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**COURSE: NEUROANATOMY (ANA 303).**

**ASSIGNMENT TITLE: CEREBELLUM AND ITS CONNECTIONS.**

**QUESTION.**

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

**ANSWER.**

1. The cerebellum represents 10% of the brain's total volume, but contains more than half of our neurons. It acts as a coordination center, using sensory inputs from the periphery to fine-tune our movement and balance. It is one of the first structures in the brain to begin to differentiate, but one of the last to mature, and its cellular organization continues to change for many months after birth. The study of mouse homologues of Drosophila genes has provided valuable insights into the molecular basis of cerebellar development.

In humans, the cerebellum develops from the dorsal region of the posterior neural tube, and its cells arise from two germinal matrices. Most cells are derived from the ventricular zone, but the granule neurons come from a specialized germinal matrix called the rhombic lip.

The mesencephalon and metencephalon both contribute to the developing mouse cerebellum. The patterning of these two regions depends on signals from the isthmus organizer (IO), located just caudal to their junction. Otx2 and Gbx2 are central to IO development. Otx2 is expressed in the mesencephalon, with a posterior boundary at the rostral metencephalon; Gbx2 is expressed in the metencephalon, and its anterior boundary abuts the Otx2 boundary. Reciprocal repression maintains a sharp boundary between these domains. Otx2 and Gbx2 form part of a regulatory loop that includes Wnt1, En1 and Fgf8. Many other genes, including members of the Pax and Hox families, are also involved in patterning this region.

Purkinje cells (PCs), Golgi neurons, stellate and basket cells all arise from the ventricular neuroepithelium. PCs are born around embryonic day 13, and they migrate along radial glial fibres into the cerebellar anlage. During their final maturation phase, PCs develop extensive dendritic arbors and synapse onto granule neurons. This depends on granule neuron signals, probably including Wnt3. Various growth factors are required for PC survival, including nerve growth factor, acetylcholine, neurotrophin 4/5, brain-derived neurotrophic factor and ciliary neurotrophic factor.

The rhombic lip, located between the fourth ventricle and the metencephalic roof plate, gives rise to granule neurons. Proliferation in its germinal epithelium is governed by the Math1 gene. Rhombic lip cells migrate to the cerebellar anlage and settle on its periphery to form the external granule layer, another zone of proliferation. As the cells begin to migrate, they express markers that include RU49/Zipro1, Zic1 and Zic3. RU49/Zipro1 and Zic1 are thought to be involved in cell proliferation, which requires interaction with PCs. PCs might release a diffusible factor such as sonic hedgehog (Shh), and Zic1 could control cell proliferation by indirectly regulating the Shh pathway. The final stage of granule neuron maturation occurs after precursor cell migration into the inner granule layer.

Many genes, including En1, En2, Pax2, Wnt7b, and some of the ephrins and their receptors, show characteristic patterns of spatial expression in the cerebellum, but only En2 has been studied specifically for its role in compartmentalization. In addition to the patterning genes, several other gene families, such as the heat shock proteins and proteins involved in neuronal migration, are also expressed in specific patterns. Spatial- and temporal-specific knockout strategies should yield more information about the roles of these genes in patterning the cerebellum.

ATAXIA.

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. 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, 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.

NYSTAGMUS.

Mutations in the FRMD7 gene cause X-linked infantile nystagmus. The FRMD7 gene provides instructions for making a protein whose exact function is unknown. This protein is found mostly in areas of the brain that control eye movement and in the light-sensitive tissue at the back of the eye (retina). Research suggests that FRMD7 gene mutations cause nystagmus by disrupting the development of certain nerve cells in the brain and retina. In some people with X-linked infantile nystagmus, no mutation in the FRMD7 gene has been found. The genetic cause of the disorder is unknown in these individuals. Researchers believe that mutations in at least one other gene, which has not been identified, can cause this disorder.

This condition is inherited in an X-linked pattern. A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two copies of the X chromosome), one altered copy of the gene in each cell can cause the condition, although affected females may experience less severe symptoms than affected males. Approximately half of the females with only one altered copy of the FRMD7 gene in each cell have no symptoms of this condition.

HYPOTONIA.

There are several genetic causes of hypotonia, these include:

- Down Syndrome – This is a genetic disease with a chromosomal abnormality where the 21st pair of chromosome has an extra chromosome. This leads to heart defects, mental retardations and other neurological complications.

- Prader-Willi syndrome is a rare genetic disease that causes restricted growth and learning difficulties

- Tay-Sachs disease is another rare and fatal genetic disorder that causes progressive damage to the nervous system.

- Williams Syndrome – is a rare genetic condition that causes defects in development, co-ordination and language.

- Spinal muscular atrophy is an inherited disease that leads to muscle weakness and a progressive loss of movements.

- Charcot-Marie-Tooth disease is yet another inherited condition that affects the myelin covering of nerves. Myelin forms a protective covering over all major nerves of the body.

- Connective tissue disorders include Marfan’s syndrome and Elher-Danlos syndrome. These are inherited and lead to defects in connective tissues which provide support to other tissue and organs.

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