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MBBS 300LVL

NEUROANATOMY ASSIGNMENT

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

DEVELOPEMENTAL GENETICS OF THE CEREBELLUM

Overview of cerebellar development

The cerebellum arises from both the mesencephalic and rhombencephalic vesicles of the neural tube and develops over a relatively long period of time between early embryogenesis and late childhood. Development of the cerebellum can be described in four basic stages.

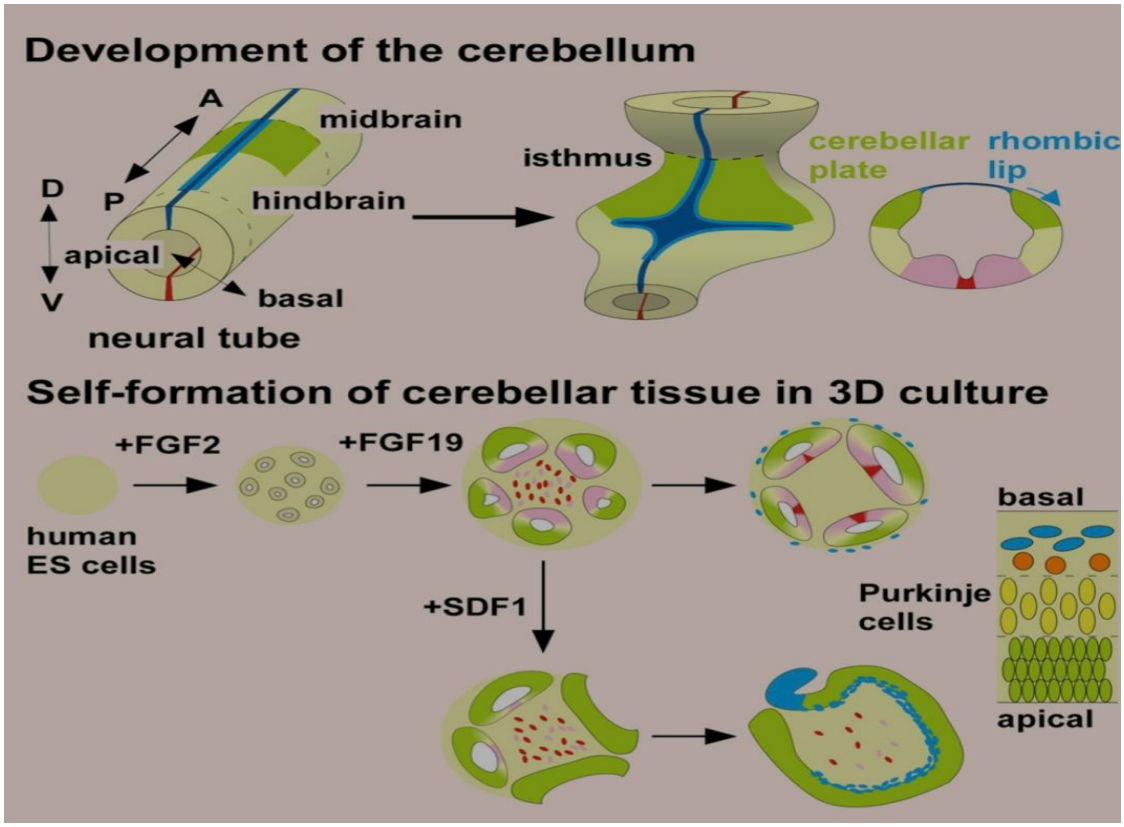
In the first stage, characterization of cerebellar territory occurs at the midbrain–hindbrain boundary. Transplantation studies in chicken and mouse have found that the isthmus organizer (IsO), a region corresponding to the midbrain–hindbrain boundary expression, is crucial for specifying midbrain and cerebellar structures. At the isthmus, restricted expression of secreted factors, such as fibroblast growth factor 8, FGF8 and Wnt1, the mammalian homolog of Drosophila wingless gene, as well as homeobox proteins En1 and En2 and paired box genes Pax2 and Pax5 are required for early specification of midbrain and hindbrain structures.

In the second stage, two compartments for cell proliferation are formed. Purkinje cells and cells of the deep cerebellar nuclei are generated in the roof of the fourth ventricle, and granule cell precursors, as well as cells of the

precerebellar nuclei are formed in the rhombic lip. Development of Purkinje cells is not well understood, but they are known to secrete Sonic hedgehog which regulates proliferation of granule cells. By this time point, granule neuron precursors express a number of markers, Math1, nestin, zipro1/RU49 and Zic genes 1, 2. Purkinje cells migrate radially to their final positions, whereas granule neurons migrate over the surface of the developing cerebellum, forming the external granule layer (EGL).

In the third stage, cells of the EGL migrate inward along the processes of Bergman glia to their final position in the internal granular layer (IGL).

Finally, cerebellar circuitry is established and further differentiation occurs. The lower portion of the rhombic lip also gives rise to cells of the precerebellar nuclei such as the inferior olivary nuclei, which migrate to positions in the brainstem.



GENETIC BASIS OF KNOWN 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.

1. **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. 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.

2. **Dandy Walker's 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 with cerebrospinal fluid. Most of those affected develop hydrocephalus within the first year of life, which can present as increasing head size, vomiting, excessive sleepiness, irritability, downward deviation of the eyes and seizures. Dandy-Walker malformation has also been associated with many chromosomal abnormalities. This condition can be a feature of some conditions in which there is an extra copy of one chromosome in each cell (trisomy). Dandy-Walker malformation most often occurs in people with trisomy 18 (an extra copy of chromosome 18), but can also occur in people with trisomy 13, trisomy 21 or trisomy 9. This condition can also be associated with missing (delitions) or copied (duplications) pieces of certain chromosomes. Dandy-Walker malformation can also be a feature of genetic syndromes that are caused by mutations in specific genes. However, the brain malformations associated with Dandy-Walker malformation often occur as an isolated feature (not associated with other health problems), and in these cases the cause is frequently unknown.

3. **Joubert Syndrome**

Joubert syndrome is a rare brain malformation characterized by the absence or underdevelopment of the cerebellar vermis - an area of the brain that controls balance and coordination -- as well as a malformed brain stem. Many cases of

Joubert syndrome appear to be sporadic (not inherited). In most other cases, Joubert syndrome is inherited in an autosomal recessive manner (meaning both parents must have a copy of the mutation) via mutation in at least 10 different genes, including NPHP1, AHI1, and CEP290.

4. **Cerebellar Hypoplasia**

Cerebellar hypoplasia is characterised by a reduced cerebellar volume due to the maldevelopment of one or both hemispheres and a small but normally shaped vermis. This heterogeneous condition is associated with trisomies 9, 13 and 18, congenital disorders of glycosylation, anticonvulsant drugs (valproic acid) or cocaine.

References

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