The Developing Human Brain: Differences from Adult Brain

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The purpose of this chapter is to introduce the reader to the great differences between the fetal, neonatal, childhood, adolescent, and adult brain.

Overview

Human brain development is innately beautiful and bewildering in its complexity. To assemble its integrated parts and circuits all neurons must move from their ventricular wall origin to other locations, sometimes over considerable distances, or complicated trajectories. Once appropriately deployed, the neurons usually extend one long process (if they have not done so during migration), sometimes over great lengths, and other shorter processes usually nearby the cell. All of these cellular movements are tightly choreographed genetically, from the timing of origin in ventricular wall to the ultimate destination of their processes [1]. Activation of gene sets in different combinations and sequences of at least one half of our entire human genome of 20–30,000 genes (only a third more than the roundworm *C. elegans*) is devoted to producing this most complex organ that will constitute only 2% of our body weight. The adult human brain probably contains at least one hundred billion neurons, perhaps five to ten times as many neuroglial cells, and trillions of synaptic connections. During intrauterine growth, a great excess of neurons is produced, but these are culled towards the third trimester end and the first few postnatal months. For the 9 months of intrauterine life and for a short but indeterminate postnatal period, brain growth and development is largely genetically determined. However, environmental factors begin taking a role shortly after conception and become increasingly important with advancing development.

These rapidly evolving changes throughout the developing brain lead to humans who are distinguished from other primates by cognitive capacities that have consummated in language, an *advanced* technology, and complex social behavior. The adult brain comprises only a few percent of body mass but expends one-fifth of the body's energy. The developing brain is just the opposite. The newborn brain, representing only one-fifth body mass, expends four-fifths of the baby's energy.

Particular vulnerabilities relate to distinct stages in brain development such as neurogenesis, neural migration, forebrain or hindbrain growth, gray matter or white matter maturation, dendritic sprouting, synaptogenesis, and possibly lifelong neural stem cell production and migration.

Conceptual Limitations

Neither pathologists nor neuroradiologists can see *hypoxia*, *hypoxischemia*, or *ischemia*. These diagnoses are merely interpretations needing confirmation, that is, autopsy verification of imaging findings. Nevertheless, decreasing autopsy rates coupled with a serious decline in neuroanatomy training for neuropathologists and neuroradiologists result in a cascade of confusion in recognizing anatomic location of brain lesions and specific brain functions. The result often is serious misunderstanding of pathologic processes. For instance, a commonly used term *periventricular*, as an anatomic location, is of little value since all brain and spinal cord is periventricular, and the term includes gray as well as white matter. Additionally, not all necrosis is infarct, even though all infarction is necrosis. Furthermore, designations such as *stroke*, *brain attack*, *frontoparietal*, or *prefrontal* have no anatomic or pathologic specificity and their use as outcomes is of little value in epidemiologic, statistical, or functional imaging studies. In neuroimaging, terms are often conflated to mean something else, such as *periventricular*

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leucomalacia (multiple focal white matter necroses, as originally defined [2–4]) to mean diffuse white matter astrocytosis, or diffuse neuroimaging changes.

Labels used as antecedents or *causes* need to be specific. For instance, some 34 different pathologic abnormalities, ranging from hemorrhage to necrosis, have been attributed to anoxia, hypoxia, hypoxischemia, and asphyxia without adequate clinical or pathologic definitions of any of these conditions. This suggests the possibility of having overlooked other risk factors which might have been potentially modifiable by the obstetrician or neonatologist [5].

Growth

Growth is generally a continuous process; however, one cannot sample a single growing fetus repeatedly except for some forms of neuroimaging. For pathologists, this limits us to providing best estimates of growth at different times in development from images or autopsied fetuses. The traditional strategy of measuring growth uses the independent variable of estimated gestational age. Unfortunately, the argument of defining *normal* brain weight as a ratio relative to some other body parameter (allometric relationship) continues. If brain weight is defined as a ratio to body weight alone, adverse influences affecting both the brain and body are likely to be missed because both might be influenced similarly.

Brain growth is a dynamic active process varying not only in time and space but also from one neural subdivision to another. Growth consists of a proportional daily (or weekly) gain in mass (weight) and is a very complex process for each organ [6]. During development, an individual's body size, shape, and proportions change due to differential growth of body parts. Growth cannot be discussed without considering its relation to rate. Since most human embryonic and fetal growth processes cannot be measured continuously, mathematical growth models are used. The advantage of such models is that growth curve characteristics such as maximum rate and points of inflection can be estimated. Growth rate is the percentage increase in weight and spatial dimensions per unit of time, which varies over time, particularly for specific brain parts. Inflection points reflect major changes in growth acceleration or deceleration. The models also estimate unobserved values, smooth measurement values, and minimize stochastic errors.

Both neuropores close at the end of the first postovulatory month, and most cranial nerve ganglia are present at this time [7]. The future cerebral hemispheres begin to bulge from the diencephalic ventricle at approximately 32 days. In prosencephalon, the hypothalamic, amygdaloid, hippocampal, and olfactory anlage are discernible. Both ganglionic eminences (medial and lateral) arise at approximately 33 days, and epithalamus, dorsal thalamus, ventral thalamus, and subthalamus are apparent. Spinal axodendritic synapses arise first in cervical region [8, 9]. The neurohypophysis evaginates at approximately 37 days, and 4 days later olfactory bulb and first amygdaloid nuclei become evident and a deep longitudinal interhemispheric fissure is conspicuous. The future corpus striatum, inferior cerebellar peduncle, and dentate nucleus are evident at approximately 44 days. Slightly later, the fourth ventricular choroid plexuses appear followed by lateral ventricular plexuses 3 days later (about 51 days). The cortical plate is visible in cerebral hemispheres at approximately 52 days and 2 days later axons in the internal capsule and olfactory tract appear. The embryonic period ends at approximately 57 days, with the cortical plate extending over most of cerebral surface.

When does the developing brain require particular large amounts of metabolites necessary to support rapid tissue growth? The weight of all brain components during the growing period must be considered, including the entire vascular bed and the intravascular blood necessary to support the brain's remarkable growth and activity [10]. The brain, and its various subdivisions, new cells, axons, dendrites, neural supporting cells, and vasculature all individually contribute to weight gain with each component added during separate developmental times. At term the brain is growing at its greatest rate; during the second year it will triple its birth weight. Myelin deposition in large amounts in the last gestational weeks and over the first few months of life probably accounts for a large proportion of weight gain. This transient and special variety of tissue (myelinating white matter) is potentially vulnerable to a unique array of insults, and estimation of its degree of maturation is of great importance to the neuroradiologist and neuropathologist.

Growth Functions

The Gompertz function is superior to the logistic, and also to several nonsigmoid functions, such as the generalized exponential and the polynomial, even though the latter has been considered important [11]. The first and second Gompertz function derivatives provide prenatal brain instantaneous and maximum growth rate and acceleration. The prenatal brain growth model is

$$Y = 1{,}190e^{-e^{(1.99-0.0437X)}}$$

where Y is brain weight in grams and X is gestational age in weeks (Fig. 1.1a). Maximum growth acceleration occurs at 24.5 weeks and maximum growth rate occurs at or just after term. This model confirmed the Dobbing and Sands original smaller study [12] and was corroborated in a second larger fetal brain population [11]. The inflection point and rates of maximal growth are similar to the original Gompertz model (above), namely second trimester's end and end of term gestation.

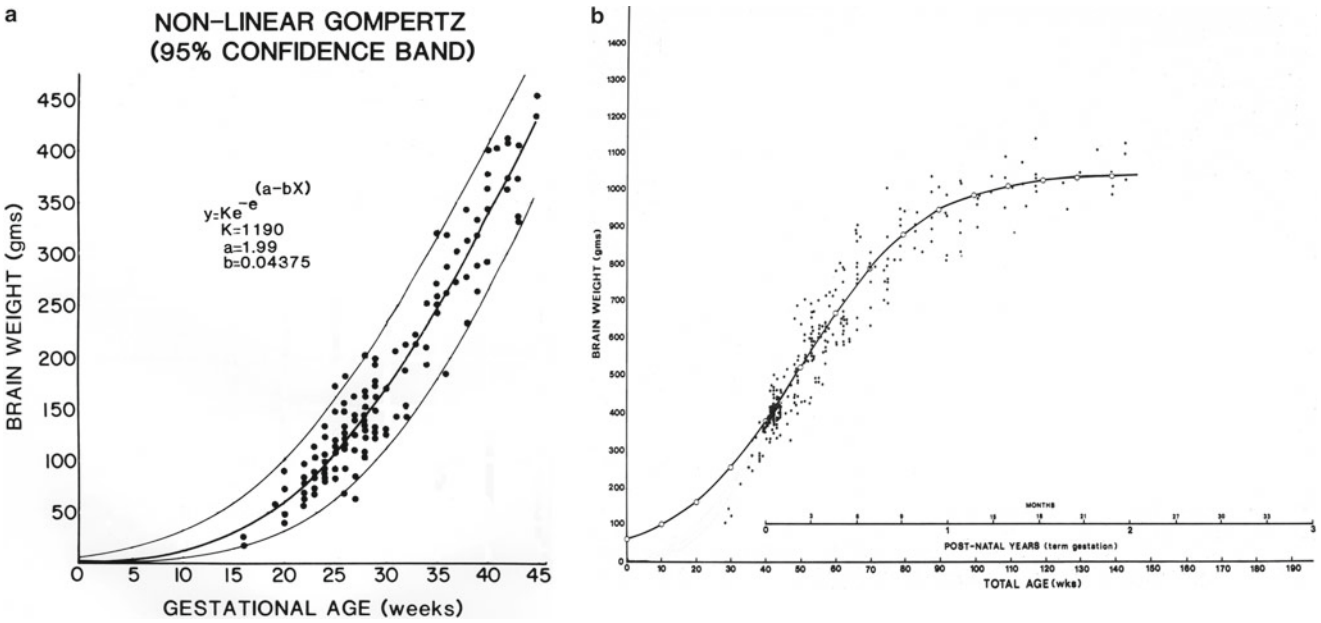

Fig. 1.1 (**a**) Nonlinear Gompertz (**b**) Sigmoid growth curve

In a separate newborn and childhood group, a sigmoid growth curve was generated from birth to 2 postnatal years (Fig. 1.1b) (McLennan and Gilles, 1983, unpublished data). Postnatal brain growth in our model is similar to Dobbing and Sands, although they had only a small number of cases beyond 12 months [12]. Again, there is a wide range in brain weight at each specific week. The significant implication is that most postnatal brain growth is completed within the first 2 postnatal years, similar to other reports [13, 14].

New Tissue Addition

If one assumes a large figure for the ultimate human neuronal number (for instance, estimated at 10^{11}—L. Swanson, personal communication, 2009), then during the first half of gestation, neuronal precursor cells develop in ventricular zone, move to some new location, mature in very large numbers (for example, many hundreds of thousands every second), and make innumerable connections.

Gyri, Cortical Thickness, Neuronal Maxima, and Synapses

Cortical layer thickness increases linearly with age and cortical neuronal density reaches a maximum at 20–28 weeks and then declines by about 70% [15], with additional decreases during adolescence [16]. The human infant's cerebral cortex at term has a gyral pattern similar to the adult cortex, but has only one third the total surface area. The gyral pattern is probably unique for each hemisphere and for each individual. Postnatal cortical expansion varies considerably from lobe to lobe and within lobes: regions of lateral temporal, parietal, and frontal cortex expand nearly twice as much as locations in insular and medial occipital cortex [17]. Within cerebral cortex, homotypical association cortices mature only after heterotypical agranular somatic motor and granular sensory and visual cortices are developed, and phylogenetically older brain areas mature earlier than newer ones [18]. Thus, primary sensory and motor areas generally attain peak cortical thickness before adjacent secondary areas, and before other polymodal association areas. Specifically, in brain behind the central sulcus, the first region to reach peak thickness is granular somatic sensory cortex (8 years), followed by calcarine cortex, containing striate granular primary visual area (7 years on the left and 8 years on the right), and then the remaining homotypical parieto-occipital cortex, with polymodal regions (such as the posterior parietal cortex) reaching peak thickness later (9–10 years). In the frontal cortex, the primary agranular motor cortex attains peak cortical thickness early (9 years), followed by the supplementary motor areas (10 years) and most of the frontal pole (10 years). High-order cortical areas, such as the dorsolateral homotypical

frontal cortex and cingulate cortex, reach peak thickness later (10.5 years). The anterior insular transition cortex reaches its maximum thickness at 18 years. In the medial views, the occipital and frontal poles attain peak thickness early, and then a wave sweeps from these areas, with the medial frontal and cingulate cortex attaining peak thickness last. There is also a marked dorsal to ventral progression of development [19].

Studies in nonhuman animals suggest that cortical dimensions during critical periods for the development of cognitive functions reflect experience-dependent molding of the architecture of cortical columns along with dendritic spine and axonal remodeling [20–24]. Such morphological events likely contribute to the childhood phase of increase in cortical thickness, which occurs in regions with either a cubic or quadratic trajectory. The phase of cortical thinning, dominating adolescence, likely reflects the use-dependent selective elimination of synapses that could refine neural circuits, including those supporting cognitive abilities [19, 25–27].

Functionally, the posterior medial orbitofrontal areas have been linked with the limbic system and autonomic nervous system control. These areas are thought to monitor the outcomes associated with behavior, particularly punishment or reward [28, 29], cognitive functions so fundamental that they are unlikely to undergo prolonged development. In contrast, isocortical regions often support more complex psychological functions, which show clear developmental gradients, characterized by rapid development during critical periods. The delineation of critical periods for human skill development is complex, but late childhood is a period of particularly rapid development of executive skills of planning, working memory, and cognitive flexibility, an age period which coincides with an increase in cortical thickness in the lateral frontal cortex [30]. In contrast, the critical period for certain visual functions (such as letter acuity and global motion detection) has been estimated as ending in middle childhood (age 6 or 7) [31]. Likewise, the period of increase in cortical thickness in the visual cortex also ends around this time (approximately ages 7–8).

The fate of all cerebral cortical cells is tied to the cortical vasculature, which supplies oxygen and nutrients, maintains homeostasis, and removes metabolic waste. Considering the increasing surface area of neuronal soma, dendrites, and axons that accompany brain enlargement, it has been estimated that each human neocortical neuron consumes 3.3 times more ATP to fire a single spike than in rats, and 2.6 times more energy to maintain resting potentials [32].

Synaptic Maxima

There is regional dendritic variation in neonatal human isocortex [33]. Synaptogenesis occurs concurrently with dendritic and axonal growth and with subcortical white matter myelination. Postnatal synaptic density rises after birth, reaches a plateau in childhood and then decreases to adult levels by late adolescence. In macaque monkeys, subsets of terminal synapses, as well as a subset of en passant synapses, appear and disappear each week with no net change in overall density, suggesting ongoing processes of synaptogenesis and elimination [34]. Huttenlocher's examination of visual cortex synapse number and density in brain tissue of deceased infants, children, and adults shows an exuberant growth of number and density of synapses between birth and about 8 months of age from a neonatal level at about 30–40% of the adult level to about 80% above the adult level at 6–8 months followed by a gradual decline to the norm, an approximate plateau from adolescent to adult age [25]. Synapse formation in granular auditory cortex and homotypical middle frontal gyrus begins before conceptual age 27 weeks, and reaches a maximum before 1 year of age in primary auditory and visual cortices, and at approximately three and a half years of age in the middle frontal gyrus. Interestingly, whereas in the human auditory cortex synaptic elimination is complete by 12 years of age, pruning continues until mid-adolescence in the middle frontal gyrus. The frontal cortex develops somewhat more slowly and declines somewhat later. Further, in human brains there is a separation in time of a few years between peaks in visual cortex synapse density and metabolic rate [35].

Myelination

Fetal and postnatal myelination is dramatic [36–38]. In autopsy material, tracts in which 50% of cases contained grossly visible myelin at second trimester end included: medial longitudinal fasciculus, fasciculus gracilis, fasciculus cuneatus, trapezoid body, and inferior cerebellar peduncle. In term infants, 50% of cases contained grossly visible myelin in the following tracts: proprius, spinocerebellar, spinothalamic, medial lemniscus, spinal trigeminal, lateral lemniscus, parathalamic posterior limb, parasagittal cerebellum, superior cerebellar peduncle, capsule of red nucleus, optic chiasm, optic tract, ansa lenticularis, inferior olivary nucleus amiculum, and habenulointerpeduncular tract. The additional tracts at 1 year in which 50% of cases were grossly myelinated included: hilus inferior olivary nucleus, auditory radiation, transverse gyrus of Heschl, transpontine, middle cerebellar peduncle, cerebellar hemisphere, dentate hilus, pontine corticospinal, occipital optic radiation, cingulum, corona radiata, distal radiation to precentral gyrus, posterior frontal, occipital pole, calcarine subcortical association fibers, and body, splenium, and rostrum of corpus callosum. Similarly, additional myelinated tracts at 2 years included: inferior colliculus brachium, lateral crus pedunculi; mid-

brain, cervical, and thoracic corticospinal; lateral olfactory stria; deep white matter in posterior parietal, temporal, and temporal and frontal pole deep white matter; external capsule; subcortical association fibers in frontal, temporal, and occipital poles, parietal, and posterior frontal; and stria medullaris thalami. Late or slowly myelinating tracts (> 2 years) included: central tegmental, solitary, medial crus pedunculi, lumbar corticospinal, putamen, globus pallidus, alveus, fimbria, fornix, extreme capsule, temporal subcortical association fibers, and anterior commissure [39].

Prematurity and Its Long-term Complications

More than half a million babies are born prematurely each year in the United States and the rate of premature birth has been increasing since 1980. Premature babies face an increased risk of lasting disabilities, such as mental retardation, learning and behavioral problems, neurologic deficit, lung problems, and vision and auditory problems. These long-term problems occur in greater proportions of premature births as the gestational age decreases. For instance, babies born at the end of the second trimester have brain weights half of those born at term and are more likely to have developmental delays [40], but even adults who were born at 34–36 weeks gestation are more likely than those born full-term to have mild disabilities and to earn lower long-term wages.

These neurologic and cognitive delays are accompanied by delays in myelination and development of *N*-acetylaspartate [41] that are accompanied by delays in motor skills at 6 years [42]. Structural abnormalities including cerebellar size, persist throughout childhood [43, 44], and small brain volume and corpus callosum persist into adulthood [45, 46].

Neonatal Brain Edema Likely Differs from That in Adults

Clinically important cerebral swelling, without concomitant necrosis or hematoma, is thought to contribute to necrosis. The few pathologic studies of fetal, term, or neonatal brain edema are in conflict, and whether edema occurs without necrosis remains in dispute. This confusion resulted from supposed analogies to adult swelling, poorly defined criteria, and high fetal brain water content relative to myelinated adult brain. Furthermore, the fetal and neonatal brain adds weight during fixation, often attaining a postfixation weight 30% greater than fresh weight [47]. What some call edema in fixed fetal or neonatal brain (cerebral hemisphere enlargement, sulcal and ventricular narrowing) likely reflects initial high brain water content plus fluid accumulated during fixation. Since immature brain differs from mature brain so markedly in its structure and composition as well as in its responses to insult, one cannot directly extrapolate information from the adult to neonatal brain.

Many neonatal brain edema experimental studies used lethal asphyxia or anoxia (for example, [48–50]). Whether or not this adequately measures uncomplicated water accumulation in cerebral tissue is a moot point; it certainly measures tissue swelling associated with functional endothelial and other cellular loss. Following asphyxia in an airtight jar until death, 5-day-old rat pup brain exhibits only a minimal increase in water content, but no brain weight change. Similar results were obtained with nitrogen anoxia and asphyxia with CO_2. As expected with cellular death, shifts in sodium and potassium occur concomitantly with water shift. Whether the fluid and electrolyte changes concomitant with complete cellular function loss are tantamount to uncomplicated edema, as the term is used for the mature brain, is not clear. Other experiments support the conclusion that "neonatal brain does not have a tendency to edema" [51–53].

A prospective study of all neonatal autopsies in a maternity hospital, defining brain swelling as cerebral hemisphere enlargement, gyral flattening, and sulcal narrowing observed that, without intraventricular hemorrhage, swelling was not found under 33 weeks [54, 55]. Yet, at about term, 89% of brains were "pathologically swollen." They did not attribute the swollen brain proportion to prolonged postmortem interval, but found that flattened gyri were more likely in stillbirths than early neonatal deaths. The most swollen brains contained the least water.

Diseases Differ Between the Child and Adult

Metabolic and Mitochondrial Inborn Errors

Many metabolic diseases affecting the infant or child have milder presentations in later life. Metabolic errors are generally grouped according to defects in their biochemical pathways. Those caused by energy failure can involve citric acid cycle or respiratory chain, such as mitochondrial disorders, or defects in glycogen mobilization, such as glycogen storage disease, or fats, such as fatty acid oxidation defects. Defects in amino acid metabolism include the urea cycle defects, such as citrullinemia, organic acidemias, such as methylmalonic acidemia, or aminoacidopathies, such as phenylketonuria. Finally, there are disorders of carbohydrate metabolism such as galactosemia. The lysosomal storage disorders, characterized by large carbohydrate–lipid complex accumulation, such as Hurler's disease, constitute the next general group. Peroxisomal biogenesis disorders include Zellweger's syndrome and adrenoleukodystrophy. Finally, there is a group of white matter disorders such as metachromatic leukodystrophy.

Brain Tumors

Brain tumors in children differ in location and kind from those in adults. Starr pointed out their predominance below the tentorium in the nineteenth century [56]. Schultz and Cushing recognized that the types of neoplasms also differed from those in adults [57, 58]. The clinical courses, symptoms, and signs in children with brain tumors were sufficiently distinct to prompt Bailey, Buchanan, and Bucy to introduce their classic monograph with the statement that "experience … early taught us that in the case of intracranial neoplasms also, one should not reason in the same manner when confronted with a child suffering from such a lesion as when dealing with an adult" [59]. The distributions of brain tumor locations also differ by age within childhood [60].

Kernicterus and Liver Disease

Bilirubin encephalopathy is a newborn syndrome, in which increased plasma levels of unconjugated bilirubin outstrip albumin-binding capacity and gain access to the brain. Jaques Hervieux described brain jaundice in 31 of his 44 autopsied jaundiced babies in 1847. Orth, an assistant to Virchow, in 1875 found intense yellow staining in basal ganglia, third ventricular wall, hippocampus, and deep cerebellar nuclei in a jaundiced term infant. In 1903, Schmorl reported 120 autopsies of jaundiced infants [3]. Schmorl coined the term kernicterus (basal ganglia jaundice) for this staining pattern. Although the following century of scientific study has added an enormous amount of information about the epidemiology and pathophysiology of neonatal jaundice and kernicterus, the contributions of Hervieux, Orth, and Schmorl will likely continue to be seen as historic landmarks in our quest for understanding of these phenomena [61, 62]. Commonly involved are the cerebellar roof nuclei, cranial nerve nuclei, inferior olives, dorsal funicular nuclei, globus pallidus, thalamus, and subthalamus. Hippocampus, putamen, and lateral geniculate are less often involved. Yellow staining of central nervous system nuclei also occurs in some neonatal brains, despite low levels of serum bilirubin [63].

The relative importance of blood–brain barrier, unconjugated bilirubin levels, serum binding, and tissue susceptibility in this process is only partially understood. Even at dangerously high serum levels, bilirubin traverses the intact blood–brain barrier slowly, requiring time for encephalopathy to occur [64]. Unconjugated bilirubin, the end product of heme catabolism in mammals, causes neonatal jaundice when it accumulates in their plasma. Under low unbound conditions it is a potent antioxidant, but when slightly elevated is toxic to astrocytes and neurons, damaging mitochondria (causing impaired energy metabolism and apoptosis) and plasma membranes (causing oxidative damage and disrupting neurotransmitter transport). With higher concentrations, unbound bilirubin accumulates in neurons and glial cells in several specific brain regions resulting in kernicterus. Unconjugated bilirubin accumulation in cerebrospinal fluid and central nervous system is limited by its active export, probably mediated by multidrug resistance-associated protein present in choroid plexus epithelia, capillary endothelia, astrocytes, and neurons [65–67]. The mechanism(s) by which severe hyperbilirubinemia engenders cytotoxic effects in selected brain regions is poorly understood but has been attributed previously to differences in permeability of blood–brain barrier and blood–cerebrospinal fluid barrier, regional blood flow, and bilirubin oxidation rates.

Brain Trauma

Falls or head blows in the adult result in brain contusions – wedge-shaped brain necroses, usually hemorrhagic, with the base of the wedge located at a gyral apex or the apices of several gyri. For the first half or two-thirds of the first postnatal year, falls or head blows result in unmyelinated white matter tears rather than cortically based contusions [68, 69].

Therapeutic Effects Differ in Children

One of the major limiting factors in treatment of childhood brain tumors is the sensitivity of the young brain to the effects of conventional radiation [70, 71]. The complications include defects in cognition, endocrine, and neurologic sequelae. Another major concern is the induction of secondary tumors in long-term survivors [72], Moyamoya disease [73], and arterial disease leading to infarction. Even very low brain irradiation doses in childhood can diminish later adult intellectual function [74].

Chemotherapy is not spared. Methotrexate is associated with a leucoencephalopathy [75–77], as is L-asparaginase [78, 79], ifosfamide [80, 81], and amphotericin B [82].

Conclusions

The great dissimilarities between infant and adult brains include the remarkable facts of fetal and childhood brain development, the long-term structural and functional abnormalities associated with premature birth, and the differences in gyral development, cortical thickness, neuronal maxima and loss, synaptic maxima and loss, functional cortical regional growth, metabolic and mitochondrial diseases, tumors, kernicterus, and differing therapeutic responses of childhood and adult brains.

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