**NANCY NNANNA CHINEMEREM**

**17/MHS01/203**

**MBBS 300level**

**NEURO ANATOMY**

**COURSE TITLE : CEREBELLUM & ITS CONNECTIONS**

**COURSE CODE: ANA 303**

**Question:**

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

**Answer :**

**Developmental genetics of the Cerebellum and highlights on the genetic bases of Pronoun Cerebellar Disorders**

**ABSTRACT:**

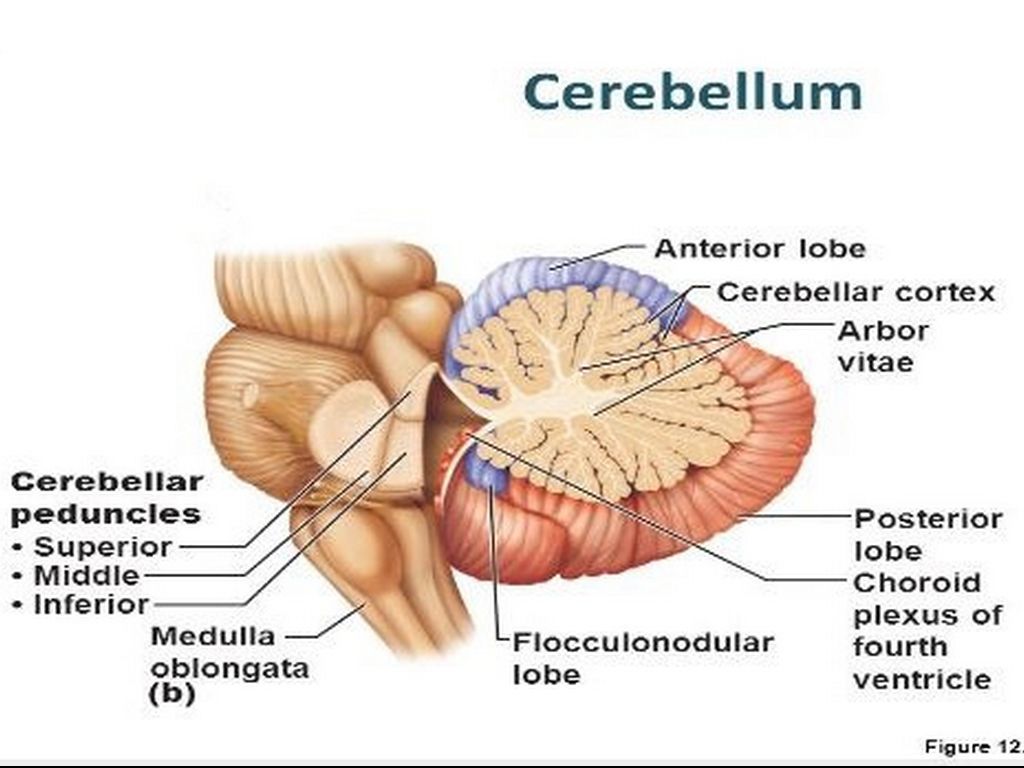
One of the key goals of neural development is to make specific cell types that originate from multipotent progenitor cells. The process of cell specification is only beginning to be understood. Evidence thus far suggests that it occurs in a stepwise fashion, and it is likely that each step requires the coordinated expression of a unique set of genes. The cerebellum is an excellent model system for understanding cell fate questions because it contains only a handful of defined cell types that are each located in a specific lamina and are therefore easily identified. These features have made the cerebellum an essential brain region in the understanding of the gene networks that give rise to specific cell types during development.

**THE CEREBELLUM**

The cerebellum, which stands for “little brain”, is a structure of the central nervous system. It has an important role in motor control, with cerebellar dysfunction often presenting with motor signs. In particular, it is active in the coordination, precision and timing of movements, as well as in motor learning.

During embryonic development, the anterior portion of the neural tube forms three parts that give rise to the brain and associated structures:

* Forebrain (prosencephalon)
* Midbrain (mesencephalon)
* Hindbrain (rhombencephalon)



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.

**Cerebellar Structure and Development**

The cerebellum originates from the alar plate of the neural tube, and this region is known to give rise to the sensory structures of the nervous system. Functionally, the cerebellum is at the crossroads between the sensory and motor systems and is essential for coordinating communications between these two systems. The cerebellar cortex has a trilaminar organization and each layer contains a defined set of cell types – the outer most molecular layer contains stellate and basket interneurons in addition to glial cells; located beneath the molecular layer, the Purkinje cell layer contains the cell bodies of the namesake neuron; located immediately beneath the Purkinje layer is the granule layer which contains granule cells, Golgi cells, unipolar brush cells, Golgi epithelial cells, and a few other minor cell types. Internal to the cerebellar cortex is the cerebellar white matter, which contains the majority of the cerebellar astrocytes and oligodendrocytes. The final major cell type in the cerebellum is the cerebellar nuclear neurons, which are restricted to four bilateral pairs of nuclei symmetrically distributed on either side of the midline.

During development, the cerebellar territory is established through the actions of the isthmic organizer (IO). The IO sets up the boundary between the mes – and metencephalic vesicles around embryonic day (E) 8.5–9 in the mouse. The cerebellum arises from rhombomere 1 of the metencephalic vesicle. Mutations in the genes encoding the key morphogens secreted by the isthmic organizer, which include Otx2, Gbx2, Fgf8, and Wnt1, typically result in the absence of a cerebellum and/or midbrain. These mutations demonstrate the essential nature of the IO to the development of the caudal CNS. Because of the essential nature of these genes for the establishment and maintenance of the IO, inducible transgenics, which allow temporal control over gene inactivation, have been invaluable in establishing the role of many of these genes . Around the time that the midbrain-hindbrain territory is established, the neural tube closes. Like most areas of the brain, the ventricular surface of the neural tube in the hindbrain serves as the germinal zone for the developing cerebellum. In the cerebellum, there are two germinal zones –

the roofof the fourth ventricle, known as the neuroepithelium,

and the edges of neural tube surrounding the fourth ventricle, known as the rhombic lip.

**Cerebellar Cell Specification**Cerebellar cells have well-defined developmental profiles that are characterized by discrete time periods in which each cell type is generated. Despite that understanding, there is a poor knowledge of the processes that regulate how each specific cell type is produced. Evidence suggests that combinations of transcription factors may work together in cerebellar development to specify various cell types. For example, glutamatergic nuclear neurons and progenitor populations express transcription factors known to influence cell fate such as Meis1 and 2, Irx3, and Lhx2/9. Components of the notch-signaling cascade also define discrete zones in the roof of the fourth ventricle during periods where cell birth is ongoing in this germinal zone.

There are mutant alleles in mice that also predict the action of broadly actingregulators of cell specification in the cerebellum. For example, the absence of granule cells in the anterior cerebellum of the meander tail mutant points to the actions of a gene on a subpopulation of granule cell progenitors. Chimera experiments demonstrate that these effects are mediated in a cell autonomous manner. Currently, the best-understood process in cerebellar cell differentiation is the specification of cells along either the GABAergic or glutamatergic lineages . There is growing evidence indicating that the rhombic lip produces glutamatergic neurons, whereas GABAergic neurons originate from the neuroepithelium. Thus, granule neurons, unipolar brush cells, and the glutamatergic cerebellar nuclear cells arise from the rhombic lip. By contrast, Purkinje neurons, GABAergic cerebellar nuclear neurons, the interneuron populations, including stellate, basket, Golgi, and Lugaro neurons, are all generated from progenitors that originate in the neuroepithelium of the forth ventricle.

**Glutamatergic Cells**The first cerebellar cells are initially generated around the time when the neural tube closes. The glutamatergic cerebellar nuclear neurons are the earliest cells produced in the cerebellum between E10.5 and 12.5 in the mouse. These cells arise from the rhombic lip and take a tangential course within the cerebellar parenchyma where they migrate near to the dorsal surface of the cerebellum. They arrive at the region termed the nuclear transitory zone before being displaced to their ultimate destination – the cerebellarnuclei – situated in the ventral aspect of the mature cerebellum. Whether this process is by active migration or passive mechanical forces is not currently known.

The next glutamatergic cells born in the cerebellum are granule cells, which are born over a protracted period of time beginning with the allocation of the precursor population in the rhombic lip between E12 and 14.5. Following their generation, these precursors migrate out over the dorsal surface of the cerebellum and form a layer known as the external germinal layer (EGL), which covers the dorsal surface of the cerebellum. Beginning around E15, these precursors proliferate and give rise to the terminally differentiated granule neurons that then migrate inward, radially,from their position in the EGL to the internal granular layer, inside of the cerebellum. Unipolar brush cells (UBCs) are the latest born glutamatergic neuron generated between E14 and 19 in the rhombic lip. Once born, UBCs migrate away from the rhombic lip through the inner cerebellar parenchyma finally ending up largely in lobules VI/VII and IX/X in the mature cerebellum.Recent research indicates that the master transcription factor for the glutamatergic lineage in the cerebellum is Math1. This transcription factor is essential to promote glutamatergic neuron production both in the cerebellum as well as several nuclei in the neighboring brainstem.Math1 is a bHLH transcription factor and the mouse orthologue of the Drosophila Atonal. Math1 is expressed in the mouse rhombic lip as early as E9.5. Math1 knockout mice produce very few glutamatergic cells and lack almost all granule neurons, unipolar brush cells,and glutamatergic cerebellar nuclear neurons.

Math1 is the earliest known marker of granule cell precursors,and the first granule cell precursors express this gene as early as E12.5. Mouse chimeras demonstrate that Math1 acts cell autonomously in granule cells during development, as there are no mutant Math1 granule cells present in cerebella consisting of predominantly wild type cells Granule cells have the best-understood lineage of all glutamatergic cells in the cerebellum, and there are multiple genes involved in specifying these cells. For example, there is evidence that bone morphogenetic proteins (BMPs) may modulate Math1 in order to specify granule cells. BMPs are a group of protein related to the TGFß transcription factor family, and they are released from the roof plate, including that overlying the cerebellum. Ectopic expression of constitutively activated BMP receptor 1b results in an upregulation of the chick Math1 homologue – Cath1-transcripts. Conversely, mice with null mutations for both BMP receptors (BMP1a and 1b) fail to induce Math1 expression and have a disorganized cerebellum. Mice with either BMP receptor singly knocked out have no Math1 phenotype and suggest that the two BMP receptors are functionally redundant. Exogenous application of BMPs to cultured granule cells can also induce Math1 expression in culture.

Together, these observations suggest that BMPs can induce

Math1and indicate that Math1 signaling occurs downstream from BMPs.GABAergic Cells.The GABAergic cells first generated in the cerebellum are the Purkinje cells, which are born between E11 and 13.5 in the neuroepithelium lining the fourthventricle. GABAergic nuclear neurons are also generated beginning around E11, and like Purkinje cells, the progenitors for nuclear neurons originate in the neuroepithelium of the fourth ventricle. In contrast to the narrow time window for Purkinje cell genesis, nuclear neurons are generated into postnatal time periods and also arise from progenitor populations that reside in the white matter inaddition to the neuroepithelium.GABAergic interneuron precursors also originate in the neuroepithelium and begin to produce terminally differentiated neurons as early as E16; however,most interneurons are not born until P0–12. Most interneurons are born from progenitors that arise from the neuroepithelium and then come to reside in the cerebellar white matter.Finally, Lugaro cells are likely born in late embryogenesis or early postnatal stages.The pancreatic transcription factor 1a (Ptf1a) is essential to produce neurons with a GABAergic phenotype in the cerebellum. As its name suggests, Ptf1a was originally characterized for its essential role in the pancreas, where it functions to specify cells during development. Interestingly, knockout mice lacking functional Ptf1a do not have Purkinje cells orother GABAergic cerebellar interneurons, including basket, stellate, and Golgi neurons. These observations suggest that it is a master regulator for the GABAergic phenotype in the cerebellum. During development, Ptf1a is expressed in the neuroepithelium of the fourth ventricle at a time when Purkinje cells and nuclear neurons are normally generated. In the absence of Ptf1a, some of the progenitors adopt a granule cell like phenotype, suggesting that Ptf1a may function to repress the glutamatergic phenotype.

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**Cerebellar Glial Cells**Classically, it was found that cerebellar glia have a postnatal birthdate. More recent birthdating evidence suggests that some glial progenitors are detected as early as E13–14 in the mouse, arising from the neuroepitheliumof the fourth ventricle. There is conflicting evidence that suggests glial progenitors may also reside in the EGL. For example, experiments where replication-deficient retroviruses were applied directly to the EGLresulted in no glial cells becoming labeled. However, recent experiments using GFAP-cre based lineage tracing methods indicate that both glial and granule cells from the GFAP lineage could arise from the EGL.

There is compelling evidence to suggest that at least some cerebellar oligodendrocytes are derived from extracerebellar sources Recent evidence suggests that Pax2-expressing interneurons could share a common progenitor with glial cells in the developing cerebellum. In addition to decreased numbers of Pax2+ interneurons, Ascl1/ knockout cerebella also have reduced numbers of oligodendrocytes and increased numbers of astrocytes. Transfecting the neuroepithelium of the fourth ventricle with vectors expressing Ascl1 reduces the number of astrocytes (identified by Glast and/or Sox9 expression). Interestingly, these overexpression experiments do not affect the number of oligodendrocytes in the nascent cerebellum. This observation is consistent with the hypothesis that oligodendrocytes at least, partially, originate from extracerebellar sources.

**Strategies to Identify Novel Factors Necessary for SpecifyingCells During Cerebellar Development**

In an effort to better understand cerebellar development from a molecular perspective, a project aimed at assembling a microarray-based developmental transcriptome for two strains of mice – C57B6/J and DBA across embryonic and postnatal development was recently initiated. RNA from cerebellar tissue was obtained from each strain from each day during embryogenesis (E12-birth) and every third day postnatally, currently up until P9. These RNA isolates were then analyzed using the Illumina microarray platform to assess the expression levels of each gene on each particular day. These data are publicly available on the Internet. Analysis of these data using novel bioinformatic tools to identify developmentally important genes is currently underway. Two bioinformatic approaches are being employed to identify genes that play candidate roles in cell specification and differentiation in cerebellar development.

**Cerebellar disorders and their genetic bases**

1. **Joubart syndrome** : Joubert syndrome is disorder of brain development that may affect many parts of the body. It is characterized by the absence or underdevelopment of the cerebellar vermis (a part of the brain that controls balance and coordination) and a malformed brain stem (connection between the brain and spinal cord).
2. **Dandy walker malformation** : Dandy–Walker malformation (DWM), also known as Dandy–Walker syndrome (DWS), is a rare congenital brain malformation in which the part joining the two hemispheres of the cerebellum (the cerebellar vermis) does not fully form, and the fourth ventricle and space behind the cerebellum (the posterior fossa) are enlarged.
3. **Ponto cerebellar hypoplasia :** Pontocerebellar hypoplasia (PCH) is a heterogeneous group of rare neurodegenerative disorders caused by genetic mutations and characterised by progressive atrophy of various parts of the brain such as the cerebellum or brainstem (particularly the pons).
4. **Cerebellar vermis hypoplasia** : Isolated cerebellar vermis hypoplasia is a rare, non-syndromic cerebellar malformation characterized by an underdeveloped cerebellar vermis. ... Brain MRI may reveal diffuse or selective (mostly posterior) vermian cerebellar hypoplasia and EEG may show focal paroxysms. Cerebellar hypoplasia most commonly occurs when a pregnant cat becomes infected with feline panleukopenia virus and passes the infection to her unborn kittens. The panleukopenia virus preferentially attacks rapidly dividing cells.

( CONTINUATION BELOW).

## Gross anatomy (brief)

The cerebellum is located at the base of the brain, with the large mass of the cerebral cortex above it and the portion of the brainstem called the pons in front of it. It is separated from the overlying cerebrum by a layer of tough dura matter ; all of its connections with other parts of the brain travel through the pons. Anatomists classify the cerebellum as part of the metencephalon which also includes the pons; the metencephalon in turn is the upper part of the rhombencephalon or "hindbrain". Like the cerebral cortex, the cerebellum is divided into two hemispheres; it also contains a narrow midline zone called the *vermis*. A set of large folds are conventionally used to divide the overall structure into ten smaller **lobules**.

Because of its large number of tiny granule cells the cerebellum contains more  neurons than the rest of the brain put together, but it only takes up 10% of total brain volume. The cerebellum receives nearly 200 million input fibers; in contrast, the optic nerve  is composed of a mere one million fibers.

The unusual surface appearance of the cerebellum conceals the fact that the bulk of the structure is made up of a very tightly folded layer of gray matter, the cerebellar cortex. It has been estimated that if the human cerebellar cortex could be completely unfolded it would give rise to a layer of neural tissue about 1 meter long and 10 centimeters wide—a total surface area of 500-1000 square cm, all packed within a volume of 100-150 cubic cm. Underneath the gray matter of the cortex lies white matter, made up largely of myelinated nerve fibers running to and from the cortex. Embedded within the white matter—which is sometimes called the *arbor vitae* (Tree of Life) in the cerebellum because of its branched, tree-like appearance—are four deep cerebellar. nuclei

The cerebellum can be divided according to three different criteria: gross anatomical, phylogenetical, and functional.]

|  |  |
| --- | --- |
| Key facts about the cerebellum | |
| Location | Posterior cranial fossa |
| Relations | Superior: tentorium cerebelli, great cerebral vein, lingual gyrus  Anterior: brainstem, medullary vela, cerebral aqueduct, [corpora quadrigemini](https://www.kenhub.com/en/library/anatomy/corpora-quadrigemina), posterior cerebellomedullary cistern, foramen of Magendie, medulla oblongata, foramen magnum  Posterior & lateral: occipital bone, sigmoid sinus, occipital sinus, confluence of sinuses |
| Fissures | Horizontal, posterolateral, postlunate, primary, retrotonsillar fissures |
| Lobes | Anterior, posterior, flocculonodular lobes |
| Lobules | Central vermal: **L**ingula, **C**entral, **C**ulmen, **D**eclive, **F**olium, **T**uber, **P**yramid, **U**vula, **N**odule ('**L**oving **C**aring **C**hildren **D**onate **F**ood **T**o **P**oor **U**nfed **N**eedy')  Horizontal: quadrangular, simple, superior semilunar, inferior semilunar, biventer, cerebellar tonsils |
| Blood supply | Superior cerebellar, anterior inferior cerebellar, posterior inferior cerebellar arteries |

**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.

**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 formation ) 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" \l "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 rest 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, parkonism, and possibly dystonia, facial twitching, opthalmoplegia, 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 scelrosis, 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" \l "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).

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