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Congenital, Developmental, and Neurocutaneous Disorders

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This chapter describes some of the most important congenital nervous system malformations and neurodevelopmental disorders. Advances in imaging and molecular genetic diagnostic technology have improved our understanding of these disorders. Neuroimaging facilitates diagnosis and informs early management of malformations of the brain and spinal cord. The remarkable advances in genetic sequencing and microarray technology are improving our understanding of the etiology and pathogenesis of neurodevelopmental disorders due to single genes, like Fragile X syndrome, Rett syndrome, tuberous sclerosis, and neurofibromatosis, as well as the genetically heterogeneous disorders autism and ADHD.

CONGENITAL MALFORMATIONS

Malformations of the central nervous system develop during fetal life. Table 115-1 summarizes the timeline of early neural and cortical development and the defects that may occur during these stages. Malformations developing early in embryogenesis can be more severe than those arising later, after the basic structures of the nervous system are in place.

Brain Malformations

Disorders of Ventral Induction

Definition/Epidemiology

Ventral induction is the early stage of brain development where brain vesicles and the face begin to form. Malformations that arise during this time include holoprosencephaly (HPE), agenesis of the corpus callosum (ACC), and septo-optic dysplasia (SOD). In clinical practice, ACC is the most commonly seen, with an estimated prevalence in the general population of greater than 0.5%, higher in those with developmental disabilities. The estimated prevalence of HPE is 1/10,000, and SOD is even rarer, occurring in 3/100,000.

Pathology

During ventral induction, the prosencephalon forms and undergoes cleavage and midline formation. Abnormal prosencephalon cleavage leads to HPE, a spectrum of abnormalities ranging from alobar HPE (cortex with a single ventricle) to semi-lobar and lobar HPE (cerebral hemispheres are mostly separated except for the frontal lobes) (Figure 115-1). In all cases, there is some fusion between the two cerebral hemispheres, often accompanied by facial anomalies. ACC and SOD represent more discrete abnormalities localized to specific midline structures and occur later in prosencephalic development.

Clinical Presentation

Children with HPE, ACC, and SOD have varying degrees of developmental disability and other congenital anomalies. In HPE, especially, the close timing of this defect with facial development may lead to midline anomalies like cleft lip, hypotelorism, or cyclopia. Children with SOD will have vision problems and optic nerve hypoplasia on examination; they can also have pituitary dysfunction. The clinical presentations range from severe—where individuals develop multiple complications related to their severe neurologic impairments—to nearly normal, as in the case of ACC associated with no other defects.

TABLE 115-1 STAGES OF PRENATAL NEURAL DEVELOPMENT (SIMPLIFIED)

	STAGE	STRUCTURES FORMING	POST-CONCEPTUAL AGE	ANOMALIES SEEN*
NEURAL TUBE, BRAIN VESICLE DEVELOPMENT (KANEKAR)	Dorsal induction	Neural tube closure	18-26 days (3-5 weeks)	Anencephaly, spina bifida, myelomeningocele, Chiari 2 malformation
	Ventral induction (ref Kanekar)	Brain vesicle and face development	5-10 weeks	Holoprosencephaly agenesis of the corpus callosum, septo-optic dysplasia
CORTICAL DEVELOPMENT (REF BARKOVICH, OSBORNE)	Proliferation	Development of neuroblasts and glioblasts	2-4 months (neuroblasts)	Microcephaly, megalencephaly
	Migration	Formation of 6 cortical layers	Peak occurrence at 2-4 months, though occurs from 8 weeks to 8 months	Lissencephaly, periventricular heterotopias
	Post-migrational organization	Cortex formed		Polymicrogyria, schizencephaly

*NB: Some anomalies (such as microcephaly, polymicrogyria) can arise from different stages. So even though it may seem intuitive to think of microcephaly as a disorder of neuronal proliferation, there are some forms of microcephaly that develop well after migration.