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300 LEVEL
MEDICINE AND SURGERY
NEUROANATOMY

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

ANSWERS

The cerebellum major role is in role in sensory-motor processing that in the adult human contains more than half of all the brain's neurons. The adult cerebellum anatomy consists of three parts, the vermis (median) and the two hemispheres (lateral), which are continuous with each other.
The adult human cerebellum contains 69,030,000,000 ± 6,650,000,000 (sixty-nine billion thirty million) neurons and 16,040,000,000 ± 2,170,000 other cell types.
Neural development is one of the earliest systems to begin and the last to be completed after birth. This development generates the most complex structure within the embryo and the long time period of development means in utero insult during pregnancy may have consequences to development of the nervous system.

Within the neural tube stem cells generate the 2 major classes of cells that make the majority of the nervous system : neurons and glia. Both these classes of cells differentiate into many different types generated with highly specialized functions and shapes. This section covers the establishment of neural populations, the inductive influences of surrounding tissues and the sequential generation of neurons establishing the layered structure seen in the brain and spinal cord.

Neuralation begins at the trilaminar embryo with formation of the notochord and somites, both of which underly the ectoderm and do not contribute to the nervous system, but are involved with patterning its initial formation. The central portion of the ectoderm then forms the neural plate that folds to form the neural tube, that will eventually form the entire central nervous system.

Early developmental sequence: Epiblast - Ectoderm - Neural Plate - Neural groove and Neural Crest - Neural Tube and Neural Crest.

6 weeks (CRL 12–16 mm) - anlage of the cerebellum was first identified as a pair of thickenings on the lateral site of the alar plate that faced the fourth ventricle.

7-9 weeks (CRL 28 mm) - rhombic lip (a pair of thickenings of the alar plate) protruded dorsally, bent laterally, extended ventrolaterally and fused with the medially located midbrain. During that process, the primitive choroid plexus appeared to become involved in the cerebellar hemisphere to form a centrally located eosinophilic matrix. At that stage, the inferior olive had already developed in the thick medulla. Thus, the term 'bulbo-pontine extension' may represent an erroneous labelling of a caudal part of the rhombic lip. The cerebellar vermis developed much later than the hemisphere possibly from a midline dark cell cluster near the aqueduct.

11–12 weeks (CRL 70–90 mm) - cerebellar hemisphere became as thick as the mid- brain. In the hemisphere, a laminar configuration became evident but the central eosinophilic matrix remained present. Fissures of the future vermis appeared in the midline area: the developing fissures provided island-like structures in horizontal sections. The hemisphere and vermis, including the surfaces of the fissures, were covered by the external germinal cell layer.

15–16 weeks (CRL 110–130 mm) - cerebellar hemisphere contained the primitive dentate nucleus. The nodule and flocculus were identified, vermis became as thick as the hemisphere and it accompanied several deep fissures.

ABNORMALITIES/CEREBELLAR DISORDERS

1. Dandy-Walker Syndrome/Malformation (DWS) is a cerebellar hypoplasia and upward rotation of the cerebellar vermis with ventricular enlargement (cystic dilation of the fourth ventricle). Named in 1954 after the earlier identification by Walter Dandy (1914) and Arthur EarlcWalker (1942), two USA neurosurgeons.

2. Joubert syndrome (Joubert-Boltshauser syndrome, Cerebelloparenchymal disorder 4, Cerebellar vermis agenesis) is a rare disease of the cerebellum. Identified as a ciliopathy, characterized by the absence or underdevelopment of the cerebellar vermis, that controls balance and coordination. There is also malformation of the stem, connecting the brain and spinal cord. A recent super-resolution microscopy study has shown that the syndrome is caused by disruption of the ciliary transition-zone architecture. Ciliopathies are a class of cell abnormalities that can be caused by mutations in components of the cellular transition zone, a domain near the base of the cilium, that controls the protein composition of its membrane.
-Hypotonia - weak muscle tone
-Ataxia - difficulty coordinating movements
-Hyperpnea - episodes of fast breathing (improves with age and usually disappears around 6 months of age)
-Oculomotor apraxia - difficulty moving the eyes from side to side.
-Language and motor skills
-Mild to severe intellectual disability
-Distinctive facial features - broad forehead, arched eyebrows, droopy eyelids (ptosis), widely spaced eyes, low-set ears, and a triangular-shaped mouth.

3. Pontocerebellar Hypoplasia (PCH) are very rare, inherited progressive neurodegenerative disorders with prenatal onset. The major features are: hypoplasia or atrophy of cerebellum and pons, progressive microcephaly, and variable cerebral involvement. There is a further classification of 7 different subtypes (PCH1-7) and there is prenatal testing for the related inherited mutations.

A. PCH2, PCH4, PCH5 - Mutations in the 3 tRNA splicing endonuclease subunit genes.
B. PCH6 - Mutations in the nuclear encoded mitochondrial arginyl- tRNA synthetase gene.
C. PCH1 - Mutations in the tRNA splicing endonuclease, the mitochondrial arginyl- tRNA synthetase and the vaccinia related kinase1.

4. Medulloblastomas are the most common childhood primary central nervous system tumour. They are thought to arise in the developing cerebellum from the precursors of the granule cell.

5. Rhombencephalosynapsis (RES) is a unique cerebellar malformation characterized by fusion of the cerebellar hemispheres with partial or complete absence of a recognizable cerebellar vermis.
A. Craniofacial features - prominent forehead, flat midface, hypertelorism, ear abnormalities
B. Somatic malformations - heart, kidney, spine, and limb defects.