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Review and Update on Malformations of Cortical Development and Neuronal Migration Disorders

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Abstract: Cortical development malformations (CDM) and specifically disorders of neuronal migration are a group of congenital malformations of the central nervous system (CNS) that are linked to some of the neurodevelopment disorders frequently described in children, such as mental retardation, autism, schizophrenia and epilepsy, among others. CDM are classified into three groups: Group I for alterations in proliferation and/or glial and neuronal apoptosis; Group II for neuronal migration disorders; and group III for secondary malformations due to postmigrational alterations of development. Neocortical neurons migration occurs preferentially from the fifth week of gestation until the twenty-second gestational week. Neuronal migration disorders are classified into four groups: II. A lissencephaly, II. B periventricular heterotopia, II. C subcortical heterotopia and II. D sublobar dysplasia and "cobblestone" malformations.

Keywords: Cortical Development Malformations, Lissencephaly, Schizencephaly, Polymicrogyria

1. Introduction

Cortical development malformations (CDM) and specific neuronal migration disorders (NMD) are a group of congenital malformations of the central nervous system (CNS) that are linked to some of the most common neurodevelopment disorders in children, such as intellectual disability, autism, schizophrenia and epilepsy, among others.

Under normal conditions, neurons undergo a migration process that goes from its original location in the germinal matrix to the place where they reside the rest of their life. Alterations of migration, as well as in the cytoarchitecture, proliferation, lamination and neuronal physiology are the pathophysiological basis of CDM. In recent years, Molecular Biology and Genetics research has significantly expanded knowledge about the regulation of neuronal migration during neurodevelopment.

2. Cortical Development Malformations Classification

CDM are classified into three groups. Group I includes alterations in proliferation and / or glial and neuronal apoptosis; group II refers to neuronal migration disorders secondary CDM and group III to neuronal migration malformations disorders.

Genetic mutations, environmental toxins and neurotropic virus have been associated as etiological agents related to neuronal migration. Neuronal migration dysgenesis is a frequent cause of epilepsy and epileptic syndromes classically considered as cryptogenic. They can be part of some genetic syndromes such as Miller-Dieker, Aicardi-Goutièrs or Walker-Walburg syndrome.

CNS development is a complex process which can be arranged schematically in the following steps: I. Primary neurulation (3-4 weeks) and neuronal migration onset (fifth week of gestation); II. Forebrain development (2-3 months gestation); III. Neuronal proliferation (3-4 months gestation); IV. Neuronal migration (1-5 months gestation); V. Neuronal organization (from fifth month of gestation until birth and beyond). VI. Myelination (after birth to 2 years of age) [1].

Neural stem cells can undergo a self-renewal process or differentiate to neurons that are located in the ventricular and subventricular zone [2-3]. Depletion of this cell population

due to a decreased or altered neuronal pool can result in isolation microcephaly [4]. However, microcephaly may also appear associated with other disorders such as pachygyria, as in Norman Roberts syndrome [5]. Thus, neurogenesis and cell renewal disorders lead to defects in neuronal migration and positioning in the developing brain.

Neuronal migration consists of neuron displacement from their source in ventricular and subventricular level to their final locations. There are two types of neuronal migration named as radial and tangential migration. Pyramidal neurons (which function is excitatory) perform the radial migration, which takes place from birth in the ventricular zone to the cortical zone. Ventricular cells and radial glia cells (a type of differentiated astroglia) have extensions that serve as scaffolding for young neurons to reach their destination [6, 7]. Inhibitory neurons migration takes place from medial ganglionic eminence of ventral telencephalon (where they come from) to the dorsal telencephalon, to subsequently enter the radial cortical spot, constituting an example of tangential migration [8]. Thus, neuronal migration determines the positioning of neurons at the cortical level, a key concept for the formation of sheet-specific neural circuits [9, 10].

Neuronal migration is a definite "inside-outside" model, so that first neurons which migrate will be established in the deeper cortical layers, and those which migrates the last ones form the outermost layers of the cerebral cortex [11].

Human neocortical neurons migration occurs mainly from the fifth week of gestation when the telencephalic vesicle appears to the twenty-second week of gestation [11].

Barkovich et al [12] classified CDM focusing on clinical, radiological and genetic findings, and it entails a useful tool in the diagnosis and therapy for clinicians. This classification divides the CDM into three groups:

Group I is likewise divided into three categories: malformations secondary to a decreased neuronal proliferation or accelerated apoptosis (congenital microcephaly) [12]; increased proliferation or decreased apoptotic activity (megalencephaly, except hemimegalencephaly which is not included in this group due to the presence of dysmorphic cells) [13]; and abnormal cell proliferation (both dysplasia and focal or diffuse cortical dysgenesis) [12].

Group II refers to secondary neuronal migration CDM disorders and is subdivided into four subtypes: the first one refers to secondary malformations due to neuro-ependymal alterations (related to the onset of migration), including periventricular heterotopia (groups of abnormally located neurons, due to the arrest of their migration along radial glial fibers). The second subtype are generalized disorders of migration at the level of the mantle, such as lissencephaly, literally defined as "smooth brain" due to absence (agyria) or reduction (pachygyria) of the cortical convolutions. The third subtype is the mantle-located migration disorders, such as subcortical heterotopia (clusters of neurons at the level of deep white matter) and sublobar dysplasia (cerebral dysmorphia located in an apparently normal hemisphere). Finally, the fourth subtype is referred to the alterations of migration at the level of limiting pial membrane. This group corresponds to the lissencephaly dysplasia type II or "cobblestone" type, although less severe forms have been associated with fetal alcohol syndrome and with mutations in transcription factors such as Foxc1 in mice [14]. The most characteristic malformations derived from neuronal migration disorders (group II) are described below.

2.1. Disorders of Neuronal Migration: Group II. A (Heterotopy)

This group includes the pathologies based on the accumulation of heterotopic neurons. The location and morphology varies, including nodular periventricular heterotopia, which is the most common form, linear periventricular heterotopia, a smooth layer of gray matter that lines the ventricular wall, columnar heterotopia, a collection of heterotopic neurons arranged linearly in the mantle, extending from the pia mater to the ependyma, and subcortical heterotopia (from II. C group) as described below.

The periventricular heterotopia seems to have a different embryonic origin to the rest, and it is considered a malformation of neuroependimary origin. A ventricular epithelium injury may produce a functional loss of the radial glia causing an inability for neuronal migration. It has been associated with mutations of the ARFGEF1 gene. In addition, layer-specific genetic tests suggest a characteristic pattern of the layers. Thus, the outermost layers of the heterotopic nodules contain six neuronal layers (expressing Rorß), the next one five layers (expressing Er81) and four layers the subsequent layer (expressing Nurr1). This suggests that neurons experiencing a later migration would be less affected when compared with controls [12, 15, 16].

2.2. Neuronal Migration Disorders: Group II. B (Lissencephaly)

Lissencephaly is due to a mantle-level migration disorder, which includes in its spectrum: agyria, pachygiria and subcortical band heterotopia. It has been associated with mutations in the TUBA1A gene responsible for 4% of classic forms and up to 30% of the lissencephalies associated with cerebellar hypoplasia. Mutations of the TUBA1A gene are also associated with multiple dysgenesis. Also, this mutation can be presented in association with others such as p. R402C, which is translated phenotypically into frontal pachygiria with posterior agyria. It is also associated with other dysgenesias such as: partial or total absence of the corpus callosum, leukodystrophies, as well as rotation of the cerebellar vermis with dilatation of the fourth ventricle and enlargement of the posterior fossa diameter, constituting the Dandy-Walker malformation. Clinical forms caused by mutations of the TUBA1A gene are severe forms that are related to congenital microcephaly, mental retardation and delayed psychomotor development with di/tetraplegia [15, 16].

2.3. Neuronal Migration Disorders: Group II. C (Subcortical Heterotopy and Sublobar Dysplasia)

Subcortical heterotopia is postulated to be due to a late

alteration of neuronal migration. It is a malformation by accumulation of neurons that are located in the deep white substance. They can be located in a linear way in the mantle in a pathology known as columnar heterotopia, or acquiring a curvilinear or nodular conformation. A characteristic of the subcortical heterotopia is that the affected hemisphere is smaller and with a thinner cortex than the contralateral one.

Sublobar dysplasia is characterized by presenting a dysmorphic brain region within a hemisphere with normal features [12, 17].

2.4. Neural Migration Disorders: Group II. D (Cobblestone Malformations)

It is a cerebral malformation complex composed of 5 types of alterations: lissencephaly, ventriculomegaly, abnormalities of the white matter, cerebellum and trunk-cerebellum hypoplasia and cerebellar polymicrogyria. It is associated with ocular malformations and / or congenital muscular dystrophy. Mutations of genes involved in O-glycosylation affect a muscle glycoprotein, α-dystroglycan, and can cause a wide range of disorders ranging from Walker-Warburg syndrome, muscle-eye-brain syndrome, Fukuyama congenital muscular dystrophy, congenital muscular dystrophy types 1C and 1D, and waists muscular dystrophy (LGMD2I, LGMD2K, LGMD2M). An abnormal basal membranes (skeletal muscle, retina, brain and cerebellum) formation is found. This leads to alterations in the anchoring of the radial glial cells to these basement membranes. Secondly, abnormal cortical lamination and neuronal migration excess through the incomplete basement membrane occur in the pial layer. Some papers relate the cobblestone malformation with mutations in GPR56 and COL4A1. Besides, it has also been associated with genes involved in glycosylation SRD5A3 and ATP6V0A2 [12, 15, 16].

Finally, group III comprises postmigrational secondary CDM due to an abnormal development, which corresponds to the beginning of the cortical organization (on completion of neuronal migration). This group includes: true polymicrogyria with its variants, the schizencephaly, focal cortical dysplasias and microcephaly of postmigrational development. Polymicrogyria is characterized by the presence of excessive cortical folds, with shallow grooves. It is subdivided into four groups. Group IIIA presents with associated schizencephaly. This is a type of abnormal porencephaly with grooves or crevices that affects one or both hemispheres and can be open or closed depending on the depth lip cleavage). IIIB group courses without schizencephaly. In the IIIC group polymicrogyria comprehends part of certain genetically polymalformation syndromes; and the IIID group polymicrogyria is associated with inborn errors of metabolism. Focal cortical dysplasias (FCD) of this group are due to late neurodevelopmental disorders such as extreme prematurity or hypoxic-ischemic encephalopathy [12]. The FCD are subdivided into three categories: FCD type I or minor malformations of cortical development, which may be caused by abnormal radial, tangential or both cortical lamination and FCD type III (which can be associated with hippocampal sclerosis, tumors or vascular malformations). Postmigrational microcephaly as last entity belonging group III of the CDM may be clinical or genetically defined (as an example, deletion of 1q43q44 including AKT3 gene that occurs with microcephaly and variable agenesis of the corpus callosum) or associated with encephalopathies (for instance, autosomal recessive inheritance diseases such as PEHO syndrome which is characterized by progressive encephalopathy, edema, hypsarrhythmic electroencephalogram and optic atrophy) [12, 15].

CDM could also categorized according to their profile of inheritance, such as autosomal recessive, autosomal dominant or X-linked and also if the alteration is clinically or genetically defined [12].

3. Conclusions

The aim of this review is to clearly establish a neurobiological and chronobiological correlation of malformations resulting from disorders of cortical ontogenesis, focusing specifically on those derived from neuronal migration disorders. Besides, we tried to fully organize the multiple subgroups of these diseases. CDM and, specifically, neuronal migration disorders are a group of congenital CNS malformations that are linked to some of the most frequent neurodevelopmental disorders in the pediatric age, such as intellectual disability, autism, schizophrenia and epilepsy, among others. CMDs are classified into three groups: group I includes changes in neuronal and glial proliferation and / or apoptosis; group II includes neuronal migration disorders; and group III includes secondary malformations due to abnormal postmigrational development. Group II is subsequently divided in four subgroups: II. A lissencephaly, II. B periventricular heterotopia, II. C subcortical heterotopia and sublobar dysplasia and II. D "cobblestone" malformation.

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