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A CONCISE REVIEW ON THE DEVELOPMENTAL GENETICS OF THE CEREBELLUM AND THE GENETIC BASES OF KNOWN CEREBELLAR DISORDERS

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DEVELOPMENTAL GENETICS OF THE CEREBELLUM

Introduction

The cerebellum ("little brain") is a structure that is located at the back of the brain, underlying the occipital and temporal lobes of the cerebral cortex. Although the cerebellum accounts for approximately 10% of the brain's volume, it contains over 50% of the total number of neurons in the brain. Historically, the cerebellum has been considered a motor structure, because cerebellar damage leads to impairments in motor control and posture and because the majority of the cerebellum's outputs are to parts of the motor system. Motor commands are not initiated in the cerebellum; rather, the cerebellum modifies the motor commands of the descending pathways to make movements more adaptive and accurate.

The cerebellum has 3 parts:

- **Archicerebellum (vestibulocerebellum):** It includes the flocculonodular lobe, which is located in the medial zone. The archicerebellum helps maintain equilibrium and coordinate eye, head, and neck movements; it is closely interconnected with the vestibular nuclei.
- **Midline vermis (paleocerebellum):** It helps coordinate trunk and leg movements. Vermis lesions result in abnormalities of stance and gait.
- **Lateral hemispheres (neocerebellum):** They control quick and finely coordinated limb movements, predominantly of the arms.

There is growing consensus that in addition to coordination, the cerebellum controls some aspects of memory, learning, and cognition.

DEVELOPMENT

The cerebellum is developed in the roof of the anterior part of the hind-brain. The alar laminæ of this region become thickened to form two lateral plates which soon fuse in the middle line and produce a thick lamina which roofs in the upper part of the cavity of the hind-brain vesicle; this

constitutes the rudiment of the cerebellum, the outer surface of which is originally smooth and convex. The fissures of the cerebellum appear first in the vermis and floccular region, and traces of them are found during the third month; the fissures on the cerebellar hemispheres do not appear until the fifth month. The primitive fissures are not developed in the order of their relative size in the adult—thus the horizontal sulcus in the fifth month is merely a shallow groove. The best marked of the early fissures are:

(a) the fissura prima between the developing culmen and declive, and

(b) the fissura secunda between the future pyramid and uvula. The flocculus and nodule are developed from the rhombic lip,

and are therefore recognizable as separate portions before any of the other cerebellar lobules. The groove produced by the bending over of the rhombic lip is here known as the floccular fissure; when the two lateral walls fuse, the right and left floccular fissures join in the middle line and their central part becomes the post-nodular fissure.

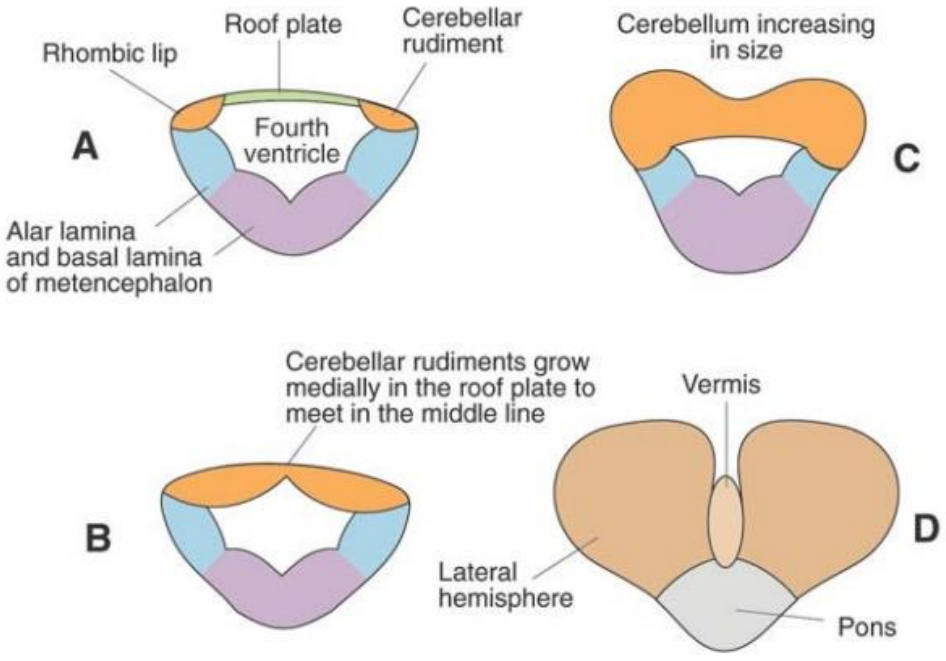
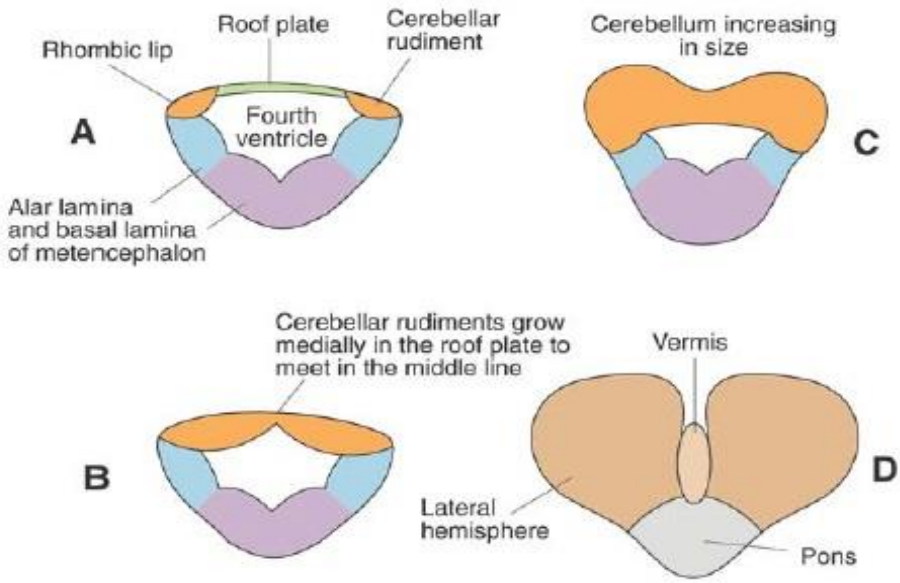


Fig. 7.5. Some stages in the development of the cerebellum. (A) Cerebellar rudiments appear from alar lamina of metencephalon. (B) They grow into the roof plate of the metencephalon to meet in the midline. (C) Cerebellum enlarges and bulges out of the fourth ventricle. (D) Lateral hemispheres and vermis can be distinguished.

The cerebellum develops from the dorsolateral part of the alar lamina of the metencephalon. Obviously, there are at first two primordia of the cerebellum, right and left. These extend medially in the roof plate of the metencephalon to eventually fuse across the midline. As the cerebellum increases in size, fissures appear on its surface. The lateral lobes and vermis can soon be distinguished, as a result of differential growth.

The developing cerebellum can be divided into: (a) an *intraventricular part* that bulges into the cavity of the developing fourth ventricle, and (b) an *extraventricular part* that is seen as a bulging on the surface. At first the intraventricular part is the larger of the two, but at a later stage, the extraventricular part becomes much larger than the intraventricular part and constitutes almost the whole of the organ.



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The cerebellum, at first, consists of the usual matrix cell, mantle and marginal layers. Some cells of the mantle layer migrate into the marginal layer to form the cerebellar cortex. The cells of the mantle layer that do not

migrate into the cortex, develop into the *dentate, emboliform, globose* and *fastigalnuclei*.

The *superior cerebellar peduncle* is formed chiefly by the axons growing out of the dentate nucleus. The *middle cerebellar peduncle* is formed by axons growing into the cerebellum from the cells of the pontine nuclei, while the *inferior cerebellar peduncle*is formed by fibres that grow into the cerebellum from the spinal cord and medulla.

CEREBELLAR DISORDERS

Cerebellar disorders have numerous causes, including congenital malformations, hereditary ataxias, and acquired conditions. Symptoms vary with the cause but typically include ataxia (impaired muscle coordination). Diagnosis is clinical and often by imaging and sometimes genetic testing. Treatment is usually supportive unless the cause is acquired and reversible.

The most common cause of cerebellar disorders is

- Alcoholic cerebellar degeneration

1. Congenital malformations

Such malformations are almost always sporadic, often occurring as part of complex malformation syndromes (eg, Dandy-Walker malformation) that affect other parts of the central nervous system (CNS).
Malformations manifest early in life and are nonprogressive.
Manifestations vary markedly depending on the structures involved; ataxia is usually present.

2. Hereditary ataxias

Hereditary ataxias may be autosomal recessive or autosomal dominant. Autosomal recessive ataxias include Friedreich ataxia (the most prevalent), ataxia-telangiectasia, abetalipoproteinemia, ataxia with isolated vitamin E deficiency, and cerebrotendinous xanthomatosis.

a. Friedreich ataxia

It results from a gene mutation causing abnormal repetition of the DNA sequence GAA in the *FXN* gene on the long arm of chromosome 9; the *FXN* gene codes for the mitochondrial protein frataxin. The GAA sequence is repeated 5 to 38 times within the *FXN* gene in people who do not have Friedreich ataxia; however, in people with Friedreich ataxia, the GAA sequence may be repeated 70 to > 1000 times (1). Inheritance is autosomal recessive. Decreased frataxin levels lead to mitochondrial iron overload and impaired mitochondrial function.

In Friedreich ataxia, gait unsteadiness begins between ages 5 and 15; it is followed by upper-extremity ataxia, dysarthria, and paresis, particularly of the lower extremities. Mental function often declines. Tremor, if present, is slight. Reflexes and vibration and position senses are lost. Talipes equinovarus (clubfoot), scoliosis, and progressive cardiomyopathy are common. By their late 20s, patients may be confined to a wheelchair. Death, often due to arrhythmia or heart failure, usually occurs by middle age.

b. Spinocerebellar ataxias

(SCAs) are the main autosomal dominant ataxias. Classification of these ataxias has been revised many times recently as knowledge about genetics increases. Currently, at least 43 different gene loci are recognized; about 10 involve expanded DNA sequence repeats. Some involve a repetition of the DNA sequence CAG that codes for the amino acid glutamine, similar to that in Huntington disease.

Manifestations of SCAs vary. Some of the most common SCAs affect multiple areas in the central and peripheral nervous systems; neuropathy, pyramidal signs, and restless leg syndrome, as well as ataxia, are common. Some SCAs usually cause only cerebellar ataxia.

SCA type 3, formerly known as Machado-Joseph disease, may be the most common dominantly inherited SCA worldwide. Symptoms include ataxia, parkinsonism, and possibly dystonia, facial twitching, ophthalmoplegia, and peculiar bulging eyes.

3. Acquired conditions

Acquired ataxias may result from nonhereditary neurodegenerative disorders (eg, multiple system atrophy), systemic disorders, multiple sclerosis, cerebellar strokes, repeated traumatic brain injury, or toxin exposure, or they may be idiopathic. Systemic disorders include alcoholism (alcoholic cerebellar degeneration), thiamin deficiency, celiac disease, heatstroke, hypothyroidism, and vitamin E deficiency.

Examples of acquired conditions include;

a. Dysarthria: Dysarthria is a motor speech disorder in which the muscles that are used to produce speech are damaged, paralyzed, or weakened. The person with dysarthria cannot control his or her tongue, larynx, vocal cords, and surrounding muscles, which makes it difficult for the person to form and pronounce words. The area of the nervous system that is affected determines the type of the dysarthria and how seriously it affects the speech.

CAUSES OF DYSARTHRIA

Central dysarthria

Damage to the brain leads to central dysarthria. Damage may be caused by trauma and may occur at birth or develop over time. Causes of central dysarthria include:

- Stroke
- Traumatic brain injury
- Brain tumors
- Cerebral palsy
- Dementia
- Huntington's disease
- Lou Gehrig's disease/amyotrophic lateral sclerosis (ALS)
- Multiple sclerosis
- Muscular dystrophy
- Myasthenia gravis
- Parkinson's disease
- Other degenerative brain diseases

- Side effects of medications

b. 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. This problem is often seen in patients with multiple sclerosis or other conditions that impair coordination.

CAUSES OF DYSDIADOCHOKINESIA

It's believed that dysdiadochokinesia is often caused by lesions in the cerebellum, a part of the brain that controls voluntary muscle movements, posture, and balance. Damage to the cerebellum can also result in hypotonia, or decrease in muscle tone, which can contribute to the problem.

Other causes of acquired cerebellar disorders include;

- Toxins that can cause cerebellar dysfunction include carbon monoxide, heavy metals, lithium, phenytoin, and certain solvents. Toxic levels of certain drugs (eg, antiseizure drugs, sedatives in high doses) can cause cerebellar dysfunction and ataxia.
- Rarely, subacute cerebellar degeneration occurs as a paraneoplastic syndrome in patients with breast cancer, ovarian cancer, small cell carcinoma of the lung, or other solid tumors. Cerebellar degeneration may precede the discovery of the cancer by weeks to years. Anti-Yo, now called PCA-1 (Purkinje cell cytoplasmic antibody type 1) is a circulating autoantibody that occurs in the serum or cerebrospinal fluid (CSF) of some patients, especially women with breast or ovarian cancer.
- In children, primary brain tumors (medulloblastoma, cystic astrocytoma) may be the cause; the midline cerebellum is the most common site of such tumors. Rarely, in children, reversible diffuse cerebellar dysfunction follows viral infections.

CAUSES OF CEREBELLAR DISORDERS

Cerebellar disorders have various causes like,

- Developmental cause
- Vascular
- Infective
- Neoplastic
- Demyelinating
- Nutritional deficiency
- Trauma
- Degenerative
- Drugs and toxins
- Metabolic

There are various signs of cerebellar damage and they include;

- **Vertigo;** a sudden internal or external spinning sensation, often caused by moving your head too quickly
- **Ataxia**; a condition where a person lacks muscle control during voluntary movements, such as picking up an object or walking
- **Nystagmus**; involuntary oscillation of the eyes, characterized by a slow phase, followed by a fast phase.
- **Intentional tremor**
- **Slurred speech**
- **Hypotonia**; diminished tone of skeletal muscle associated with decreased resistance of muscle to passive stretching
- **Exaggerated broad based gait**
- **Disdiadochokinesia**; is an impaired ability to perform rapid alternating movements, movements are irregular with a rapid loss of range and rhythm especially as speed is increased. There is a mnemonic for it, which is **"VANISHED"**

CONCLUSION

In conclusion, the cerebellum performs a lot of important functions which includes coordination of voluntary movements such as posture and coordination, taking memory of habits and motor activities and so on. Cerebellar disorders may be congenital, as a result of hereditary ataxias or acquired conditions such as brain damage, stroke or even ALS.

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