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Pediatric Neuropathology
A Text–Atlas

With 1,020 Figures, Including 917 in Color
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*Pediatric Neuropathology: A Text–Atlas* is dedicated to our friend and colleague

Dr. Laurence E. Becker
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1974–2002
Preface

Dr. Takashima and Dr. Becker were planning this text–atlas when Dr. Becker was prematurely taken from us. We have, with enthusiasm, completed the book according to the original plan. The material is gathered from our combined experiences over 30 years at the Hospital for Sick Children, Toronto; the Texas Children’s Hospital, Houston; the Health Sciences Centre (Winnipeg Children’s Hospital), Winnipeg; and the National Institute of Neuroscience, Tokyo. We acknowledge with gratitude the families who have allowed us to study these cases. It is our hope that our involvement has contributed to a better understanding of pediatric neuropathology.

The discipline of neuropathology with its interpretation of morphology stands between the patient with his or her physician and the neurobiologist with his or her science. It requires a correlation of clinical, morphological, and biological information. When interpreting pediatric neuropathology, brain development must also be considered. Thus, each case at its unique age can potentially (1) disclose critical periods of brain development that may be interrupted by a particular disease process or (2) define cell populations of selective vulnerability.

The past three decades have provided amazing techniques that increase the neuropathologist’s ability to define morphology. Histochemistry, immunocytochemistry, in situ hybridization, and fluorescence in situ hybridization (FISH) now allow us to define specific cell types, proteins, and chromosomes that are involved in pediatric neurological disease. Brain imaging reveals exquisite details of brain lesions, and neurobiologists offer tests that define tissue-specific genetic abnormalities. Our new technologies have required increased interaction between clinician, pathologist, and scientist; but they also rely heavily on the knowledge and techniques of classic neuropathology.

In the text–atlas we have attempted to summarize the categories of disease that affect the pediatric patient and have used examples of these diseases taken from our case records. In each case, when possible, there is a brief paragraph summarizing the current clinical, morphological, and biological information about the disease. This information is greatly abbreviated, but with illustrative images we have emphasized morphology—the hallmark of neuropathology and the starting place for further investigation.

The text–atlas is incomplete. There are many diseases we do not understand, especially those most debilitating disorders of childhood—the pervasive developmental disorders, which interrupt neural connectivity and function with no obvious morphological alteration. It is our hope that the text–atlas will be a useful guide for students of neuropathology, neurology, and neuroscience, and that these students will go on to make our understanding more complete.

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1 Normal Development
1. Normal Development

1.1 Developmental Characteristics of the Fetal Brain: Gross Brain

**Characteristics of Fetal Cerebral Hemispheres**

The cerebral surface develops gradually from the fetal flat (lissencephalic) brain to the adult gyral pattern, increasing the cortical surface area until the second year of life. The sylvian fissure is apparent at approximately 14 weeks' gestation (GW). The primary sulci, such as rolandic, calcarine, superior temporal, and precentral sulci, appear after 20GW, the secondary sulci appear from 28GW, and the tertiary sulci from 36GW. The gestational age of a brain can be estimated by counting the number of convolutions (gyri) crossed by a line drawn from the frontal to the occipital pole above the insula and adding 21 to the gyral count [1]. Gestational age can also be estimated by counting gyri and sulci in neuroimages [ultrasonography and magnetic resonance imaging (MRI)].

The posterior horns of lateral ventricles are large (colpocephalic) during the second trimester of fetal life. The volume of the germinal matrix increases until 26GW and begins to decrease at 30GW. The germinal matrix, or neuroepithelium, persists as small islands in the wall of the ventricle until after birth. The largest island is the ganglionic eminence between the thalamus and the caudate. It is present at birth and disappears during the first year of life [2]. The periventricular germinal matrix produces neural stem cells in the innermost zone of the epithelium. These progenitor cells first produce neurons, which are translocated and migrate toward their final destination. The immature astrocytes and oligodendrocytes differentiate and migrate later.

**Fig. 1.1-1.** Fetal brain at 23 weeks' gestation, lateral view. The Sylvian fissure is widely open, and the first sulci are found in the central area.

**Fig. 1.1-2.** Fetal brain at 31 weeks' gestation, lateral view. The Sylvian fissure is slightly open, and secondary sulci are found in the whole hemisphere.
Fig. 1.1-3. Left. Basal view of the fetal brain in 1.1-1. The cerebellum is very small compared with the brain stem. Right. Horizontal section of the fetal brain in 1.1-1. Posterior horns are large in the very immature brain.

Fig. 1.1-4. Left. Basal view of the fetal brain seen in 1.1-2. The cerebellum is still small. Right. Horizontal section of the fetal brain seen in 1.1-2. Posterior horns are still large in the preterm fetus. The cavum septi pellucidi is normally present in all fetuses and newborns and disappears during the first 2 years.

Fig. 1.1-5. Preterm fetal brain. The coronal section shows no sulcus formation (except sylvian fissures) and a thick subependymal germinal layer. H&E.

Fig. 1.1-6. Term neonatal brain. The coronal section shows various depths of sulci and little subependymal germinal layer. H&E.
1.2 Developmental Characteristics of Neurons

Neurons, astrocytes and oligodendrocytes are derived from neural stem cells in the neuroepithelium of the ventricular wall [3]. Neurons develop in a caudal-rostral order from spinal cord to cerebral cortex. Those in the spinal cord and brain stem develop during the early fetal period; most neurons in the cerebral and cerebellar cortex develop and mature during the late fetal and infantile periods.

In the telencephalon, at 6–8 GW, Cajal Retzius (CR) and subplate neurons migrate from the neuroepithelium to form the preplate [4]. Subsequently, maturing pyramidal cortical neurons migrate along the radial glia [5] separating the CR and subplate neurons to form the six-layered cerebral cortex. The neurons of layer VI migrate first in an “inside-out” sequence. Tangential migration of granular neurons follows, completing the population of the cortex. Proteins such as Lis-1 [6] and Reelin [7] regulate neuronal migration and cortical organization. Reelin is produced by the CR neurons. A superficial granular layer, originating from the periventricular germinal epithelium, appears transiently underneath the leptomeninges of the cortex at 13–39 GW [8].

In the cerebellum Purkinje cells from the alar plate of the neural tube and the granule cells from the rhombic lip migrate toward the cortex of cerebellar folia, forming a complex circuitry with the brain stem, spinal cord, cerebellar nuclei, and basal ganglia. The external granular cell layer is under the control of Math1, which influences the normal development of the internal granular cell layer [9]. The maturation of the cerebellum lags behind the cerebral hemisphere, so mature numbers of folia and of internal granular neurons develop after birth. Involution of the external granular layer proceeds until 1 year of age. The maturation of the vermis occurs before that of the cerebellar hemispheres [10].

Fig. 1.2-1. The developing telencephalon and cerebellum at 14 weeks.

Fig. 1.2-2. The developing telencephalon and cerebellum at 17 weeks.
Fig. 1.2-3. The developing cerebral hemisphere and cerebellum at 19 weeks.

Fig. 1.2-4. The developing cerebral cortex and cerebellum at 28 weeks.

Fig. 1.2-5. The developing cerebral cortex and cerebellum at 33 weeks.

Fig. 1.2-6. The developing cerebral cortex and cerebellum at 40 weeks.
1.3 Dendritic and Synapse Development

Neurons are composed of soma, dendrites, and axons. The soma (nucleus and cytoplasm) has a variable shape and size depending on its location in the brain and its function. The soma of the developing neuron extends several neurites: one becomes the axon, developing presynaptic specializations; the others become dendrites, developing postsynaptic specializations. Many factors determine the destiny of the neurites. Axons produce growth cones that are guided to target neurons by extracellular matrix, the cell surface, and diffusion molecules. Some factors cause revulsion, inhibition, or cessation of movement. Neuronal survival is influenced by factors from the neurons they innervate, synaptic inputs, and neighboring neurons and glia. The point of communication between neurons is the synapse, formed when the growth cone contacts an appropriate “postsynaptic cell”; and there is expression of chemical transmitters required for neural transmission. The synapse is about 1μm in size and is localized to dendritic protrusions, the spines [11,12]. In the immature brain, neuronal somas are closely packed. When the neurons mature, the packing density decreases as the individual neurons develop expanding dendritic branches and axonal arborizations.

Dendritic and spine development can be defined in camera lucida drawings of Golgi preparations. Dendritic and synaptic development of neurons varies in each area of the cerebral cortex. For example, the neurons in the motor cortex mature a month ahead of those in the visual cortex. Within the cortical layers there is also variation in the time of dendritic maturation. For example, at 20GW basal dendrites are developed only in the deeper pyramidal cell layers [11,13].

Fig. 1.3-1. The visual cortex at 24 weeks’ gestation. The cell processes of superficial and poorly differentiated neurons remain attached to the pia. The deep pyramidal neurons are relatively developed, exhibiting short basal dendrites.

Fig. 1.3-2. At 28 weeks’ gestation the superficial neurons are poorly differentiated. Layer 3 pyramidal neurons are more developed, with small branched basal dendrites and occasional spines on the apical dendrites. Layer 5 neurons have more basal dendrites and spines.
**Fig. 1.3-3.** At 40 weeks’ gestation (term) there is a marked increase in the number of satellite and other association neurons. Fusiform cells are present in the deepest cortical layers. Spines are less on the proximal portions of pyramidal cell dendrites and are increased on the more distal portions of dendrites.

**Fig. 1.3-4.** At 6 months of age many more stellate neurons have appeared. The length and thickness of dendrites has increased, and apical dendrites have numerous branches.

**Fig. 1.3-5.** At 28 weeks’ gestation there are more spines on the proximal dendrites than on the distal dendrites.

**Fig. 1.3-6.** At 6 months of age, there is a small number of spines on the proximal portions of the apical and basal dendrites. The numbers gradually increase with increasing distance from the neuronal soma.
1.4 Glial Development and Myelination in the Cerebral White Matter

The glial cells are the astrocyte, the oligodendroglial cell, and the microglial cell. The astrocyte and oligodendrocyte arise from specific neural precursor cells and migrate from the germinal matrix. There are several astrocytic types based on their morphology and position in the nervous system: The protoplasmic astrocyte has glutamate transporters and contributes to the blood–brain barrier; the reactive astrocyte shows marked glial fibrillary acidic protein (GFAP) immunoreactivity and contains neurotrophic factors. There are Bergman astrocytes in the cerebellum, Müller cells in the retina, and radial glia in cerebral vesicles during development. The astrocyte, which has been identified to have voltage-gated ion channels and receptors for neurotransmitters, serves important functions in brain development, maintaining neurons, and the blood–brain barrier. The oligodendroglial cell is responsible for the production and maintenance of myelin. Myelination glia are immature forms of oligodendroglia with pale vesicular nuclei, nucleoli, and wispy tails of eccentric cytoplasm [8]. The maturing oligodendroglial cells can be identified by markers: the late oligodendroglial progenitor (NG2 proteoglycan+, O1+), the immature oligodendrocyte (O4+O1+), and the mature oligodendrocyte (myelin basic protein +) [14,15]. They are increased during the premyelination period. Microglia are the resident macrophages of the brain and are derived from mononuclear phagocyte precursor cells, which enter the brain during the period of developmental cell death. They are small, elongated bipolar cells with several finger-like processes and are ubiquitous in the parenchyma; they react to brain injury by producing cytokines [16,17], proteases, and nitric oxide.
Fig. 1.4-4. Myelination of cerebral white matter at 40 weeks’ gestation represented in a T2-weighted magnetic resonance (MR) image and a whole mount of brain stained with luxol fast blue (LFB).

Fig. 1.4-5. Myelination of cerebral white matter at 8 months represented in a T2-weighted MR image and in a whole mount of brain stained with LFB.

Fig. 1.4-6. Myelination of cerebral white matter at 3 years represented in a T2-weighted MR image and in a whole mount of brain stained with LFB.
1.5 Vascular Architecture in Developing Brains

The vascular pattern in the meningeal vessels varies with gestational age. The anterior, middle, and posterior cerebral arteries appear during the fourth month of gestation. The middle cerebral artery spreads out more rapidly with aging than the other cerebral arteries. In the venous system, the superior, inferior, anterior, and posterior cerebral veins are present. The superior, inferior, and posterior cerebral veins develop most rapidly.

In the cerebral hemispheres, the perforating arteries branching from the leptomeningeal arteries supply the cortex and underlying superficial and deep white matter as the cortical, subcortical, and medullary arterial branches, respectively. As the brain matures with the formation of gyri, the medullary arteries arising from the sulci appear shorter and their number of lateral branches increases.

The venous drainage of the cerebral mantle is divided, with cortical and subcortical veins draining into the meninges, and medullary veins from the deep white matter draining toward the ventricle. The deep white matter is drained by a fan-shaped array of medullary veins that flow vertically into the subependymal veins. The medullary veins in the deep cerebral white matter mature before the subcortical veins and before the arteries of the deep white matter [19]. This developmental discrepancy between deep white matter arteries and veins may be a predisposing factor for periventricular leukomalacia (PVL) and periventricular white matter hemorrhage [20].

Fig. 1.5-1. Arterial architecture of the frontal lobe in a preterm neonate at 26 weeks’ gestation.

Fig. 1.5-2. Arterial architecture of the cerebral hemisphere in a preterm neonate at 30 weeks’ gestation.
Fig. 1.5-3. Arterial architecture of the cerebral hemispheres at the level of the mammillary body in a 1-year-old child.

Fig. 1.5-4. Arterial architecture of the cerebral hemispheres and cerebellum at the level of the occipital horn in a 1-year-old child.

Fig. 1.5-5. Venous architecture of the cerebral hemisphere in a preterm neonate at 28 weeks' gestation. Note the brush-like veins in the subependymal matrix.

Fig. 1.5-6. Venous architecture of the cerebral hemisphere in a full-term neonate.
2 Malformations
2.1 Neural Tube Defects, Anencephaly

The brain and upper spinal cord form from the neural plate during primary neurulation beginning at 22 days’ gestation; the sacral spinal cord forms from the tail bud during secondary neurulation [1]. The various classifications of neural tube defects (NTDs) is complex and somewhat contradictory [2]. Practically, they can be considered as “open” (e.g., anencephaly, craniorachischisis, myelomeningocele) or “closed” (e.g., encephaloceles, meningoceles, split spinal cord). There are several pathoetiologies [3]. Folic acid supplementation before and during early pregnancy prevents most NTDs [3,4]. A mutant mouse model for NTD, Splotch, is being used to define the mechanism of teratogenesis by folate insufficiency [5]. A second mutant, curly tail, has an NTD that responds to myoinositol [6].

Craniorachischisis is the most severe form of NTD in which the brain and spinal cord are exposed to the surrounding amniotic fluid, resulting in neural tissue degeneration and angioma-like formations. Anencephaly is characterized by the absence of the calvarium and abnormalities of the base of the skull and the sphenoid bone with shallow orbits causing protrusion of the eyes. The cerebral hemispheres are replaced by the area cerebrovasculosa, a mass of neuroglial tissue and vessels. Exencephaly is rarely described in human fetal brain because the brain tissues usually become necrotic when exposed to amniotic fluid; the exencephalic appearance is converted to anencephaly by mid to late gestation [7].
Fig. 2.1-3. Acalvaria (acrania). The head appears intact but lacks the calvarium (skull cap).

Fig. 2.1-4. Acrania (same case as in 2.1-3). The brain situated underneath the skin and scalp appears complete.

Fig. 2.1-5. Acrania (same case as in 2.1-3). Coronal section of both hemispheres shows relatively normal gyral formation.

Fig. 2.1-6. Acrania (same case as in 2.1-3). The brain stem (right) is small compared with that of a normal age-matched control (left). H&E.
2.2 Meningoencephalocele, Encephalocele

A meningocele is the herniation of dura and arachnoid through a vertebral or calvarial defect, with the spinal cord or brain remaining in the spinal canal or cranium. A midline vertebral or cranial defect without any herniation is termed spina bifida or cranium bifidum respectively. Myelocele or encephalocele consists of a developmental vertebral or cranial defect through which there are herniations of the spinal cord or brain tissues.

Meningomyelocele or meningoencephalocele is herniation of part of the brain or spinal cord and meninges through a vertebral or calvarial defect associated with skin and hair abnormalities. In 80% of meningoencephalocele cases, the defect occurs in the occipital region and is associated with skin abnormalities. Occipital encephalocele occurs through the occipital bone and contains fragments of disorganized cerebral hemispheres with ventricular cavities. Polymicrogyria may be associated with meningoencephaloceles. The occipital encephalocele is an important component of Meckel-Gruber syndrome, which is a lethal autosomal recessive disorder that maps to 17q21–14 and consists of polydactyly, polycystic kidney, hepatic fibrosis, and various brain malformations (see Section 2.24) [2].

Fig. 2.2-1. Occipital meningoencephalocele in a fetus of 20 weeks’ gestation.

Fig. 2.2-2. Lateral views of the brain in 2.2-1 shows a meningoencephalocele at the level of the cerebellum.
Fig. 2.2-3. Meningoencephalocele of a fetus. Histology shows spongy changes and increased vascularity in thin cerebral hemisphere under thick meninges and normal skin. H&E.

Fig. 2.2-4. Meningoencephalocele of a fetus. Note the marked astrogliosis in the molecular layer and part of the cellular layer of the cortex. GFAP immunohistochemical stain.

Fig. 2.2-5. Meckel-Gruber syndrome in a term neonate. This lethal autosomal recessive syndrome consists of occipital encephalocele, polydactyly, polycystic kidney, and hepatic fibrosis with bile duct proliferation.

Fig. 2.2-6. Meningoencephalocele in the nuchal region.
2.3 Iniencephaly

Iniencephaly is a rare axial dysraphic complex malformation characterized by (1) an occipital bone defect, (2) cervical dysraphic changes, and (3) retroflexion of the whole spine [8,9]. Iniencephaly differs from anencephaly in that the cranial cavity is present and skin covers the head and retroflexed region [9]. Severe retroflexion of the neck is found by fetal ultrasonography and magnetic resonance imaging (MRI).

Anomalies of the central nervous system (CNS) may be numerous, ranging from lesions similar to those in anencephaly to less-advanced dysgenesis of the brain. NTDs affecting the spinal cord consist of iniencephaly, meningocele, and meningomyelocele. Iniencephaly is characterized by spina bifida of the cervical vertebrae usually associated with anomalies of the brain stem.

Fig. 2.3-1. Iniencephaly: retroflexion of the neck.

Fig. 2.3-2. Iniencephaly. Radiograph from lateral side of the whole body.