Brain Imaging and Genetic Risk in the Pediatric Population, Part 2

Congenital Malformations of the Central Nervous System

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KEYWORDS

• Brain imaging • MRI • Magnetic resonance • Congenital malformations • Genetics

KEY POINTS

- Structural abnormalities of the central nervous system (CNS) are increasingly recognized by applying high-resolution imaging techniques, particularly MRI.
- As the number and complexity of recognized congenital malformations of the CNS have increased significantly, a multidisciplinary approach is mandatory, involving experts from neuroembryology, neurogenetics, neurochemistry, pediatric neurology, and pediatric neuroradiology.
- The MRI pattern recognition approach evolved, and integrated classifications of congenital malformations have been proposed based on embryology, genetics, and neuroimaging findings. As a result, different neuroimaging phenotypes have been observed, guiding genetic analysis and, frequently, resulting in the identification of causative genes.
- It is essential for every pediatric neuroradiologist to be aware of potential genotype-MR phenotype in congenital disorders of the CNS.

INTRODUCTION

Congenital malformations (CM) of the central nervous system (CNS) are commonly encountered in daily neuroimaging practice, and the significant and continuous development of the various imaging techniques, particularly MRI, has revolutionized the analysis and understanding of these disorders.[1–6] Because the number and complexity of recognized CMCNS have increased significantly, a multidisciplinary approach is mandatory, involving experts from neuroembryology, neurogenetics, neurochemistry, pediatric neurology, and pediatric neuroradiology.

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malformations have been proposed based on embryology, genetics, and neuroimaging findings.[1] As a result, different neuroimaging phenotypes have been observed guiding genetic analysis and, frequently, resulting in the identification of causative genes. In this context, it is essential for every pediatric neuroradiologist to be aware of potential genotype-MR phenotype in congenital disorders of the CNS.

Understanding the embryology of the CNS is crucial for every neuroscientist. Although an extensive review about this topic is not presented in this article, some concepts are important to discuss. The CNS appears in the middle of the third week of development as a thickened area of the embryonic ectoderm, the neural plate. At the onset of gastrulation, there is induction of the neural plate, which folds into the neural tube in a process called neurulation. The fusion of the neural tube occurs in a zippering process at 5 different sites in humans.[7] By neurulation, the CNS is subdivided into its major transverse parts: prosencephalon, mesencephalon, rhombencephalon, and spinal cord. Modern neuroembryology integrates descriptive morphogenesis about these parts of the CNS with more recent insights into molecular genetic programming and data enabled by cell-specific tissue markers.[8]

In this article, the genotype-MR phenotype correlation of the most common or clinically relevant CMCNS in the pediatric population is reviewed. The data focus on the most commonly diagnosed diseases and those in which the neuroimaging abnormalities are better defined. The PubMed/Medline database was searched using a combination of key words such as "genotype-phenotype correlation," "genotype-imaging correlation," and "neuroimaging-genetic correlation." Relevant studies were defined based on current knowledge. For a more comprehensive review, the congenital disorders were divided based on an embryologic pattern, in which malformations were classified in 3 groups: ventral induction disorders, cortical malformations, and congenital malformations of the posterior fossa. In this review, malformations of the dorsal induction and spinal congenital disorders are excluded.

MALFORMATIONS OF THE VENTRAL INDUCTION

Malformations of the ventral induction represent a defect in the rostral closure and may result in disorders of formation, cleavage and midline development of the prosencephalon. Genetically, holoprosencephaly (HPE) and commissural abnormalities (including agenesis of the corpus callosum) are the most relevant disorders.

Holoprosencephaly

HPE is the most common developmental defect of the forebrain, with an estimated prevalence of 1 in 10 to 16,000 live births and 1 in 250 human conceptions.[9,10] Children with HPE have a failure of differentiation and midline cleavage of the prosencephalon. Therefore, in the more severe and prevalent form of HPE, called alobar HPE, these patients present a crescent-shaped and single ventricle, which occupies most of the volume of the skull, fusion of the hypothalamic and basal ganglia, and no commissural structures identified.[9,10] The poor prognosis in the most severe forms justifies the importance of genetic counseling in affected families.

The cause of HPE is heterogeneous: teratogens, chromosomal abnormalities, and single gene mutations can be involved. Most genes that have been implicated in HPE belong to the sonic hedgehog signaling pathway. Mutation of at least 12 different loci in 11 chromosomes has been implicated in the development of familial HPE, such as *SHH*, *GLI2*, *PTCH1*, *TGIF*, *ZIC2*, *TDGF1*, and *SIX3*.[9,11,12]

Recent data suggest specific genotype-phenotype correlations in HPE. *SHH* mutations result in a milder disease than mutations in the other common HPE genes.[6,12] Such microforms of HPE are represented by hypotelorism, solitary central maxillary incisor, and cleft lip/palate. Mutations in *ZIC2* (located on 13q32 chromosome) and *SIX3* (located on 2p21 chromosome), for instance, have a high prevalence in more severe HPE types (generally, alobar subtype).[10,13,14] *ZIC2* is also associated to neuronal tube defects, mainly rachischisis, and neuronal migration abnormalities. HPE-related gene mutations in the *SHH* and *TGIF* genes have been correlated with the cause of the pituitary stalk interruption syndrome and isolated pituitary hypoplasia.[15]

Agenesis of the Corpus Callosum

Agenesis of corpus callosum (ACC) is the most common type of commissural agenesis. Recent neonatal and prenatal imaging studies suggest that ACC occurs in at least 1 in 4000 live births[16,17] and up to 3% to 5% of individuals assessed for neurodevelopmental disorders by neuroimaging.[18,19] Complete and partial ACC can result from genetic, infectious, vascular, or toxic causes. Recently, Edwards and colleagues[20] described a comprehensive classification of the clinical and genetic features of syndromes associated with ACC.