**Name: Nwapa Bernard Ukachukwu**

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**Assignment Title:** Cerebrum And Its Connections
**Course Title:** Neuroanatomy
**Course Code:** ANA 303

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**Level:** 300 level

Sorry for the late submittion I mixed up the submission deadline

Assignment Question

1. Write a concise review on the developmental genetics of the cerebellum and highlight the genetics bases of the known cerebellar disorder

Note: As usual, observe every research/scholarly writing rule

Answers

1. Developmental Genetics of the Cerebellum

The development of the mammalian cerebellum is orchestrated by both cell-autonomous programs and inductive environmental influences. Here, we describe the main processes of cerebellar ontogenesis, highlighting the neurogenic strategies used by developing progenitors, the genetic programs involved in cell fate specification, the progressive changes of structural organization, and some of the better-known abnormalities associated with developmental disorders of the cerebellum.

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Keywords: Cerebellum, Progenitors, Purkinje cells, Specification, Differentiation

Introduction

The work done on cerebellar development from the late nineteenth century until the 1970s provided substantial and significant information; however, it was only descriptive and barely addressed the mechanisms involved. Over the last two decades, thanks to the technological revolution in molecular biology, our understanding of cerebellar development has drastically changed. We are now going through an exceptional period in our understanding of the mechanisms that underlie the complex development of the cerebellum. An understanding of cell specification regulated by the expression of region-specific combinations of transcription factors or proneural genes, and the formation of synaptic circuits, seems within reach.

Ferdinando Rossi, a few months before his death, undertook the monumental task of writing a monograph on the spectacular advances in our understanding of cerebellar development achieved in the last 20 years. Sadly, Ferdinando died a few months after beginning his monograph. This consensus paper, based on Ferdinando’s initial design, summarizes many of these advances and is dedicated to his memory.

The review comprises 18 brief sections, ranging from the early molecular specification of the cerebellar anlage to its mature architecture and pathology. It also includes information on neurogenesis, mainly the specification and origins of neuronal and glial progenitors. An important part of the paper is devoted to Purkinje cells (PCs) as key neurons of the cerebellar cortex responsible for the proliferation of granule cells (GCs) and the establishment of “crude” projection maps with extracerebellar afferent fibers. Finally, the biochemical heterogeneity of PCs allows for a cortical subdivision into distinct functional bands, a presumptive protomap for the development of circuit topography. In this context, the problem of synapse elimination in the process of refinement and stabilization of climbing fiber (CF) connections is also summarized.

The Cerebellum as a Genetic System

The mature cerebellum has exquisite, stereotypical morphology, foliation, and lamination, which are consistent between individuals and highly conserved across vertebrates. At the cellular level, unlike other regions of the CNS, the cerebellum is composed of very few neuronal types, each with distinct morphology, arranged in discrete lamina, and connected in stereotypical circuits. The cerebellum has essential roles in motor coordination, but is not essential for viability. Thus, compared with other regions of the central nervous system (CNS) the cerebellum has been more amenable to genetic studies since disruptions in development, which lead to abnormal morphology or function, are readily observed in obvious neurological and behavioral phenotypes. Because of this, it has been possible to obtain a precise understanding of cerebellar development. The mechanisms deciphered from the study of cerebellar development have broad applicability to other CNS regions such as the cerebral cortex. For example, while initial insights regarding the function of the Reelin gene were gleaned from studying the cerebella of reeler mice, recent studies have revealed that this gene is required for the emigration of dentate gyrus progenitors from a transient subpial zone and into the subgranular zone. Also, while Foxc1 controls normal cerebellar and posterior fossa development by regulating secreted growth factor signals from the mesenchyme, it is also required for the development of meningeal structures that in turn influence skull and cortical development.

The Genetics Bases of the Known Cerebellar Disorder

Cerebellar disorders have numerous cases, 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 imagining and sometimes genetics testing. Treatment is usually supportive unless the cause is acquired and reversible.

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.

**Ataxia** is the archetypal sign of cerebellar dysfunction, but many other motor abnormalities may occur.

Etiology

The most common cause of cerebellar disorders is

* Alcoholic cerebellar degeneration
* Congenital malformations

Such malformations are almost always sporadic, often occurring as part of complex malformation syndromes (eg, [Dandy-Walker malformation](https://www.msdmanuals.com/professional/pediatrics/congenital-neurologic-anomalies/hydrocephalus#v41359284)) 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.

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.

**Friedreich ataxia** 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](https://www.msdmanuals.com/professional/neurologic-disorders/movement-and-cerebellar-disorders/cerebellar-disorders#v48481082)). 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.

**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](https://www.msdmanuals.com/professional/neurologic-disorders/sleep-and-wakefulness-disorders/periodic-limb-movement-disorder-plmd-and-restless-legs-syndrome-rls), 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](https://www.msdmanuals.com/professional/neurologic-disorders/movement-and-cerebellar-disorders/secondary-and-atypical-parkinsonism), and possibly [dystonia](https://www.msdmanuals.com/professional/neurologic-disorders/movement-and-cerebellar-disorders/dystonias), facial twitching, [ophthalmoplegia](https://www.msdmanuals.com/professional/neurologic-disorders/neuro-ophthalmologic-and-cranial-nerve-disorders/internuclear-ophthalmoplegia), and peculiar bulging eyes.

Acquired conditions

Acquired ataxias may result from nonhereditary neurodegenerative disorders (eg, [multiple system atrophy](https://www.msdmanuals.com/professional/neurologic-disorders/autonomic-nervous-system/multiple-system-atrophy-msa)), systemic disorders, [multiple sclerosis](https://www.msdmanuals.com/professional/neurologic-disorders/demyelinating-disorders/multiple-sclerosis-ms), cerebellar strokes, repeated [traumatic brain injury](https://www.msdmanuals.com/professional/injuries-poisoning/traumatic-brain-injury-tbi/traumatic-brain-injury-tbi), or toxin exposure, or they may be idiopathic. Systemic disorders include [alcoholism](https://www.msdmanuals.com/professional/special-subjects/recreational-drugs-and-intoxicants/alcohol-toxicity-and-withdrawal) (alcoholic cerebellar degeneration), thiamin deficiency, [celiac disease](https://www.msdmanuals.com/professional/gastrointestinal-disorders/malabsorption-syndromes/celiac-disease), [heatstroke](https://www.msdmanuals.com/professional/injuries-poisoning/heat-illness/heatstroke), [hypothyroidism](https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/thyroid-disorders/hypothyroidism), and [vitamin E deficiency](https://www.msdmanuals.com/professional/nutritional-disorders/vitamin-deficiency-dependency-and-toxicity/vitamin-e-deficiency).

Toxins that can cause cerebellar dysfunction include [carbon monoxide](https://www.msdmanuals.com/professional/injuries-poisoning/poisoning/carbon-monoxide-poisoning), 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](https://www.msdmanuals.com/professional/hematology-and-oncology/overview-of-cancer/paraneoplastic-syndromes#v978032) 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.

**Diagnosis**

* Clinical evaluation
* Typically MRI
* Sometimes genetic testing

Diagnosis of cerebellar disorders is clinical and includes a thorough family history and search for acquired systemic disorders.

Neuroimaging, typically MRI, is done. Genetic testing is done if family history is suggestive.

**Treatment**

* Treatment of the cause if possible
* Usually only supportive

Some systemic disorders (eg, hypothyroidism, celiac disease) and toxin exposure can be treated; occasionally, surgery for structural lesions (tumor, hydrocephalus) is beneficial. However, treatment is usually only supportive (eg, exercises to improve balance, posture, and coordination; devices to help with walking, eating, and other daily activities).