Neural Tube Disorders (s. Dysraphism)

Last updated: January 16, 2021

Neural Tube Disorders (s. Neurulation defects, s. Dysraphia) -- most common CNS malformations!

 Classification

Etiopathophysioloqy

Embryology

Theories

- a) Reopening of closed neural tube - questionable
- b) Nonclosure (failure of neural folds to come together) -- probably correct theory!
  - normal closure begins on 20th day after fertilization and is complete by 28th day - i.e. 1-2 weeks beyond expected normal menstrual cycle - women is frequently unaware that she is pregnant during this critical time!

Etiology

- classic multifactorial:
  - epidemiological-experimental investigations have failed to identify obvious source.
  - genetic factors certainly play important role in at least conferring predisposition (neural tube disorders are occasionally associated with neural tube defects)
  - at least in cranial region, neural tube closure occurs not in single continuous closure but at multiple sites and in coordinated pattern - each defined site is under control of different genes (susceptible to different factors).

Epidemiology

- among most common major malformations (0.001-1% of all human malformations).
- incidence - overall decline in past decades.

Myelomeningocele - 1 in 1000 live births - most common anomaly of nervous system

3-4 in 1000 in England, Ireland, Scotland, and Wales

Encephalocele - 1 in 5000-10000 live births.

Anencephaly - 0.1-1 in 1000 live births (greatest frequency is in Ireland and Wales)

Risk factors:

1) maternal hyperthermia
2) maternal diabetes
3) anticonvulsants (ep. valproic acid - causes dysraphism in 1-2% patients, carbamazepine)
4) previous infant / fetus with neural tube defect (risk increases 10-fold)
5) low socioeconomic status.

Classification, Pathology, Clinical Features

All cases involve bone / soft tissues ± underlying neural tissue.

 Cranioschisis

Anencephaly *("absence of head") - cranial neuropore closure defect (develops at ≥ 28th day of gestation) - absence of brain and calvarium; no epidermal covering.

- vast majority of cases show complete absence of most of brain.
  - anterior pituitary, eyes, brainstem are usually spared.
  - spinal cord pyramidal tracts are missing due to absence of cerebral cortex.
  - neural epithelium is present in embryo, but direct contact with amniotic fluid results in degeneration of neural epithelium.
  - remaining tissue covering basal cranium is highly vascular and friable membrane (arrest cerebrovasculous).

Clinical Signs

1) polyhydramnios.
2) neurological function is limited to brainstem & spinal reflexes (seizures, at times resembling infantile spasms, have been observed in some infants).
3) significant proportion are stillborn; infants who are born alive do not survive (survival can be prolonged with life support systems, creating controversy over use of anencephalic infants as organ donors).
**EXENCEPHALY** – defect in calvarium (dura, bone, skin) – exposed brain (degenerated due to exposure to amniotic fluid):

- Transillumination of sac may indicate presence of neural tissue within.
- Incidence: 1:5 ratio to MMC.

**ENCEPHALOCELE (S. CESEPHALOCELE)**

Pathogenetic theories:

- a) Cranial neuropore closure defect
- b) Correct theory - mesenchymal defect → local herniation of fully neurulated neural tissue (at 8-12 weeks of gestation).

Pathogenetic theory for acquired cephaloceles in adults - most commonly associated either with trauma (incl. iatrogenic) or increased ICP (most common locations - where bone is already thin - tegmen tympani, middle fossa into sphenoid sinus).

**LOCATION (usually midline):**

- OCCIPITAL encephaloceles (85% in North America) - often large and have variable contents
- b) ROPPENHEIM syndrome - autosomal recessive congenital muscular dystrophy. See p. Musc >>

**ANTERIOR encephaloceles:**

- a) Most common isolated malformation in southeast Asia.
- b) Robert’s syndrome

**PARIETAL encephaloceles** – less common.
SPINO MENINGOCELE

Classification (Suwanwela and Suwanwela)
1. Occipital: often involves vascular structures
2. Cranial vault (comprises ˘ 80% of encephaloceles in Western hemisphere):
   a. interfrontal
   b. anterior fontanelle
   c. interparietal: often involves vascular structures
d. temporal
e. posterior fontanelle
3. Fronto-ethmoidal s. sinucipital: (15% of encephaloceles), external opening into face in one of the following 3 regions:
   a. nasofrontal: external defect in the nasion
   b. naso-ethmoidal: defect between nasal bone and nasal cartilage
c. naso-oral: defect in the antero-inferior portion of medial orbital wall.
4. Basal (1.5% of encephaloceles); the only group to develop a visible soft tissue mass; may present as CSF leak or recurrent meningitis; may be associated with other craniofacial deformities, including: cleft lip, bifid nose, optic-nerve dysplasia, coloboma and microphthalmia, hypothalamic-pituitary dysfunction.
   a. tranethmoidal: protrudes into nasal cavity through defect in cribiform plate
   b. spheno-ethmoidal: protrudes into posterior nasal cavity
c. transethmoidal: protrudes into sphenoid sinus or nasopharynx through patent craniopharyngeal canal (foramen cecum)
d. fronto-sphenoidal or sphenoid-orbital: protrudes into orbit through superior orbital fissure.
5. Posterior fossa: usually contains cerebellar tissue and venous component.

Clinical Features
1. protuberant mass that may be pulsatile (except basal encephaloceles); size of encephalocoele varies: barely visible bulge ÷ larger than infant's head
2. neurological deficits correlate with extent of cortex that is herniated into cele: motor deficits, visual defects, psychomotor developmental delay.
3. malformed cortex (within / adjacent to cele) ð seizures.
4. frequently associated with other intracranial anomalies (e.g. hydrocephalus), agenesis of corpus callosum, Dandy-Walker malformations, holoprosencephaly.
5. prognosis is good for many patients.

N.B. encephaloceles that contain large amount of neural tissue have poor prognosis!

NASAL GLIOMA (misleading term - not neoplasia!); better term - NASAL GLIAL HETEROPTOPA) - form of frontonasal encephalocele with no clear bony defect - may not be immediately obvious on external examination.

– may present as intranasal mass (CSF rhinorrhea following removal of nasal polyp vs. Greenberg states that it does not communicate with subarachnoid space, pharyngeal obstruction, or recurrent meningitis.

– can be associated with hypertelorism, median cleft lip, hypotalamic dysfunction.

– requires immediate imaging and prophylactic antibiotics Þ surgical repair.

A nasal polypoid mass in a newborn requires immediate imaging and prophylactic antibiotics Þ surgical repair.

SPINA BIFIDA

• most common form of neural tube defects!
• mostly occurs in lumbar region, followed by lumbosacral region (can also be located in cervical, thoracic, or sacral regions).
• spinal dysraphism is occasionally associated with other spinal defects (tethered spinal cord, spinal lipomas, sacral teratomas).

A. SPINA BIFIDA OCCULTA Ð defect in vertebral arch without any other associated defect (i.e. without involvement of cord or meninges; skin is intact over malformation).

– most commonly - L, D, S (up to 24% of population!); C7, Th.
– defect is usually near midline in lower and asymptomatic or subtle clinical signs; cutaneous markings in midline of back (mark defect location): tuft of hair, cutaneous angioma or lipoma; rarely, sinus tract may communicate from skin to underlying dura.
– no clinical significance - often found incidentally on radiographic studies.

*occasionally associated with more significant spinal abnormalities (e.g. syringomyelia, diastematomyelia, tethered cord).
– does not seem to increase risk of neural tube malformations in that individual's progeny.

B. SPINA BIFIDA MANIFESTA (S. APERTA, CYSTICA) Ð defect in vertebral arch plus:

A) MENINGOCELE - involves meninges alone (i.e. POSTNEURALIZATION DISORDER - neural elements are intact)

– transilluminating protruding / herniating meningeal sac is covered by skin; may be asymptomatic.

– meningocele distends with crying.

AYTTEL MENINGOCOELES (differentiate from dural euctasias in spondyloarthopathies):
1) ANTERIOR SACRAL MENINGOCOELE - presacral cystic mass projecting into pelvis through anterior sacral defect in sacrum*: Ñ constriction, bladder dysfunction, anomalies of female genital tract (e.g. rectovaginal fistula, vaginal septa).

2) INTRASMALL MENINGOCOELE - sacral canal is expanded by meningocele which lies below normal level of termination of thecal sac.

3) LATERAL THORACIC MENINGOCOELE - intrathoracic posterior mediastinal mass through eroded intervertebral foramens; occurs (70-85%) in association with neurofibromatosis.

4) ANTERIOR THORACIC MENINGOCOELE - with ventral spinal cord herniation; midgadigal MRI - spinal cord is displaced sharply forwards in contact with vertebral body at or very near intervertebral disc.

B) NEUMENINGOCOELE (most common derangement of neurulation) - involves meninges and underlying spinal cord; no skin covering over defect.

Skin
Bone
Meninges
Spina bifida occulta
Meningocele
Myelomeningocele
Myelomeningocele

DEV3 (3)
Myelomeningocele

Greatest disability of spinal dysraphism!

Pathology:
- focal segment of spinal cord fails to roll up and form tube (most commonly - failure of closure of caudal neuropore) - neural folds persist as flat plate of tissue referred to as neural placode.
- since neural tube does not fuse, cutaneous ectoderm does not come to cover neural tube (remains attached and lateral to neural plate, leaving cutaneous defect) - raw, exposed dorsal surface of neural placode represents tissue that should have formed interior of spinal cord (i.e. filleted spinal cord with visibly open central canal).
- CSF exiting from proximally formed central canal floods dorsal surface of placode.
- surrounding neural placode is thin layer of skin and arachnoid tissue, below which is enlarged subarachnoid space; enlarged subarachnoid space ventral to placode results in dorsally protruding sac on which neural placode is visible.
- nerve roots lie inferior to neural placode, with ventral roots lying medial to dorsal roots (i.e. dorsal roots exit from anterior surface of spinal cord just lateral to ventral roots).
- spinal cord is always tethered!

Transverse section through myelomeningocele: arrows demonstrate junction of neural placode (N) with dura mater and skin; subarachnoid space (S):


Level of defect: thoracolumbar junction (45%) > lumbar (20%) > lumbosacral (20%) > sacral (10%) > more rostral locations (5%).

*according to Nelson – 75% cases are lumbosacral; according to Grainger – 80-90%

Clinical Features:
1. Sac-like cystic structure covered by thin layer of partially epithelialized tissue. = remnants of neural tissue are visible beneath membrane, which may occasionally rupture and leak CSF.
2. Spinal cord dysfunction:
   1) Flaccid paralysis & sensory deficits below level of lesion: defects above L₂ - deficits preclude ambulation (wheelchair dependent); defects between S₁ and L₃ - assisting devices may allow ambulation; defects below S₁ - unaided ambulation.
   2) GU tract involvement (≈ 90% patients) - constant urinary dribbling, relaxed anal sphincter.
3. Superimposed infection (sac rupture → meningitis; UTI)
4. 75% patients have normal intelligence.
5. Other defects along neuraxis and surrounding mesoderm:
   1) Chiari II (s. Arnold-Chiari) malformation – most common (> 95%) finding associated with myelomeningocele! – most common cause of death!
   2) Hydrocephalus (80-95%: esp. with myelomeningoceles in lumbosacral region) - ventricular outlet obstruction and obliteration of posterior fossa subarachnoid cisterns are likely causes.
   3) Lückenschädel (> 50% cases) - regional thinning of cranial bones (radiographic and transilluminative lucencies); rarely found after 2 years of age.
   4) Platybasia.
   5) Cerebral hemisphere malformations - enlarged massa intermedia (frequent finding), agenesis of corpus callosum, polymicrogyria, pachygryia.
   6) Diastematomyelia, diplomyelia.

N.B. patients with myelomeningocele in upper thoracic ÷ cervical region usually have very minimal neurologic deficit and in most cases do not have hydrocephalus!

Late complications of myelomeningoceles:
1. Scoliosis (esp. with lesions above L₂)
2. Traction on cord.
3. Urological complications - continue to be leading cause of morbidity in myelomeningocele!

Usual causes of death: loss of renal function, shunt complications.

Source of picture: “WebPath - The Internet Pathology Laboratory for Medical Education” (by Edward C. Klatt, MD)
**Myelomeningocele (arrow):** note flaccid anal sphincter and poorly developed lower extremity musculature:

**DIAGNOSIS**

**PRENATAL DIAGNOSIS**

1. **Serum** chemistry - through routine screening programs: see p. 71-72 (3) >> p. 2700 >>
   - serum α-fetoprotein (AFP) ↑ - specificity is much lower than amniotic fluid; peak of sensitivity somewhat later than amniotic fluid (i.e. ≈ 16-18 weeks' gestation – normal AFP peak; before that time, levels may be normal).
   - most common causes of false-positive AFP↑: incorrect dating of pregnancy, multiple gestation.
   - further course is detailed (level II) ultrasound or amniocentesis

2. **Amniotic fluid** chemistry:
   1. amniotic fluid α-fetoprotein (AFP)↑ (in almost all open neural tube defects, but also in gastroschisis, etc).
   2. amniotic fluid acetylcholinesterase (AchE)↑ (only in almost all open neural tube defects).

   Amniotic fluid AFP↑ + amniotic fluid AchE↑ - sensitivity for open defects ≈ 100% → detailed (level II) ultrasound

3. Ultrasound - very high sensitivity at even 14-16 weeks' gestation.
   - lemon sign (indirect sign) - symmetrical bifrontal narrowing of skull – risk of neural tube defects.

**POSTNATAL DIAGNOSIS**

- careful MRI (!) and CT.

**Encephalocele**

- ultrasound is most helpful in determining contents of sac.

   Occipital encephalocele (MRI in newborn); at surgery, sac contained herniated dysplastic cerebellar tissue as well as CSF:

**Spina bifida**

- cervical spine – absence of cortical line on anterior surface of spinous process (on lateral and AP X-ray).
- lumbosacral spine – defect best seen on AP X-ray.

**Myelomeningocele**

- imaging is not necessary preoperatively – diagnosis is obvious clinically.
- do not overlook Chiari II, tethered spinal cord.
- every child must be screened for hydrocephalus (daily occipital-frontal circumference measurements and baseline transfontanellar ultrasound).
- orthopedic & urological assessment.
Lumbosacral myelomeningocele - MRI shows spinal dysraphism and tethered cord:

**MANAGEMENT**

**Prevention of meningitis / ventriculitis is extremely important** (intellectual outcome is inversely related to occurrence of such complications) - antibiotic prophylaxis before and around time of surgery (esp. with open defects).

**Atraumatic delivery** (damaged CNS is more vulnerable to perinatal insults) - prelabor Cesarian section significantly improves neurological outcome in large encephaloceles, myelomeningoceles.

**ENCEPHALOCELES**

Surgical management – as early as clinical conditions permit: more details – see p. Op300 >>

1. Encephalocele contents:
   a) relocation into cranium
   b) resection (amputation)
2. Watertight dural closure
3. Bone grafting to cover calvarial defect (usually at later operation).

- indicated in most situations (exceptions – very small defects*, large defects with associated microcephaly) even if there are significant associated malformations**
- *may decrease with time

- goal of surgery here - to simply improve caregiving for such infant.

- temporal encephalocele has high epileptogenicity - excellent outcome with resection and is commonly missed if not specifically looked for.

**MYELOMENINGOCELE**

- child is kept prone or in lateral recumbent position.
- defect is covered with warm saline-moistened nonadherent dressing (e.g. Telfa - to prevent injury and desiccation of neural placode).
- antibiotics (NAFCILLIN + GENTAMICIN), esp. if defect is leaking CSF; continue until clear that shunt is not needed.
- HUS then daily HC.
- genitourinary system evaluation.

Surgical management - closing all but prognostically worst cases. see p. Op250 >>

Conservative management

- urological management plays prominent role:
  - regularly catheterize neurogenic bladder - avoid secondary dilatation of proximal urinary system – pyelonephritis, hydronephrosis.
  - periodic urine cultures, assessment of renal function, renal imaging.
  - some can become continent with implantation of artificial urinary sphincter at later age.
- incontinence of fecal matter is common and socially unacceptable (but does not pose same risks as urinary incontinence); many children can be "bowel-trained" with timed enemas or suppositories that allows evacuation at predetermined time once or twice day.
- ambulatory aids, orthopedic care.

**PROPHYLAXIS**

1. Folate supplementation 4 mg/day before conception* and during early pregnancy (until 12th week).

*general diet fortification with folate in case of unplanned pregnancy

- for women who have had infant / fetus with neural tube defect.
- folate mechanisms are poorly understood.

**MORTALITY RATE**:

- myelomeningocele (treated aggressively) – 10-15% (most deaths occur before 4 yrs).

**PROGNOSIS**

- recurrence rate for neural tube defect in subsequent pregnancy ≈ 3-5%*;
- raises to 7-10% after two previous abnormal pregnancies

*it is general recurrence risk for multifactorial disorders
U.S. Public Health Service 1992 recommendations:

1) All women of childbearing age capable of becoming pregnant must take 0.4 mg folate daily (dose should not exceed 1.0 mg/day to avoid secondary vit. B12 deficiency).

2) Women who had pregnancy with in neural tube defect must take 4 mg folate daily (beginning 1 month prior to time pregnancy is planned).

3. Avoid heat exposure (esp. hot tub).

4. Change VALPROATE to another anticonvulsant.

BIBLIOGRAPHY for ch. “Developmental Anomalies” – follow this LINK >>