Development of the Human Cerebellum and Its Disorders

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KEYWORDS

- Cerebellar development • Pontocerebellar hypoplasia
- Joubert syndrome • Dandy-Walker malformation
- Congenital disorders of glycosylation
- Rhombencephalosynapsis

The cerebellum is one of the best studied parts of the brain. Its three-layered cortex and well-defined afferent and efferent fiber connections make the cerebellum a favorite field for research on development and fiber connections of the central nervous system.[1,2] The cerebellum plays a role not only in motor control but also in motor learning and cognition.[3,4] The cerebellum develops over a long period of time, extending from the early embryonic period until the first postnatal years. This protracted development makes the cerebellum vulnerable to a broad spectrum of developmental disorders, ranging from the Dandy-Walker and related malformations to medulloblastoma, a neoplasia of granule cell precursors.[2,5–8] Ultrasonography and MRI make it possible to detect cerebellar malformations at an early stage of development.[9–12] In mice, the molecular mechanisms of cerebellar development are rapidly being unraveled.[13–18] Similar mechanisms are likely to be involved in the development of the human cerebellum. This article reviews the morphogenesis and histogenesis of the cerebellum, the mechanisms involved, and its more frequent developmental disorders, such as the Dandy-Walker and related malformations and the pontocerebellar hypoplasias.

MORPHOGENESIS OF THE CEREBELLUM

The cerebellum arises bilaterally from the alar (dorsal) layers of the first rhombomere.[19,20] The two cerebellar primordia are generally considered to unite dorsally to form the vermis, early in the fetal period. Rostrally, the paired cerebellar anlagen

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are not completely separated. Sidman and Rakic[21] advocated Hochstetter's[22] view that such a fusion does not take place, and suggested one cerebellar primordium (the tuberculum cerebelli) in the form of an inverted V (**Fig. 1**A). Recent genetic fate mapping studies of *Engrailed1* and *Engrailed2* in mice corroborate this view.[23] The arms of the tuberculum cerebelli are directed caudally and laterally, and thicken enormously, whereas its rostral, midline part remains small and inconspicuous. During the sixth week of development, the limbs of the cerebellar tubercle thicken rapidly and bulge downward into the fourth ventricle on each side giving rise to the internal cerebellar bulge, which together form the corpus cerebelli (see **Fig. 1**B). One week later, the rapidly growing cerebellum bulges outward as the external cerebellar bulges; these represent the flocculi, delineated by the posterolateral fissures. In the early fetal period, growth of the midline component accelerates and begins to fill the gap between the limbs of the tuberculum cerebelli, thereby forming the vermis. By the twelfth to thirteenth weeks of development, lateral and rostral growth have reshaped the cerebellum to a transversely oriented bar of tissue overriding the fourth ventricle (see **Fig. 1**C). Then, fissures begin to form transverse to the longitudinal axis of the brain, first on the vermis and then spreading laterally into the hemispheres. The first fissure to appear (ie, the posterolateral fissure) separates the main body of the cerebellum from the flocculonodular lobe.

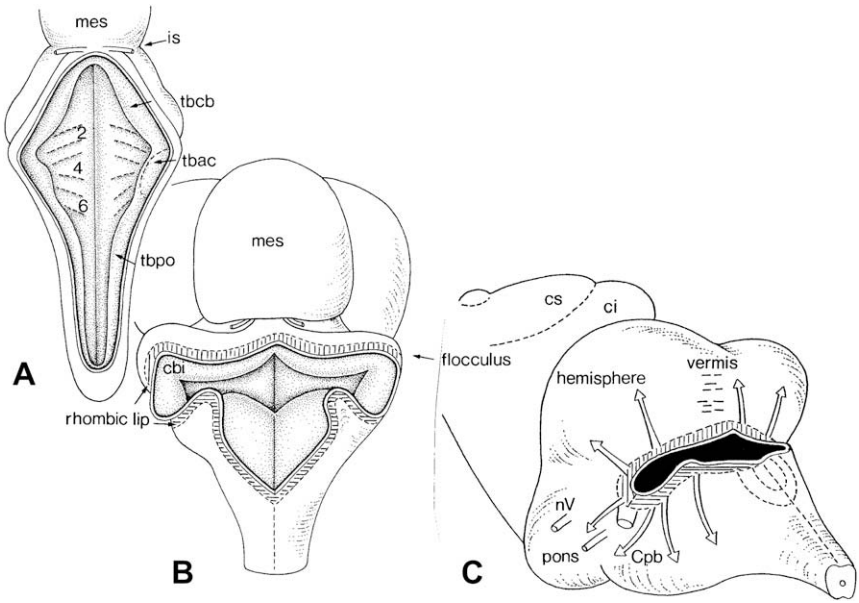

Fig. 1. Embryonic development of the human cerebellum. (*A*) At approximately 4 weeks of development. (*B*) At the end of the embryonic period. (*C*) At 13 weeks of development. The V-shaped cerebellar tubercle surrounds the rostral part of the fourth ventricle. The upper and lower rhombic lips are indicated by vertical and horizontal hatching, respectively. cbi, internal cerebellar bulge; ci, colliculus inferior; Cpb, corpus pontobulbare; cs, colliculus superior; is, isthmus; mes, mesencephalon; nV, trigeminal nerve; tbac, tuberculum acusticum; tbcb, tuberculum cerebelli; tbpo, tuberculum ponto-olivare; 2, 4, 6, rhombomeres. (*Data from* references[8,21,22]).