyria is an abnormality of brain gyration characterized by too many abnormally small convolutions. The basic cytoarchitectonic lesion in polymicrogyria is a midcortical ischemic laminar necrosis predominating in layer 5. Because the late migrating neurons reach their normal positions before the laminar necrosis takes place, this type of microgyria, also called 4-layered microgyria, may be considered postmigratory. However, in some instances, a varying amount of localized cortical disorganization has been described in polymicrogyria. Heterotopic neurons are found in the intermediate zone beneath a microgyric cortical area; this type of microgyria originates slightly before the end of neuronal migration. Another variant, the unlayered form, presents no cell-sparse layer. The mechanisms of formation of polymicrogyria are mostly unknown. Many authors suggest that in the majority of cases, polymicrogyria might result from ischemic cortical damage during gestation. Other authors suggest that polymicrogyria might result from injury to the external limiting membrane (the “glial-pial” barrier) or might be the consequence of the disruption of normal cellular interactions at the level of this membrane.

Congenital bilateral perisylvian syndrome, which we found in patient 2, is a distinct neuronal migration disorder characterized by faciopharyngomasticatory diplegia, cognitive deficits, and bilateral perisylvian abnormalities on imaging studies. The epileptic syndrome commonly consists of atypical absence, atonic/tonic, tonic-clonic seizures, and, less frequently, complex partial seizures. Magnetic resonance imaging scans show bilateral perisylvian cortical malformations consistent with polymicrogyria. The cause of this syndrome remains unknown. Genetic predisposition and ischemia during gestation have been postulated as possible mechanisms.

Gray matter heterotopias have also been described in EDS. These collections of normal neurons in abnormal locations are secondary to the arrest of radial migration of neurons. This arrest could result from damage to the radial glial fibers, to premature transformation of the glial radial cells into astrocytes, or to a deficiency of the specific surface molecules that promote migration along the radial fibers. Continuous periventricular nodular heterotopias are known to be inherited as a sex-linked dominant trait, and in some families, bilateral perisylvian polymicrogyria is also inherited in this way (F.A., personal observation, 1998).

Several subtypes of EDS are the result of an impairment of the synthesis of various extracellular matrix (ECM) proteins, including several subtypes of collagen. Collagen is a pivotal factor in neuronal growth and differentiation. On the basis of in vitro experimental work using an artificial environment, Ferri and Levitt suggested that regional specification of cerebral cortical neurons during neurogenesis was regulated in part by interactions between epidermal growth factor–like growth factors and ECM proteins, such as collagen type IV. Type IV collagen, as well as laminin, fibronectin, and elastin, is a major component of the base-
ment membrane of the central nervous system that is produced by mesenchymal cells of the blood vessels in contact with astroglial processes. The basement membrane provides a substrate for cell attachment, differentiation, and migration. It has been proposed that the establishment of an intact basement membrane is of critical importance in the final positioning of migrating neurons. Another subtype of collagen, ubiquitously expressed collagen type I, is implicated not only in EDS types VIIA and VIIB, but also in the migration inhibition of neural cell adhesion molecule–expressing neurons in vitro. Experimental data have also shown that several subtypes of collagen, including collagen types I and IV, are directly implicated in the migration of neurons derived from neural crest. At the molecular level, collagen plays an important role in the control of cell growth, differentiation, metabolism, and migration by direct binding and activation of receptor tyrosine kinases.

Recently, a mutation in the gene of another ECM protein, tenasin X, has been found in a patient with EDS. Tenascins are a family of ECM glycoproteins that include at least 3 members: tenasin C, tenasin X, and tenasin R. Tenasin C and tenasin X are expressed ubiquitously, and tenasin R is expressed in the surface of neurons and glial cells. Tenasin glycoproteins are, like collagen, a pivotal factor in neuronal growth and differentiation. Different in vitro and in vivo studies have established that tenascins possess cell-binding sites for neural cells and have suggested that these molecules support both neuronal growth and formation of neurites. However, the role of tenascins in the central nervous system seems to be more complex than previously thought, when the contradiction between the normal development observed in mice lacking the gene encoding tenasin C and the impaired neural crest cell migration following in vivo injection of antitenasin antibodies into chick embryos is considered. This discrepancy might reflect species-related differences or the possibility that the effect of the antitenasin antibody used in the immunological studies might be of wider reactivity than just being restricted to the tenasin C isofrom. This difference also suggests that the mode of migration of neural crest cells, which are at the origin of the peripheral nervous system, likely implicates tenascins and that this mode of migration is probably different from the mode of migration of the cells that are at the origin of the central nervous system. Actually, the function of tenasin glycoproteins in the normally developing central nervous system remains to be clearly specified.

If not coincidental, the association of EDS with a disorder of cortical organization suggests that an ECM protein, such as one particular subtype of collagen or tenasin, could be implicated in both disorders in our patients. In 1981, Cupo et al suggested that normal migration of primitive neurons away from the periventricular germinal layer zone is prevented by abnormal collagen, resulting in heterotopic clumps. This theory is in keeping with the concept that collagen acts as a strut over which cells migrate and tissues are organized. Extending this view, we think that a defect in collagen or in another ECM protein like tenasin during fetal development could result in cortical malformations, such as bilateral focal polymicrogyria. Considering in vitro and in vivo experimental evidence for interactions between ECM proteins and neurons during cortical development, one may hypothesize that in the presence of abnormal ECM proteins, as is the case in patients with EDS, cortical organization may be impaired. This impairment could be the result of abnormal neuronal migration leading to the formation of gray matter heterotopias, as suggested by Cupo et al and Thomas et al. It could also be the result of the disruption of normal cell interactions at the level of the external limiting membrane leading to the formation of polymicrogyria, as suggested by the 2 cases presented herein. However, one must keep in mind that there remain many clinical and pathological findings reported in patients with EDS whose exact significance remains unclear. The problem is whether bilateral focal polymicrogyria in EDS represents merely a chance association between rare entities or whether the findings presented herein can be understood as having a cause-and-effect relationship or a common pathogenesis. Until the precise defects in each case of EDS are elucidated, we can only speculate that bilateral focal polymicrogyria in EDS is due to maldevelopment that is related to defective ECM proteins.

In the clinical setting, as is emphasized by all who report on EDS, clinical variability and genetic heterogeneity are the rules. Of the cases referred to genetics clinics because EDS is suspected, nearly half cannot be classified clinically into one of the known variants. Such unclassifiable cases are rarely reported, which possibly explains the paucity of reports of polymicrogyria in patients with EDS. Therefore, we suggest that cerebral cortical dysplasia should be carefully searched for using MRI in patients with EDS and neurological symptoms, such as seizures or mental retardation.

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REFERENCES