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**NEUROANATOMY ASSIGNMENT**

**TOPIC: Write a concise review on the developmental genetics of the cerebellum and highlight the genetic bases of known cerebellar disorders.**

Abstract

The cerebellum is a pre-eminent model for the study of neurogenesis and circuit assembly. Increasing interest in the cerebellum as a participant in higher cognitive processes and as a locus for a range of disorders and diseases make this simple yet elusive structure an important model in a number of fields. In recent years, our understanding of some of the more familiar aspects of cerebellar growth, such as its territorial allocation and the origin of its various cell types, has undergone major recalibration.

Introduction

 The cerebellum (Latin for "little brain") is a major feature of the hindbrain of all vertebrates. Although usually smaller than the cerebrum, in some animals such as the mormyrid fishes it may be as large as or even larger. In humans, the cerebellum plays an important role in motor control. Developmental genetics, on the other hand, is the study of how genes control the growth and development of an organism throughout its life-cycle.

Developmental genetics of the cerebellum

 The internal structure of the cerebellum reflects an intriguing paradox; its cytoarchitecture is relatively simple and repeated throughout, yet the connections between its neurons are wired into a complex array of gene expression domains and functional circuits. The developmental mechanisms that coordinate the establishment of cerebellar structure and circuitry provide a powerful model for understanding how functional brain networks are formed. Two primary germinal zones generate the cells that make up the cerebellum.

 Each zone expresses a specific set of genes that establish the cell lineages within the cerebellar anlage. Then, cohorts of differentiated projection neurons and interneuron progenitors migrate into the developing cerebellum. Thereafter, a number of remarkable patterning events occur including transformation of the smooth cerebellar surface into an intricately patterned series of folds, formation of three distinct cellular layers, and the demarcation of parasagittal gene expression domains. Together, these structural and molecular organizations are thought to support the proper connectivity between incoming afferent projections and their target cells.

 After birth, genetic programs and neural activity repattern synaptic connections into topographic neural networks called modules, which are organized around a longitudinal zone plan and are defined by their molecular, anatomic, and functional properties.

Development of the cerebellum

The metencephalon develops from the rhombencephalon and gives rise to the pons and cerebellum. The cerebellum is developed in the roof of the anterior part of the hind-brain.

* The cerebellum is formed from the rhombic lips, which are the two dorsolateral thickened alar plates.
* The rhombic lips thicken at week 6 to form the cerebellar plate, which has a dumbbell appearance.
* The cerebellar plate is separated into cranial and caudal portions by a transverse groove.
* The caudal portion forms the flocculonodular lobe, which is the most primitive part of the cerebellum.
* The cranial portion forms the vermis and the cerebellar hemispheres, both of which undergo extensive formation of fissures and folia.
* Like the rest of the neural tube, the rhombic lips consist of neuroectoderm arranged in the ventricular zone, intermediate zone, and marginal zone.
* In third month, the neuroectoderm in the ventricular zone undergoes another wave of proliferation to form the internal germinal layer. The internal germinal layer gives rise to the following: a. Deep cerebellar nuclei (i.e., dentate, emboliform, globose, and fastigial nuclei) b. Purkinje cells c. Golgi cells
* Some neuroectodermal cells from the internal germinal layer migrate through the marginal zone to form the external germinal layer. External granular layer (EGL) is a germinal (proliferative) layer on the surface of the cerebellum, which is present from week 8 of development to 2 years of age. It gives rise to the following: a. Basket cells b. Granule cells c. Stellate cells
* Both the external and internal germinal layers give rise to astrocytes, Bergmann cells, and oligodendrocytes within the cerebellum.

Cerebellar Disorders

1. The Arnold-Chiari malformation

It is caudal displacement and herniation of cerebellar structures through the foramen magnum. Arnold-Chiari malformation occurs in virtually every case of spina bifida cystica and is usually accompanied by hydrocephalus. It occurs when the caudal vermis and tonsils of the cerebellum and the medulla oblongata herniate through the foramen magnum. Clinical signs are caused by compression of the medulla oblongata and stretching of CN IX, CN X, and CN XII and include spastic dysphonia, difficulty in swallowing, laryngeal stridor (vibrating sound heard during respiration as a result of obstructed airways), diminished gag reflex, apnea, and vocal cord paralysis. This malformation is commonly associated with a lumbar meningomyelocele, platybasia (bone malformation of base of skull) along with malformation of the occipitovertebral joint, and obstructive hydrocephalus.

1. Ataxia: The term ataxia refers to a lack of fine control of voluntary movements

Acute cerebellar ataxia (ACA) is a disorder that occurs when the cerebellum becomes inflamed or damaged. The cerebellum is the area of the brain responsible for controlling gait and muscle coordination.

Manifestation: Reeling, wide-based gait. For hereditary ataxias, the abnormal proteins hamper the function of nerve cells, primarily in your cerebellum and spinal cord, and cause them to degenerate.

1. Dysarthria: Could be caused by
* mutation of FMR1 Gene on the x chromosome; by expansion or lengthening of FMR 1 gene on the X chromosome (Fragile X syndrome)
* deletion on chromosome 15q11, long arm of the paternally derived chromosome (Prader Willi syndrome)
* Downs syndrome
* Huntington’s disease
* Spina bifida with hydrocephalus causes malformation of the cerebellum

Manifestation: Inability to articulate words correctly, with slurring and inappropriate phrasing

1. Dysdiadochokinesia:Dysdiadochokinesia (DDK) refers to the inability to perform rapid, alternating movements, such as flipping one's hand from back to front on a flat surface, or screwing in a light bulb. DDK can cause problems with upper and lower extremities as well as with speech. DDK most often comes from a disturbance in the cerebellum

Manifestation: Inability to perform rapid alternating movements

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