neural tube defects

- Malformations are permanent deformities of the entire body or parts thereof.
- Malformations result from maldevelopment.
- Congenital malformations of the central nervous system are among the commonest malformations.
- There is possibility of antenatal diagnosis (USG, genetic counseling).

CNS development

since 19th g.d.

19th g.d. neural plate

4th g.w. neural plate → groove → tube (brain primordium - 5 vesicles)

8th g.w. growth of hemispheres, cerebellum primordium

malformations are related to:
- cells proliferation
- and/or cells migration

- Approximately 3% of newborns have major abnormalities.
- Chromosomal abnormalities are found in about 0.062% neonates.
- The most common form of neural tube defects (1 in 1000 pregnancies in USA, approximately 4000 fetuses are affected every year, but about 30% are lost (spontaneous or elective abortions)) are:
  - spina bifida
  - anencephaly.

neural tube defects

CNS development

3 g.m. spinal cord and tectum of brain stem; end of stage I ventricles formation

3-5 g.m. gyri and sulces formation (unequal growth of white and grey substance); myelination of anterior horns

7-8 g.w. disappearance of subependymal neuroblasts

at birth brain mass 330-430g

1-y-old disappearance of periventricular matrix

CNS developmental diseases

- etiology → ???
- failure of normal development or tissue destruction

  60% are of unknown cause,
  20% interaction of hereditary tendency and undefined factors
  7.5% monogenic basis
  6% major chromosomal anomalies
  12% environmental causes
CNS developmental diseases

- There are primary and secondary malformations.
  - the former is a morphological defect resulting from an intrinsically abnormal developmental process;
  - the latter results from breakdown/interference with an originally normal developmental process (vascular accidents, infections, and chemicals).
- But if an injury occurs before 20-22 week of gestation without genetic studies it is difficult to confirm if the malformation is primary or secondary.

CNS developmental diseases

- AFP → ?
- recurrence 4-5% in subsequent pregnancy
- folate deficiency

CNS developmental diseases

- genetic (AR, AD, X-linked, chromosomal aberrations)
  - Holoprosencephaly → HPE1 gene → 21q22.3
    → HPE2 gene → 2p21
    → HPE3 gene → 7q36
    → HPE4 gene → 18p
  - Lissencephaly type 1 → LIS1 gene → 17p13.3
    (Miller-Diaker syndrome)
  - X-linked hydrocephalus → Xq28

CNS developmental diseases

- external trauma
- radiation
- maternal diabetes
- ischemia
- vit. A deficiency
- intrauterine viral infection (enteroviruses, adenoviruses, rubeola, measles, influenza, smallpox)
- antimitic drugs
- Thalidomide ??

CNS developmental diseases

- other infectons (toxoplasmosis)
- antiepileptic drugs (valproic acid)
- teratogens
- organic mercury
- fetal alcohol syndrome ?
- other (fever or hyperthermia in early pregnancy, obesity - ??)
- ethnic and geographical differences
  (in USA Hispanics > non-Hispanics > blacks)

neural tube defect

- defects in which some part of the neural tube has failed to complete neurulation or the neural tube coverings have not closed (from anencephaly to encephalocele)
- Neural tube closure defects /
  dysraphism
- usually related to autosomal recessive diseases or external factors
neural tube defect

- STATUS DYSRAPHICUS:
  - vertebrae, skull
  + sternum, ribs, hands and feet

- SPINAL DYSRAPHISM/SPINA BIFIDA
  a) spina bifida occulta
  b) meningocoele
    (a skin-covered protrusion of meninges through the spinal column)
    meninges without the spinal cord
  c) myelomeningocoele/meningomyelocele

neural tube defect

- SPINAL DYSRAPHISM/SPINA BIFIDA
  in 80% of cases ➞ lumbosacral region (S1-2)
  ➞ clinically silent
  ➞ or present deficits in function of:
    - lower extremities (sensory and motor)
    - bowel
    - bladder
  ➞ sometimes life-long disabilities (neurologic defects or neurologic deficits) and psychosocial maladjustment

other spinal defects

- diastomatomyelia/diplomyelia
  (one or two menigeal "systems")

- syringomyelia/syrinx**
  (cleft-like cavity)

- hydromyelia**
  (continuos expansion of central canal)

**destruction of white and gray matter + gliosis

brain developmental defects

encephalocele

- is the presence of brain tissue outside of cranial cavity;
- cause is probably a primary mesodermal defect in postneurulation;
- brain dysraphism is far less frequent as spinal dysraphism (1 : 6).
- the most common localization is occipital region (80-90%), posterior fossa, and nasal region.
- frontal encephaloceles may be associated with facial deformities (high incidence in Thailand)

MICROCEPHALUS

- CNS (most commonly hemispheres) being smaller than normal, although otherwise grossly and microscopically indistinguishable from normal;
- the skull size is proportionate to that of the brain. Often the spinal cord is also hypoplastic. This condition may be visible at birth or noticed later;
- causes:
  - in most cases unknown
  - rubella virus infection, at the beginning of pregnancy
  - X-ray radiation (before 5th month of gestation)
  - HIV
  - Down syndrome
### ANENCEPHALUS

- Is the most extreme example of a defect in closure of the neural tube (due to primary failure either in neuroepithelium or in surrounding mesoderm). The abnormality is determined at 18 (28) days postfertilization.
- The abnormality involves the derivatives of the most anterior portion of the neural tube and the structures that encase it.
- Face has a characteristic appearance: the eyes bulge forward, the ears are usually thick and irregular, the neck is short or absent.

### ANENCEPHALUS

- The cranial vault is invariably absent and cerebral hemispheres are completely missing or reduced to small formless masses attached to the base of the skull.
- Frontal bones are not present above the supraorbital ridge.
- Parietal bones are usually absent.
- Occipital bone most commonly is present, but its squamous portion is usually missing.

### ANENCEPHALUS

- The anterior cranial fossa is foreshortened, but the degree of posterior fossa extension is varying.
- The foramen magnum does not exist, and the spinal canal is partially or completely open.
- The eyes are present but the optic nerves are usually absent.
- The cerebellum occasionally appears fairly normal.

### ANENCEPHALUS

- The cerebral hemispheres consists of formless masses composed largely of vascular channels separated by small irregular masses of nervous tissue (area cerebrovasculosa).

### ANENCEPHALUS

- An infant may live for several days (!).

### Causes:
- Local (inhibition of the neural tube closure; ± 28g.d.);
- Generalized (eg.: single gene mutation; multifactorial inheritance; teratogens - aminopterin, thalidomide);
- Often accompanied by the maternal hydramnios

### Incidence:
- 1-5/1000; F>M

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**forebrain abnormalities**
### HOLOPROSENCEPHALY

- inappopite separation of hemispheres
- is a failure of the normal outgrowth of the telencephalic vesicles from mediobasal prosencephalon;
- can be described as a failure of normal lateralization of structures initially represented in the medial position.
- the clinical presentation can occur as:
  - cyclops,
  - anencephaly,
  - and cebocephalus.
- typically present single optic nerve, and absent: olfactory nerves, corpus callosum, septum pellucidum.

### CYCLOPS

- macroscopically described as a presence of a central eye showing a greater or lesser degree of fusion;
- the nose is invariably abnormal (from absent to tubular appendage);
- the skull is small and several bones are missing;
- the cerebral hemispheres are fused with a single open ventricle.
- olfactory nerves, corpus callosum and septum pellucidum are not present.
- convolutions are poorly developed and the number of blood vessels on the surface is increased;
- additionally, polydactyly and malformations of the viscera are common.

### AGNEXUS OF CORPUS CALLOSUM

- anteroposteriorly oriented bundles (Probes bundle)
- clinic: no/mild anomalies
- causes:
  - autosomal recessive
  - X-linked
  - exogenous

### Migrational/Gyral Defects

- Often associated with:
  - seizures, mental/psychomotor retardation, learning disorders, etc.
  - Timing of insult (ischemic, infectious, genetic, etc.) determines abnormality
- Normally, neuroblasts migrate from periventricular germinal matrix to cortex and other sites; excess neurons removed by apoptosis, remaining neurons mature

### gyral abnormalities

- **LISSENCEPHALY/AGYRIA** → only major fissures are present
  - disturbances in migration
    - microcephalia
    - psychomotor retardation
    - seizures
    - death before age of 2
    - neocortex (4-layers)
- **MACROGYRIA** → moderate reduction in the number of sulci; mental retardation
- **MICROGYRIA** → decreased size of gyr; mental retardation
- **PACHYGYRIA** → disturbances in migration
- **POLYMICROGYRIA** → injury during neuronal migration
other abnormalities

- cerebellum abnormalities → agenesis or hypoplasia cerebelli
- megaencephaly* and microencephaly**
  [**more common than *]**

hydrocephalus

→ abnormal accumulation of fluid in the cranial vault (internal and external)

- N: lateral ventricles → foramen of Monro → third ventricle → aqueduct of Sylvius → fourth ventricle → foramens of Luschka and Magendie → cisterna magna → subarachoid space → absorption (4/5 arachnoid vili of the cerebral meninges)

- causes:
  - increased production of CSF
  - decreased resorption
  - circulation abnormalities (most common)

Posterior fossa abnormalities

- Chiari Type I malformation → herniated cerebellar tonsils with minimal displacement of the brain stem
- Arnold-Chiari malformation (Chiari type II malformation) → the hallmark is displacement of the cerebellum and distal brain stem through the foramen magnum into the upper cervical canal.
- Dandy-Waiker malformation (AR) → enlarged posterior fossa; absent cerebellar vermis; midline cyst; dysplasia of brain stem nuclei

Posterior fossa abnormalities

- Arnold-Chiari malformation → usually is associated with an opened meningomyelocle;
  - morphological anomalies consists of:
    - small posterior fossa,
    - malformed middle line cerebellum with extension through the foramen magnum,
    - hydrocephalus,
    - lumbar myelomeningocele (in about 90% occurs in thoracolumbar region, and the bony defect usually extends all the way down to the sacrum).

- Clinically the most important are cerebellar injury, cranial nerves injury, and peripheral nerves injury.
- In most cases the malformation is multifactorial, although it is occasionally seen in trisomies 13 and 18.

Perinatal brain injury

- kernicterus
- cerebral palsy
- intraparenchymal hemorrhage
- periventricular leukomalacia

- other brain development abnormalities:
  - Amaurotic familial idiocy/Tay-Sachs disease (neuraminic acid)
  - Mongolism
  - Familial dysautonomia
  - Intaruterine convulsions

Perinatal brain injury

- kernicterus
- N: bilirubin < 20 mg%.
- deposit of bile pigment in nerve cells, myelin sheath and interstitial tissue in localized parts of the cerebellum and brain stem (basal ganglions, thalamus, ependymal lining of ventricles, dentate nucleus, cranial nerve nuclei, quadregeminal body, gray matter of the spinal cord)
- Necrosis of globus pallidus and hippocampus in premies
- Unconjugated bilirubin (→ immature liver) crosses BBB to produce bright yellow gross appearance
Perinatal brain injury

Kernicterus
- caused by erythroblastosis (mother’s Rh or AB immunization, viral infections)
- iatrogenic (large doses of vit. K)
- unknown cause
- Today rare