MALFORMATIONS OF CENTRAL NERVOUS SYSTEM: GENERAL ISSUES

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ABSTRACT

Malformations of the central nervous system (CNS) encompass a heterogeneous group of congenital anomalies that may be isolated or appear as part of a genetic syndrome. Advances in identifying the genetic etiology underlying many CNS malformation and syndromes have led to the current genetic-based classifications that allows us to better estimate prognosis and potential complications. Herein, we discuss the main genetic, clinical and radiological features and their implications for diagnostic testing and disease management.

Key words*: CNS, malformations, genetic investigations, developmental delay.*

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Introduction

Congenital central nervous system (CNS) malformations are highly prevalent, affecting 1 to 10:1,000 live newborns[(1)], they may be isolated or appear as part of a genetic syndrome or a complex congenital malformation syndrome[(2)].

CNS congenital abnormalities can be considered one of the main causes of infant morbidity and mortality and fetal death. CNS anomalies can be divided into developmental malformations and disruptions.

Developmental malformations result from brain developmental anomalies. These may be caused by chromosomal abnormalities and single gene defects, or by imbalances of factors that control gene expression during brain development. Gene defects may be in the germline or may develop after conception by spontaneous somatic mutation or be related to physical or chemical agents that act as teratogens. Some malformations are caused by multifactorial etiology in relation to multiple genetic and environmental factors.

Disruptions result from destruction of a normally developing brain and are caused by environmental or intrinsic factors such as fetal infection, exposure of the fetus to harmful chemicals, radiation, and fetal hypoxia.

Similar brain anomalies are caused by different noxae and the same noxa can determine different anomalies in relation to the time of its occurrence. For example, holoprosencephaly, a condition in which the forebrain is not divided into two hemispheres, is a malformation. Hydranencephaly, in which massive destruction reduces the hemispheres into fluid-filled sacs, is a disruption. The line between malformation and disruption is sometimes blurred because an extrinsic factor (e.g. radiation) may cause both direct physical injury and gene damage (epigenetic effect).

Malformations carry a recurrence risk that can be calculated and sometimes avoided in the future, for example in case of maternal metabolic pathology like maternal hyperphenilalaninemia, and maternal diabetes. Disruptions do not recur, unless the exposure recurs or continues. Exposure to known teratogens and viral infections, can occur throughout pregnancy. The timing of exposure is critical for both, malformations and disruptions. The earlier the exposure, the more severe the CNS defect. For instance, fetal cytomegalovirus (CMV) infection before midgestation can be responsible for microcephaly and polymicrogyria. CMV infection in the third trimester causes an encephalitis, similar to postnatal CMV encephalitis responsible for other diseases as deafness[3,5]. The most critical period for malformations and disruptions is the third to eighth week of gestation, during which the brain and most organs develop.

Classically, brain malformations are classified according to the morphological and structural criteria. In the past few years there have been great advances in identifying genetic and epigenetic alterations for many isolated CNS malformations and syndromes with CNS malformations. Several genomic disorders caused by copy number variation (microdeletions and microduplications) of genes whose dosage is critical for the physiological function of the nervous system have been recently identified[6-8]. With recent advances in the understanding of underlying molecular mechanisms involved in the development of the brain, attempts are being made to categorize these malformations according to the underlying genetic factors[9].

Prenatal diagnosis

Sonography is the standard approach for evaluating those anomalies prenatally. Fetal MRI is an important complementary imaging modality for the evaluation of malformations of the CNS as suspected by prenatal US. The optimum time to perform the examination is between 30 and 32 weeks. The most common reasons for referral for fetal MRI are the presence of fetal ventriculomegaly, suspected agenesis of the corpus callosum, posterior fossa abnormalities. MRI has been employed to study disorders of neuronal migration and midline disorders, which have always been difficult to detect sonographically. Ventriculomegaly (atrial width greater than 10 mm) is the most commoncentral nervous system (CNS) abnormality identified on prenatal sonography[10].

The causes of ventriculomegaly include developmental, destructive, and obstructive processes. As many as 80% of fetuses with ventriculomegaly have extra-CNS and CNS additional abnormalities that are detected by prenatal sonography and/or by postnatal evaluation[11,12]. As the neurodevelopmental outcome of fetal ventriculomegaly depends, at least inpart, on the presence of additional abnormalities[13]. MRI should be considered to determine the etiology and to rule out complications[14].

Neural tube defects

Meningomyelocele is characterized by protrusion of the meninges and spinal cord through open vertebral arches leading to paralysis). Varying degrees of mental retardation, bowel and bladder dysfunction as well as orthopedic disabilities also occur in association[15]. In most clinical series, hydrocephalus and Chiari II malformation are frequently reported in 90%-100% of babies with open spina bifida[16]. As these neonates are at high risk of developing NICU infections, surgery should be performed within 24 to 48 hours after birth .

Disorders of regionalization

Abnormal development of the anterior portion of the neural tube (the mediobasal prosencephalon) and associated structures caused by disturbances in ventral induction may cause abnormalities of the brain and face. The most severe is holoprosencephaly in which there is failure of the prosencephalon to separate into two cerebral hemispheres[17]. Holoprosencephaly has been associated with chromosomal abnormalities in all chromosomes, the most frequent in descending order are deletions or duplications of various regions of 13q, del(18p), del(7)(q36), dup(3)(p24-pter), del(2)(p21), and del(21)(q22.3)[18].

Studies in vertebrate models indicate the importance of the sonic hedgehog pathway in foregut anomalies (i. e. esophageal atresia) some of which has been observed in association with holoprosencephaly in some human patients[19], suggesting that common signals operate in both the forebrain and the foregut during development. Prompt recognition and appropriate clinical management of these associated anomalies are important to improve the rates of morbidity, surgical complications and mortality in these infants[20].

Cortical malformation	Gene involved/ inheritance		Incidence	Ref.
Malformations due to abnormal neuronal proliferation				
Primary Autosomal Recessive Microcephaly	MCPH, CDK5RAP2, CENPJ , STIL MCPH2, MCPH4	AR	Every gene <5%	Passemard, 2009
	ASPM		37-54 %	
Malformations due to abnormal neuronal migration				
Periventricular Heterotopia	FLNA	X-linked	26 in females 100% familial	Sheen, 2009
	ARFGEF1 g	AR	-	
Lissencephaly				
Classic	LIS 1	AD	65%	Guerrini & Filippi, 2005
	DCX	X-linked	12%	
	TUBA1A	AD	1–4%	Morris-Rosendahl., 2008; Kumar , 2010
L. with cerebellar hypoplasia	TUBA1A g	AD	30%	Kumar., 2010
	RELN	AR	-	Dobyns, 2010
	VLDLR	AR	-	
L with corpus callosum agenesis	ARX	X-linked	-	
Subcortical heterotopia	DCX	X-linked	85% females 29% males	Guerrini & Filippi, 2005; Dobyns 2010
Cobblestone malformation	FKTN, FKRP, POMGnT1 POMT, POMT2, GPR56	AR	-	Dobyns and Das, 2009
Postmigrational malformations				
Polymicrogyria syndromes (PMG)	Chromosomal abnormalities	22q11 deletion syndrome	11 pts	Jansen, Andermann , 2005
		Chromosomal rearrangements	20 pts	
		Aneuploidies	3 pts	
Bilateral frontoparietal PMG	GPR56 (locus 16q21)	AR	12 families	
Bilateral perysilvian PMG	X.linked (locus unknown)	AR	75%	
Bilateral generalized PMG	Presumed	AR	3 sibship	Chang, 2004
Schizencephaly	EMX2	AR	0-72%	Faiella, 1997; Granata 1997; Barkovich , 2001, 2005;

Table 1: Non sindromic disorders of cortical development. Disorders of proliferation.

Malformation of cortical development

Current classifications of malformations of cortical development rely on the stage of development (cell proliferation, neuronal migration, cortical organization) at which cortical development was first affected and known genetics[21]. It is estimated that up to 40% of children with drug resistant epilepsy have a cortical malformation[22]. Some of these less severe migrational and organizational abnormlities my beclinicaly silent and associated with learning difficulties or seizures. Several non sindromic disorders of cortical development have been decribed (Table 1).

Microcephaly is defined as a head circumference (HC) more than 2 SDs below the mean for age and gender. Microcephaly with multiorgan involvement is frequently reported, but rather nonspecific finding in submicroscopic chromosomal aberrations, in subtelomeric deletions (>30%) and in several cases of simplex and complex chromosomal rearrangement[23-27].To date, the genes: MICROCEPHALIN (MCPH1), WDR62 (MCPH2), CDK5RAP2 (MCPH), CEP152 (MCPH4), ASPM (MCPH5), CENPJ (MCPH6) and STIL (MCPH7) found to be responsible for true congenital isolated microcephaly of 4 SD or less, are all autosomal recessive[28].

Disorders of migration

Periventricular nodular heterotopia is a malformation of neuronal migration in which a subset of neurons fails to migrate into the developing cerebral cortex. Lissencephaly-pachygyria and subcortical band heterotopia are disorders of neuronal migration and represent a malformative spectrum resulting from mutations of either LIS1 or DCX genes. LIS1 mutations cause a more severe malformation in the posterior brain regions. Most children have severe developmental delay and infantile spasms, but milder phenotypes are on record, including posterior subcortical band heterotopia owing to mosaic mutations of LIS1. DCX mutations usually cause anteriorly predominant lissencephaly in males and subcortical band heterotopia in female patients (Figure 1).

In type 1 lissencephaly the cerebral cortex lacks gyri and sulci and is thickened, either throughout the cortex or more in the posterior than the anterior regions. Several other genetic causes were later found in the lissencephaly, pachygyria, and subcortical band heterotopia spectrum, including the genes DCX RELN, VLDLR, ARX,andTUBA1A[29].

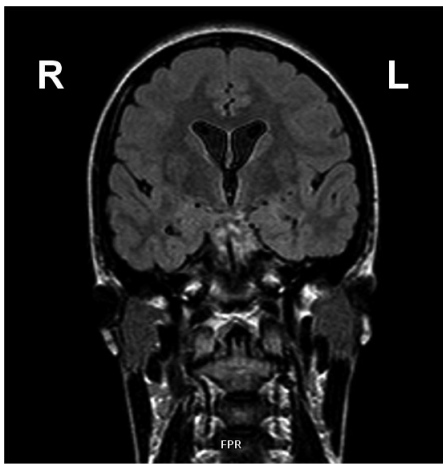

Fig. 1: Cerebral MRI Coronal T1 scan shows frontal bilateral pachigyria with ventricular enlargement in a female patient with DCX gene mutation.

In type II lissencephaly the cerebral malformations may be associated with eye or muscle abnormalities so that a comprehensive assessment is necessary. X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia in genotypic males is associated with mutations of the ARX gene, severe delay, seizures with suppression-burst EEG and early death; carrier female patients can have isolated corpus callosum agenesis[30].

Vascular malformations

Although they represent fewer than 1% of all cerebral arteriovenous malformations seen in children and adults, almost all cases diagnosed in the fetus and neonate involve the vein of Galen[31]. Very severe fetal brain disruption sequence can occur[32-34]. During the neonatal or infancy period the disease is presented with congestive heart failure diagnosed within the first week of birth, intracranial hemorrhage, seizures or focal neurologic symptoms (Figure 2).

Two angioarchitectural variants have been delineated: a choroidal type, composed of numerous feeding arteries joining the dilated midline vein around the choroidal fissure; and a mural type, composed of a single or a few arterial feeders which join the dilated vein near a single location. The choroidal type is usually characterized by much higher flow and tends to present early with cardiac failure. The mural type has lower overall flow and tends to present later in life with hydrodynamic disturbances. Newborns who presented after the first 2 weeks of life often have a mural type VGAM[35]. Patiens with cardiac failure have a particularly poor outcome even with treatment[36].

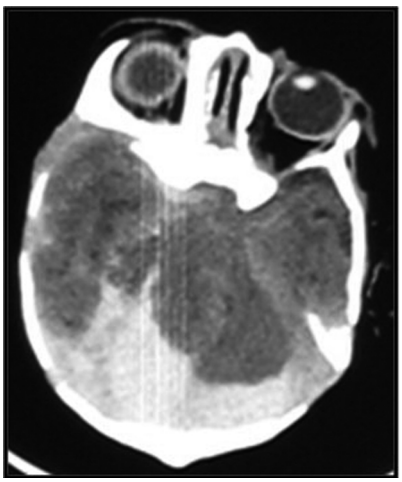

Fig. 2: Cerebral CT axial scan shows posterior fossa hemorrhage in a term newborn following rupture of the Vein of Galen.

Conclusions

Congenital CNS malformations should be suspected in patients presenting with seizures, developmental delay, microcephaly, macrocephaly, dysmorphic features especially during first year of life. Magnetic resonance imaging is essential to delineate the anatomical abnormalities. If a structural CNS abnormality is found chromosome analysis should be considered. Fluorescent in situ hybridisation (FISH) studies may detect microdeletion syndromes. As such malformations may appear as part of a genetic syndrome, it is important to look for associated anomalies in any infant with a CNS malformation[37]. Further investigations will depend on the specific diagnosis. The careful assessment of such patients is important in order to provide an accurate prognosis and genetic counselling.

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