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Case Report / Olgu Sunumu

A Cause of Intractable Epilepsy: Bilateral Posterior Agyria-Pachygyria

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ABSTRACT

A cause of intractable epilepsy: bilateral posterior agyria-pachygyria

In this case, we presented the electro-clinical findings in a patient with mental retardation, epilepsy and bilateral posterior agyria-pachygyria. Clinical findings were characterized by frequent tonic generalized and scarcely with myoclonic and absence seizures. Interictal electroencephalography (EEG) showed synchronous and asynchronous delta waves in the posterior region, spike activity predominantly on the right side and fast alpha rhythms. Cerebral magnetic resonance imaging revealed bilateral, symmetric thickened cortex in the parieto-occipital lobes and reduced volume of white matter. These findings were compatible with agyria and pachygyria of posterior regions of the brain. Consequently, in the patient with mental retardation and intractable epilepsy characterized by interictal EEG with posterior focal epileptiform abnormalities, diffuse polyspike-wave paroxysms, bilateral parieto-occipital agyria-pachygyria should be considered as a possible etiology.

Key words: Agyria-pachygyria, epilepsy, seizure

ÖZET

Dirençli epilepsi nedeni olarak bilateral posterior agiri-pakigiri

Bu vakada mental retardasyon, epilepsi ve bilateral posterior agiri-pakigirili hastanın elektro-klinik bulgularını sunduk. Klinik bulgular sıklıkla tonik jeneralize daha nadir olarak da miyoklonik ve absans nöbetleri ile karakterizeydi. İnteriktal elektroensefalografi (EEG) posterior bölgelerde senkron veya asenkron delta dalgası özellikle sağda daha belirgin diken dalga aktivitesi ve hızlı alfa ritmini gösterdi. Serebral manyetik rezonans görüntüleme bilateral, simetrik paryeto-oksipital loblarda kalınlaşmış korteks ve beyaz cevher volümünde azalmayı ortaya koydu. Sonuç olarak, mental retarde ve dirençli epilepsisi olan interiktal EEG'si posterior fokal epileptiform anormallikler, diffüz çoklu-diken dalga paroksizmleriyle karakterize hastalarda bilateral paryeto-oksipital agiri-pakigiri muhtemel etiyoloji olarak akla gelmelidir.

Anahtar kelimeler: Agiri-pakigiri, epilepsi, nöbet

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INTRODUCTION

Cortical developmental malformations (CDMs) are one of the leading causes of mental-motor retardation, persistent epileptic seizures and other focal neurological disorders, and are now more frequently diagnosed with improved neuroradiological methods. The basis of the CDMs, depending on genetic and prenatal environmental factors, includes disturbances in neuronal proliferation, migration and organization steps (1).

The term agyria (absence of gyrus), pachygyria (decreased gyrus number and depth), more commonly referred to as lissencephaly, describes a serious brain neuronal migration characterized by abnormal 4-layered thick cortex, diffuse heterotopia, and smooth brain surface with widened and dysplastic ventricles and dysplasia (2). The malformation affects excitatory and inhibitory neurons, leading to altered excitatory/inhibitory balance and abnormal neuronal network hyper excitability with the potential outcome of resistant epileptic seizures (3). Epileptic seizures involve partial or generalized attacks depending on lesion involvement. The seizures are usually seen during early life as simple partial, generalized, secondary generalized and, less commonly, as myoclonic, akinetic-myoclonic, infantile spasm and absence seizures, with varying responses to antiepileptic drugs (4).

Electro-clinic findings of a patient with mild mental retardation, who presented resistant epilepsy involving different types of episodes and was found to have agyria-pachygyria are presented herein.

CASE

A 19-year-old male patient was presented to our outpatient clinic with resistant epileptic seizures. His systemic examinations yielded normal results and his familial history included no relevant findings. He was delivered via spontaneous vaginal birth and had no microcephaly or hypotonia, postnatally. With neurological examination, he appeared apathic and was unable to provide correct answers to most of the questions. Cranial, motor, sensory, cerebellar, reflex and tonus examinations also revealed normal results. The patient had had no seizures during early childhood (including febrile convulsions). He first

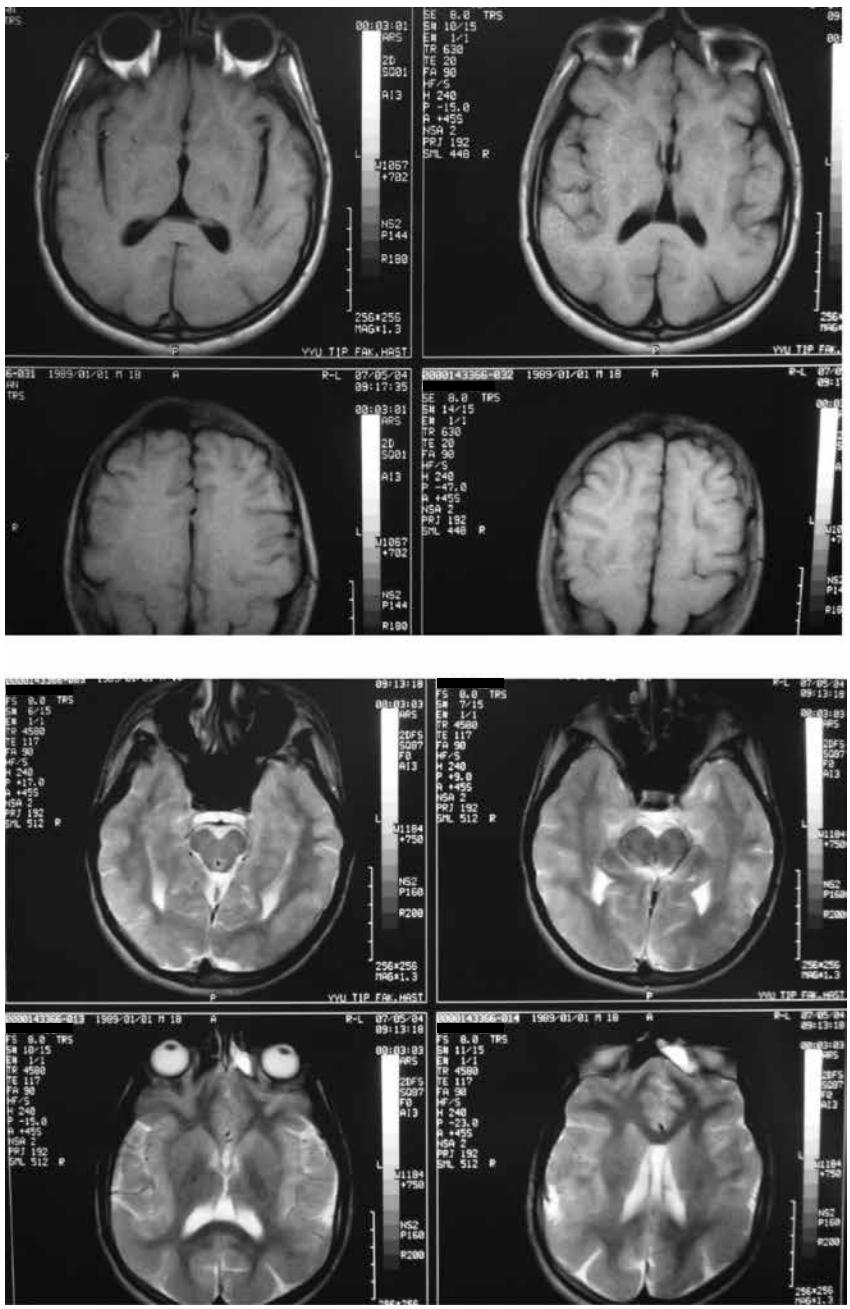

Figure 1: Cranial MRI demonstrated decreased number and depth of cortical sulci in both hemispheres which was emphasized in the parieto-occipital region, and reduced white matter volume.

experienced a generalized seizure at the age of 7 years while he was asleep following abnormal utterance where his limbs were flaccid, his color was purplish and had urinary incontinence. Similar episodes repeated in monthly intervals while he was "awake" and the patient was started treatment with carbamazepine (CBZ) 200mg tablets twice daily. The patient had no seizures for 6 months but a year later, he started having similar episodes every 1-2 weeks again, which, as reported, occurred upon skipping doses. Phenytoin was added to CBZ but it was necessary to discontinue the former drug one year later due to gingival hypertrophy, and was replaced by topiramate 100mg/day. The frequency of generalized seizures was reduced to once every 1-2 months with this combination. Over the last 3 years, however, the patient started suffering from myoclonus in the shoulders and arms, especially during morning hours, which could be as frequent as several times a day, as well as secondary generalized seizures and absences.

Cranial magnetic resonance imaging (MRI) demonstrated decreased number and depth of cortical sulci in both hemispheres, which was more pronounced in the parieto-occipital region, and reduced white matter volume (Figure 1).

Video-electroencephalography (EEG) imaging did not demonstrate ictal evidence but interictal EEG revealed synchronized and unsynchronized delta slow-wave activities in both hemispheres being pronounced at the posterior region, generalized spike-slow-waves, and synchronized spike and sharp wave discharges at the posterior of the right hemisphere and bilateral parieto-occipital rapid alpha rhythms with sharp contours.

The patient had partial benefit from treatment and still suffers from secondary generalized, myoclonic and absence seizures on occasions and is known to have significantly more frequent seizures of all types when he does not receive his treatment regularly.

DISCUSSION

The terms lissencephaly, agyria and pachygyria are used interchangeably in the absence of established diagnostic criteria in differentiating these abnormalities. Recently, a number of distinct types of lissencephaly have been described and detailed grading systems have been developed accordingly. Classical (complete/type 1) lissencephaly defines absence of gyri and sulci (agyria) in almost the whole brain surface. In classical lissencephaly, the cortex is thicker than normal, reaching 10 to 20mm in thickness. Its incidence is estimated as 11.7/1 million. It is the earliest diagnosed group of cortical dysplasias, 62.5% of the cases being diagnosed during the first years of life. The presenting complaints leading to diagnosis are often microcephaly, epileptic seizures and severe mental-motor retardation (5).

In the latest terminology, incomplete (cobblestone/type 2) lissencephaly is defined as the presence of cobblestone complexes in the cortex as well as in many parts of the brain, affected gyri at many sites which may resemble agyria, pachygyria and polymicrogyria, white matter dysmyelination, brain stem hypoplasia, ventriculomegaly and frequently hydrocephaly (6). Ocular disorders such as coloboma, retinal dysplasia, retinal detachments and optic nerve hypoplasia are more common (7). Although epileptic seizures are less frequent, they are more severe, the reason of which remains unknown.

Electro-clinical findings are often in the form of tonic or atonic, simple or complex seizures. Remarkably, in our patient, myoclonic and absence seizures were added to the above findings described in the literature.

Ferri et al. (8) have reported two siblings with mental retardation and epilepsy, whose MRIs involved symmetric agyria and pachygyria at the temporo-parieto-occipital junction, polymicrogyria parietal cortex and widened occipital horns. The patients' seizures, which were first seen in the second year of life, were refractory and frequent, and involved the trunk and the upper extremities and were in the form of flexion spasms with sudden onset, sometimes resulting in collapse. Paroxysmal fast activity of 20-24Hz, particularly at the posterior, and sharp and slow wave paroxysms, high-amplitude over 14Hz during sleep in one patient were observed with EEG, as was demonstrated in our patient. Alpha-like activity, fast rhythms, slow ground activity and focal abnormalities

with EEG have been described in patients with generalized agyria-pachygyria.

In classical lissencephaly, white matter is reduced (gray to white matter ratio is reversed: 4:1), sylvian fissures are vertical, brain surface is smooth (broad, flat fissures and shallow fissures) and the cortex is thick. Thickness is 8-12mm in pachygyria and 11-20mm in agyria. Sites of agyria and pachygyria may be diffuse and while agyria often affects parieto-occipital sites, pachygyria often affects frontal and temporal regions (9).

Gyral abnormalities are more frequent and more severe in posterior sites than in anterior sites in patients with pachygyria-agyria. Brain malformations are more serious in isolated lissencephalies. Two separate gene mutations have been identified for isolated lissencephaly recently, i.e. LISI (PAFAHIBI) at 17p13.3 and localized XLIS (DCX) at Xq22.3-q23. The pathogenesis of these lesions involves abnormalities in vascular sources and volume abnormalities in areas fed by the posterior cerebral artery. This posterior-anterior gradient is characterized by lissencephalies secondary to LISI mutation more frequently at 17P13.3. In fewer patients, reverse i.e. anterior-posterior gradient is characterized by XLIS mutation at Xq22.3-q23 (10).

Miller-Dieker syndrome (MDS) is characterized by isolated lissencephaly and craniofacial alternations including mild bilateral collapse and small chin. In MDS, extensive alpha and beta activities and high-amplitude atypical extensive theta and delta burst are observed with awake EEG, while the faster activity observed during sleep is more extensive and continuous (11).

In conclusion, possible presence of bilateral parieto-occipital agyria-pachygyria in the etiology should be considered if focal epileptiform abnormalities, particularly in the posterior area, diffuse multi-spike wave paroxysms and ictal diffuse 10-11Hz activity are observed with EEG in patients with mental retardation, mild motor deficit and resistant epileptic seizures.

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