MALFORMATIONS OF CORTICAL DEVELOPMENT

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Abstract – Malformations of cortical development (MCD) have been increasingly identified. The purpose of this presentation is to review the current knowledge of the MCD. Before we address this issue, we will briefly present a review of cortical development. The second part of this presentation will address the most important MCD. Finally, the last part of this presentation will address the correlation between MCD and epilepsy.

KEY WORDS: malformations of cortical development, focal cortical dysplasias, neuronal migration disorders, cortical organization disorders.

Malformações do desenvolvimento cortical

Resumo – As malformações do desenvolvimento cortical (MDC) são cada vez mais identificadas e diagnosticadas. O propósito desta apresentação é rever o conhecimento recente sobre as MDC. Antes de abordarmos o assunto em questão, apresentaremos brevemente uma revisão sobre a formação cortical. A seguir, abordaremos as principais entidades compreendidas dentro da classificação das MDC e, finalmente, resumiremos a correlação entre MDC e epilepsia.

PALAVRAS-CHAVE: malformações do desenvolvimento cortical, displasias corticais focais, distúrbios da migração neuronal, distúrbios da organização cortical.

Malformations of cortical development (MCD) have been increasingly identified as a major cause of several disorders, particularly in childhood. Patients with MCD present with a wide spectrum of clinical manifestations ranging from asymptomatic cases to those with epilepsy and neurodevelopmental problems. The advent of the magnetic resonance imaging (MRI) has been the most important factor in the improvement of the diagnosis, which has allowed a better clinical management. Structural imaging has become more sensitive with developments of MRI hardware, acquisition and postprocessing methods.

The purpose of this presentation is to review the current knowledge of MCD. Before we address this issue, we will briefly present a review of cortical development. The second part of this presentation will address the most important MCD. Finally, the last part of this presentation will address the correlation between MCD and epilepsy.

CORTICAL DEVELOPMENT

Barkovich et al.[1] proposed a classification of the malformations of cortical development, taking into account pathological, genetic and neuroimaging features of the different stages of development. They state that there are three main consecutive stages of cortical development, each of them partially overlapping with the previous stage. They are: cellular proliferation and differentiation, neuronal migration, and cortical organization.

The first step of cortical development is cellular proliferation and differentiation, which takes place between the 5th week and 20th week of gestation. The germinal or primordial cell multiplies and differentiates becoming either a neuron or glial cell. A general rule of the developing nervous system is that a cell is generated in a different location from its final position in the central nervous system (CNS). The process of changing position from birth to the final site is called neuronal migration[2], and this is the second stage of cortical development.

The neural tube is formed during the first four weeks of gestation. Between the 5th and 6th weeks, cell proliferation leads to the appearance of two different layers: an internal layer – subventricular and highly populated with cells – and an external layer without cells. The internal layer, or germinal layer (germinal matrix), contains primordial, non-differentiated cells. After the 6th and 7th weeks of gestation, the young neurons (neuroblasts) start migrating towards the second, external, or cortical layer. When

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the migration ends, the external layer (cerebral cortex) will be full of cells, while the internal, subventricular layer will have no cells[3].

The process of neuronal migration generates four layers or embryogenic zones: a *subventricular or subependimal zone*, where the germinal matrix is located; an *intermediate zone*, which will be formed between the two initial layers and through which the cells will move following a centrifugal direction, while developing axons; a *cortical zone* that will contain neuronal bodies; and a *marginal zone*, the external zone that will become the subpial granular layer[2,3].

The neuroblasts adhere to radial glial fibers to migrate. Together they will constitute the radial unity. The radial unity hypothesis proposes that the ventricular zone is comprised of proliferative units, which become a protomap of future citoarchitectonic areas. The neuronal migration is spatially oriented, expressing a correlation between the cell's birthplace and its final position in the CNS[4,5]. The neuronal body mass will form the gray matter and the axon mass will form the white matter.

The third stage of the developing cortex is the cortical organization. During this stage the six cortical layers will be formed. The early neurons are called Cajal-Retzius cells, which appear in the marginal zone and will disappear toward the end of the fetal life. This is the external limit of the cerebral cortex. The internal limit is the 7th layer, which also disappears toward the end of the fetal life[3]. The neuroblasts that reach the cortex after those transient cells are allocated will compose the six neocortical layers. Experimental studies have demonstrated that the first neurons to reach the cortex will stay at the deeper cortical layers, while the consecutive waves of neurons will progressively occupy more superficial layers. This process follows the so-called "inside-out" pattern. The neurons will not reach the marginal zone, which is the first cortical layer, also called the molecular layer, as it has no cells. Other cortical layers will progressively be occupied by consecutive waves of neurons, according to the "inside-out" pattern. Cortical layer VI is the deepest one and cortical layer II is a more superficial layer containing neurons[2,6].

The majority of the migration process will take place up to the 22th week of gestation, although some of it may still occur up to the first months of post-natal life[2,7].

MALFORMATIONS OF CORTICAL DEVELOPMENT

If damage occurs in one of the three stages previously described, a malformation will occur. We will present the malformations of cortical development, considering the same sequence of the three stages of cortical development. Therefore, we will initially address the malformations due to cellular proliferation and differentiation disorders. The most important focal malformations of this period are the cortical dysplasias and hemimegalencephaly, and the diffuse malformations are microcephaly and megalencephaly[8,9]. Secondly, we will address neuronal migration disorders, particularly lissencephaly/subcortical band heterotopia, and other heterotopias. Finally, we will address the malformations due to abnormal cortical organization, specifically polymicrogyria and schizencephaly.

Malformations due to abnormal neuronal and glial proliferation

Cortical dysplasia

Cortical dysplasia is also known as focal cortical dysplasia (FCD) as it usually presents with focal disturbance of the cortical lamination. It is correlated with neuronal and glial proliferation and differentiation because some of the cortical dysplasias harbor balloon cells, which are undifferentiated cells, or intermediate cells between neuron and glia cells. Balloon cells are big, rounded cells with eosinophilic cytoplasma resembling a balloon.

The first description of FCD was presented by Taylor and Falconer in 1971[10]. MRI allowed the visualization of the FCD *in vivo.* Focal cortical dysplasia is recognized as the major cause of focal intractable epilepsy in childhood, and the second most common etiology in adult epilepsy surgery patients. Refractory epilepsy is due to the intrinsic epileptogenicity of the dysplastic tissue[11].

Palmini et al.[12] presented a classification that addressed FCD exclusively. This classification considered different histopathologic subtypes and correlated them with their current status of identification by MRI, as well as with some clinical features and prognostic aspects. The authors pointed out that there are mild cortical malformations involving cortical layer I, previously recognized as microdysgenesis. The panel recommended that the use of the term microdysgenesis should be abandoned. The following terminology should be adopted:

Mild malformations of cortical development

Type I: With ectopically placed neurons in or adjacent to layer I.

Type II: With microscopic neuronal heterotopia outside layer I.

Structural imaging: Both types probably are not detectable by current MRI techniques.

Potential clinical relevance: It has been shown that these mild malformations of cortical developments may be related to epilepsy and other behavioral and cognitive abnormalities.

FCDs

Type I: No dysmorphic neurons or balloon cells.

Type IA: Isolated architectural abnormalities.

Type IB: Architectural abnormalities, plus giant or immature, but not dysmorphic neurons.

Structural imaging: It is unclear at this point whether Type I FCD can be identified *in vivo* by current MRI techniques.

Potential clinical relevance: It is likely that some of these patients will have epilepsy, whereas others will not; those without epilepsy may be either asymptomatic or in-

stead seek treatment for learning disorders or other types of cognitive impairment.

Type II: Taylor-type FCD (dysmorphic neurons with or without balloon cells).

Type IIA: Architectural abnormalities with dysmorphic neurons but without balloon cells.

Type IIB: Architectural abnormalities with dysmorphic neurons and balloon cells.

Structural imaging: These are the focal lesions most commonly identified on MRI, which may demonstrate increased cortical thickness, blurring at the gray/white matter junction, increased signal on T2-weighted, proton-density, or FLAIR (more likely to occur in balloon cell-containing lesions), and/or transmantle dysplasia.

Potential clinical relevance: Type IIA/B FCDs are characterized by truly abnormal, grossly dysmorphic cellular elements that are accompanied by unquestionable abnormalities in inhibitory and excitatory neurotransmission. The net result is a high degree of intrinsic epileptogenicity that has been demonstrated by experimental and clinical studies. Most patients have medically intractable partial epilepsy, frequently with disabling motor and secondary generalized seizures, including status epilepticus. These patients often are correctly diagnosed before surgery, but surgical results still are not fully satisfactory in many of them.

A recent study[13] showed that children with FCD Type IIB had more localized ictal electroencephalographic patterns and MRI changes, while hippocampal sclerosis and hypoplasia/atrophy were common in FCD Type I. The same authors[14] found that incomplete resection of the FCD is the main predictor of poor postsurgical outcome, because the only significant predictor of surgical success was completeness of surgical resection. Therefore, there was a trend toward better outcome in patients with FCD Type II.

Other authors[15] reached similar results when they showed that after complete resection, 80% of patients are seizure free compared with 20% with incomplete resections. Compared with Type I, patients with FCD Type II present at younger ages, have higher seizure frequencies, and are extratemporal. Type I dysplasia is found more often in the temporal lobe in adult patients and is often MRI negative.

Hemimegalencephaly

Barkovich et al.[1] categorized hemimegalencephaly together with FCD because histopathologic analysis usually shows similar findings for both entities. Balloon cells are also found in hemimegalencephaly, demonstrating a neuronal and glial proliferation and differentiation disorder. Refractory epilepsy, hemiparesis and mental retardation are common clinical features of hemimegalencephaly.

Malformations due to abnormal neuronal migration

Lissencephaly/subcortical band heterotopia spectrum

Lissencephaly refers to the occurrence of a smooth brain without gyri or sulci. Lissencephaly causes severe mental retardation and refractory epilepsy. More often, the term agyria/pachygyria is applied, as some portions of the CNS may show the absence of gyri (agyria) while other portions may show some broad and large gyri (pachygyria) in the same patient.

Subcortical band heterotopia or double cortex refers to the occurrence of a second cortical layer below the original with some white matter interspersed between the two cortical layers. A mild clinical picture is seen with a thin second cortical layer while a severe clinical picture may be found with a broad second cortical layer, meaning that more neurons were prevented from reaching their final destination.

Familial studies showed that lissencephaly and subcortical band heterotopia may occupy the two extremes of the same spectrum. Lissencephaly/pachygyria/severe band heterotopia are diffuse neuronal migration disorders causing severe, global neurological impairment. Abnormalities of the LIS1, DCX, ARX, TUBA1A and RELN genes have been associated with these malformations. In some families with X mode of inheritance, female patients present with a mild clinical manifestation and have band heterotopia while male patients present with severe clinical manifestation and have lissencephaly[16].

Heterotopia other than band heterotopia

Neuronal migration disorders affecting only subsets of neurons, such as mild subcortical band heterotopia and periventricular heterotopia, cause neurological and cognitive impairment that varies from severe to mild deficits. These migration disorders have been associated with abnormalities of the DCX, FLN1A, and ARFGEF2 genes[16].

Malformations due to abnormal cortical organization

Polymicrogyria

There are two different types of polymicrogyria (PMG): the four-layered cortex and the unlayered cortex. The most common is the four-layered cortex. In this entity, cortical layer I histology is similar to the molecular layer of the adjacent cortex. The second layer is the external cellular portion of the polymicrogyric cortex, which is composed of neuroblasts from the II, III and IV normal layers. The third layer of the polymicrogyric cortex is characterized by a partially necrosed tissue of the original normal layer V. Neuroblasts from the second layer have reached their final position, surpassing the necrotic tissue of the third layer but, although they arrived at their final destination, there has been a misarrangement of their position. The fourth layer of the polymicrogyric cortex comprises the deep portion of the original normal layer VI and this is the internal limit of the abnormal cortex[17,18].

It is believed that a vascular insult occurring between the 20th and 24th weeks of gestation may be responsible

for the necrotic part of the polymicrogyric cortex. The imbalance between populated layers and necrotic layer causes a distorted mechanical stimulus that leads to the formation of the multiple and small gyri[19-22].

The fact that this type of cortex appears mostly in cerebral areas belonging to medium cerebral artery territory, and the presence of PMG around porencephalic and schizencephalic borders, reinforces the idea that the polymicrogyric cortex results from anoxic-ischemic insult.

The two types of PMG can coexist in adjacent areas, indicating that both of them may be part of a continuum[23]. The unlayered PMG usually appears in a broad and more severe clinical picture accompanying other malformations such as corpus callosum agenesis, heterotopias, and microcephaly[24-26].

The clinical picture of the four-layered PMG depends on the localization and extent of the cortical malformation[27]. Barkovich et al.[28] analyzed 21 patients with bilateral and symmetrical PMG. They noted that the perisylvian region was the most affected cerebral area, as 13 of their patients had PMG in perisylvian regions. Frontal regions are the next most affected cerebral areas. Patients with perisylvian PMG usually present with speech delay of variable degrees, while patients with frontal PMG usually present with spastic tetraparesis, motor and speech delay, and mental retardation. Patients with parietal PMG usually present with refractory epilepsy.

In perisylvian PMG, the severity of the clinical picture usually correlates with the extent of the cortical lesion as well. Guerreiro et al.[29] observed that language disorder may be associated with PMG. The authors described a mild form of posterior parietal PMG where the abnormal cortex extends around a continuum of the Sylvian fissure in patients with language disorder[30]. This entity is the mildest extreme of a broad clinical spectrum of the perisylvian syndrome. Epilepsy is present in less than half of the patients and, when present, is easily controlled with antiepileptic drugs[31,32]. Refractory epilepsy is rarely found in patients with PMG. Mental retardation and refractory epilepsy represent the more severe extreme of the spectrum of the perisylvian syndrome.

Guerreiro et al.[32] studied several families. One family allowed linkage studies and a new *locus* was identified and mapped to the chromosome Xq27[33].

Electroencephalographic (EEG) studies in several patients with PMG[34,35] showed that the EEG is usually normal in patients with PMG, despite the fact that it can be associated with focal electrical status and electrical status epilepticus of sleep in selected patients, even when seizures are not a prominent feature. There is also a correlation between EEG abnormalities and the extent of the lesion.

Innocenti et al.[36] activated the visual polymicrogyric cortex in a patient with bilateral parieto-occipital parasagittal PMG. The authors observed that a visual stimulus activated the abnormal cortex, suggesting that the PMG cortex has normal function. Nevertheless, Boscariol et al.[37] found abnormalities in the auditory processing of children with perisylvian PMG, suggesting that the perisylvian polymicrogyric cortex is functionally abnormal.

Schizencephaly

Schizencephaly and PMG are considered to be malformations of post-migrational cortical organization. Vascular insult is the proposed mechanism for both entities. It is believed that the difference between them relies on the severity of the insult. Schizencephaly occurs when a deep vascular insult reaches the white matter, sometimes even reaching the ventricle, leading to the formation of the fissure[38].

Lopes et al.[39] studied 44 patients with schizencephaly. The authors divided the patients in unilateral versus bilateral schizencephaly. In another analysis, patients were divided according to the presence of open lips and closed lips. The data showed that the extent of the cortical malformation correlates with the severity of the clinical manifestation both for cognition and for motor dysfunction. Nevertheless, there is no correlation with epilepsy. In other words, the presence or absence of epilepsy and the treatment outcome do not correlate with the extent of the lesion.

MCD AND EPILEPSY

To address the relationship between MCD and epilepsy, we summarize a study conducted at our service. A series of 76 consecutive patients with MCD and their families were systematically questioned about their family histories of epilepsy or other neurological impairment and the occurrence of prenatal events[31]. Our findings supported the idea of a spectrum of different types of MCD. Focal cortical dysplasia was associated with more frequent and severe epilepsy, but with less obvious genetic and prenatal events; heterotopias and agyria-pachygyria were frequently associated with genetic predisposition; and polymicrogyria and schizencephaly were less frequently associated with epilepsy but had a stronger association with genetic and detectable prenatal events.

SUMMARY

To summarize, this presentation focused firstly in the three stages of cortical development. After that, we presented the most important MCD. Finally, we presented the correlation between epilepsy and MCD.

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