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NEURONAL MIGRATION DISORDERS PART I: TERMINOLOGY, CLASSIFICATION, PATHOPHYSIOLOGY, EEG AND EPILEPSY*

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Intractable epilepsies and partial epilepsies, which make up a great majority of epileptic disorders, are not better recognized and their etiologies unveiled with the help of the new imaging techniques. The development of magnetic resonance imaging (MRI) permits the accurate diagnosis while the patients are alive of the neuronal migration disorders (NMD), which constitute an important group of intractable epilepsies. Previously, NMD cases were described by neuropathologists from autopsy materials, and many of these developmental disorders were not considered compatible with prolonged survival. Cerebral malformations due to neuronal migration anomalies are described in association with motor and mental retardation, learning disabilities, microcephaly, dysmorphic features and epilepsy. Neuronal migration takes place in all parts of the central nervous system (CNS) during the shaping process of the CNS; it actually includes both the central and peripheral nervous systems. However, in common usage the meaning of "neuronal migration disorders" is restricted to the neocortex. *Key words: neuronal migration, cortical dysplasia, epilepsy.*

Terminology and Classification

The terminology of neuronal migration disorders (NMDs) is rather complex, and there seems to be an urgent need for consensus on classification (Table I). The following list consists of the most commonly accepted definitions:

1. *Cortical dysplasia (focal or diffuse)* is a general term indicating all NMDs. Nodular cortical dysplasias are superficial cortical nodules, scattered over the surface of the brain with a predilection for the frontal lobe. Neurons of varying size are grouped around a radial bundle of myelinated fibers.
2. *Heterotopia* is defined as an island of gray matter surrounded by white matter, located between the ventricular wall and the cortical mantle.

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Table I: Classification of Neuronal Migration Disorders

I. Generalized
1. Agyria or lissencephaly
a) Type I (four-layered cortex)
– Isolated forms
– Miller-Dieker syndrome
– Non-classified forms
b) Type II (cortex with no distinguishable layers)
– Walker-Warburg syndrome
– Fukuyama type congenital muscular dystrophy
– Muscle-eye-brain disease
– Non-classified forms
– Neu-Laxova syndrome
– Cerebrocerebellar syndrome
2. Pachygyria (isolated mild cases)
3. Polymicrogyria
II. Localized
1. Schizencephaly
2. Porencephaly
3. Localized forms of pachygyria
– Bilateral central pachygyria
– Hemimegalencephaly
4. Nodular or laminar heterotopias

From Dobyns et al.[26] (1984), Palmini et al.[14] (1991).

3. *Agyria (lissencephaly)* is characterized by a lack of gyration or abnormally broad or simplified gyria[1]. Only Sylvian and Rolandic fissures are partially preserved. Opercularization and demarcation of insula are not seen. There are two types of lissencephaly from the clinicopathological point of view: in type I lissencephaly, agyric and pachygyric areas are seen together. It has a four-layered cortex. Cerebellar and callosal agenesis, ventricular dilation, heterotopias and other malformations may also be associated with this condition. In type II lissencephaly, there are no cortical layers but disorganized neurons, fibroglial bands and vessels penetrating dispersed neurons are characteristic findings for this entity.
4. *Pachygyria* is the presence of thick and broad gyri decreased in number. Absence of gyri is seldom seen. There are intermediate cases with agyria-pachygyria in different areas of the brain (agyria-pachygyria complex)[1].

5. *Polymicrogyria* is when there are multiple miniature malformed convolutions. Neurons reach the cortex but are not properly located at their preprogrammed position. Bilateral, symmetric location compatible with a specific arterial tracing may be observed as well as unilateral asymmetric polymicrogyria[1].
6. *Polygyria* is characterized by multiple shallow sulci and gyri with normal microscopic structure which differentiates it from polymicrogyria[1].
7. *Macrogyria* broad gyri with normal cellular architecture.
8. *Hemimegalencephaly* denotes manifest asymmetrical enlargement, particularly but not exclusively of one cerebral hemisphere. Hemimegalencephaly is histologically characterized by disturbed neuronal migration, normal architecture and glial proliferation.
9. *Diffuse subcortical laminar heterotopia (double cortex syndrome, band heterotopia).* The surface of the brain has normal appearance with a thick cortex. Underneath the normal cortex lies a second band of heterotopic gray matter separated from the normal cortex by a thin layer of white matter.
10. *Schizencephaly* is defined as bilateral holohemispheric cleft (fused or open) in the region of sylvian fissures. Neuropathological features include failure of normal sulcal and gyral development on the hemispheric surface in the region of and within the clefts, and gray matter heterotopias in the subcortical white matter beneath the cleft(s)[2,3].
11. *Perisylvian dysplasias (unilateral/bilateral opercular macrogyria/ polymicrogyria)* are located on cortical layers of sylvian fissures. They have a pachygyric appearance which cannot be properly shown on magnetic resonance imaging (MRI). There are bilateral, symmetrical thick and broad gyri and scant sulci at the insular and opercular regions. The clinical features include mental retardation, developmental pseudobulbar palsy, epilepsy and/ or arthrogryposis multiplex congenita.
12. *Minor cortical dysgenesis* consists of nests of subpial, ectopic neurons and focally disorganized cortical layering. These lesions are causative factors for partial epilepsy and mental deficiency of unknown etiology. Several neuronal dysgeneses have been reported in autism[4].

Pathophysiology

Proliferation of neuroblasts in the periventricular germinal matrix and their migration to the cortical plate begin around the sixth week and extend to midgestation period[5]. It has been shown in the developing brain that neuroblasts, proliferating in the periventricular germinal matrix, migrate to their final

preprogrammed position in the cerebral cortex via the radial glial fibers. This neuroblast-glial fiber interaction is maintained in a dynamic fashion through cell adhesion molecules[6]. When they arrive at the cortical plate, they detach from the radial glial fibers and from the cortical layers in an "inside-out" fashion. The first cells to migrate take a deeper position in the cortex; cells migrating later are laid down more superficially[5-7]. Cortical gyrus formation is determined by physical stress generated by an imbalance between the number of cells in the superficial and deeper cortical layers[8]. New findings suggest that final functional differentiation of a given neuroblast is not predetermined before migration but rather a complex function of post-migratory chemical interactions[9-11].

Cell multiplication (cytogenesis) and cell migration (histogenesis), namely, separation of the main embryonic sheets, neurulation, neuronal multiplication, neuronal migration and regional development of the cerebral vesicles take place in the first half of gestation.

In the second half of gestation, growth and differentiation of neuronal and glial cells take place: cell growth and axonal dendritic arborization, connections and synaptogenesis, myelination and gliogenesis. Main mechanisms are disturbances of "residual" histogenesis, prenatal hydrocephalus, perfusion failures/hypoxias, infections, trauma, and metabolic disturbances[4].

Neuronal production and death determine the neuronal complement of the mature brain. Programmed cell death is a normal developmental event; however, destructive processes may result in additional neuronal loss. Disturbances in cell production, in cell death or in the balance between them are the basis for numerical neuronal deficits in many microcephalies.

Most neurons destined for the human neocortex are produced before 20 weeks of gestation. Residual but important histogenetic activities continue during the last 20 weeks of pregnancy. Depending on the timing, location and the extent of the interference with the neuronal migration process, different types of neuronal migration disorders occur. Metabolic, chromosomal, hypoxic, ischemic, and infectious disorders and toxic and physical insults in the human embryo or fetus may interfere with neuronal migration, leading to severe clinical findings in extrauterine life.

Pathology ranges in severity from complete agyria (lissencephaly) to isolated areas of cortical heterotopia. Clinical spectrum varies from asymptomatic to severely symptomatic leading to death.

Electroencephalography and Epilepsy

Modern imaging techniques contributed a great deal to the etiological classification and diagnosis of epilepsies due to NMDs. In a retrospective study

of 303 patients with epilepsy, MRI was performed over a three-year period with special emphasis on neuronal migration disorders[12]. Thirteen patients with epilepsy and NMD demonstrated on MRI were identified. Four had schizencephaly, one hemimegalencephaly, two isolated heterotopias and six had localized pachy-and/or polymicrogyria. Magnetic resonance imaging can detect focal cortical dysplasia which corresponds to the epileptogenic focus on electroencephalography (EEG), single photon emission tomography (SPECT) may help to detect a functional abnormality in the same region[13].

According to Palmini et al.'s[14] series in focal cortical dysplastic lesions, patients present with complex partial seizures (67%), atonic-tonic drop attacks (27%) and status epilepticus[14]. Although EEG may reveal an epileptic zone localized in a cerebral lobe, half of all patients have diffuse epileptic foci. In this series, 28 out of 32 patients were treated surgically, while in four patients seizures were satisfactorily controlled by antiepileptic medication. In Guerrini et al.'s[15] series, patients with a focal gyral anomaly presented with intractable, sterotypic complex partial seizures. In this group generalized seizures were never seen and the EEG abnormalities remained confined to the same area. Such patients benefit from partial frontal lobectomy. Seizures were the presenting symptom in the majority of these patients; the associated neurological features such as hemiparesis were discovered after careful neurological examination. Focal seizures beginning apparently in normal children or adolescents without obvious antecedent risk factors and evolving within three years to life threatening status epilepticus should suggest occult focal cortical dysplasia[16]. Differential diagnosis should include obvious structural lesions, Rasmussen's encephalitis, and mitochondrial disease. Normal MRI studies in such patients do not exclude NMD.

A syndrome consisting of bilateral perisylvian cortical dysplasia, pseudobulbar palsy, secondary generalized epilepsy and mental retardation has been recognized[17]. Bilateral perisylvian dysplasias present with generalized convulsive and complex partial seizures and drop attacks; in some cases perioral clonic movements are observed. Electroencephalography reveals generalized epileptiform abnormality and multifocal discharges. When drop attacks cause significant disability, callosotomy is indicated. Patients with drop attacks do not benefit from resective surgery[14]. Lesions involving the perisylvian region also lead to anterior and inferomesial temporal epileptic discharges. Resection of these structures partially improves but does not cease the seizures[18]. Infantile spasms may be the presenting seizure type in some patients with the congenital bilateral perisylvian syndrome[19].

Patients with diffuse cortical dysplasias ("double cortex syndrome") experience drop attacks, partial seizures with secondary generalization and Lennox-Gastaut syndrome. Electroencephalography reveals generalized slow spike and wave

or multifocal epileptic discharges. Drop attacks leading to disability may improve after callosotomy[14].

Hemimegalencephaly and megalencephaly present with lateralized motor manifestations, secondary generalization and drop attacks. Unilateral and focal epileptogenic regions are recognized on EEG. When the motor disability is progressing to hemiparesis, a modified hemispherectomy may be performed[14-20-21]. In patients with mild motor disability, excision of the most active epileptogenic areas within the most affected hemisphere may improve seizure control[14].

In the group of nodular and laminar heterotopias, a case with temporal lobe epilepsy is reported. Patients with subcortical nodular heterotopia present with partial motor seizures secondarily generalized. Resective surgery leads to improvement in seizure frequency and severity[14].

It is not known whether EEG is clinically significant in NMD cases. However, when surgery is the therapy of choice, EEG may be an important prognostic sign. Electroencephalography findings of different types of dysplasias are reported in Quirk et al.'s[22] series. In diffuse cortical dysplasias, sharp waves with high amplitude rhythmic activity are very specific yet sensitive. This finding is more common in agyria when compared with macrogyria. In patients with macrogyria, abnormal rapid activity is observed more frequently. Localized cortical dysplasias present with focal or lateralized anomaly in 50 percent of patients; in the other 50 percent, EEG findings findings are similar to those in diffuse cortical dysplasias. Electroencephalography may be normal in all types of cortical dysplasias, especially those with subcortical anomaly.

Schizencephaly is a regional disturbance of cerebral hemispheres presenting in childhood with partial seizures, hemiparesis and variable mental retardation. Schizencephaly is reported to present with neonatal seizures as well[16].

Most of the patients with NMDs who present with intractable epilepsy have a focal unilateral dysplastic lesion. In several series with intractable epilepsy, surgical intervention is required[23]. The success of the surgery is dependent on the extent of removal of the visible abnormal area, which is more important than the electroencephalographically or corticographically defined epileptic tissue[24]. In patients with a secondary generalized epileptic process and drop attacks, callosotomy has been proven as useful palliation[25].

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