Neutral Tube Disorders (s. Dysraphia)

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Classification: .................................................. 1
ETIOPATHOPHYSIOLOGY: ........................................... 1
  1) ETIOLOGY ...................................................... 1
  2) CLASSIFICATION, PATHOLOGY, CLINICAL FEATURES ...... 1
  3) CRANIOSCHISIS .............................................. 2
  4) ENCEPHALOCELE ........................................... 3
  5) MYELOMENINGOCELE ......................................... 3
  6) PROPHYLAXIS ................................................ 6
  7) NEURENTERIC CYST, EPIDERMIS CYST, DERMOID CYST → see p. Onc10 >>

NEURAL TUBE DISORDERS (N. NEURULATION DEFECTS, S. DYSRAPHIS) – most common CNS malformations!

CLASSIFICATION
→ see p. DevI >>

ETIOPATHOPHYSIOLOGY

EMBRYOLOGY → see p. A13 (1) >>

THEORIES

a) REOPENING of closed neural tube – questionable
b) NONCLOSED (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 (monoallelic 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

• Encephalocele – 1 in 5000-10000 live births.

Anencephaly – 0-1 in 1000 live births (greatest frequency is in Ireland and Wales)

Risk factors:
1) maternal hyperthemia
2) maternal diabetes
3) anticonvulsants (e.g. 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. → see p. DevI >>

CRANIOSCHISIS

ENCEPHALIA ("absence of head") - cranial neuroepithelial 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 crenation is highly vascular and friable membrane (arise cerebrovacularous).

Clinical Signs
1) polyhydramnios.
2) neurological function is limited to braziastem & 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 antenecphalic infants as organ donors).
NEURAL TUBE DISORDERS

EXENCEPHALY – defect in calvarium (dura, bone, skin) – exposed brain (degenerated due to exposure to amniotic fluid):

ENCEPHALOCELES, CRANIAL MENINGOCELES - defect in skull & dura (but often intact epidermal covering); vs. anencephaly, myelomeningocele) with protrusion of:

a) leptomeninges (CRANIAL MENINGOCELE), neural tissue (cerebral, cerebellar) within encephalocele is often abnormal and ischemic.
   - in few cases portions of ventricles are also included - ENCEPHALOCYSTOCELE.

b) leptomeninges and underlying brain tissue (ENCEPHALOCELE); neural tissue (cerebral, cerebellar) within encephalocele is often abnormal and ischemic.

- transillumination of sac may indicate presence of neural tissue within.

ENCEPHALOCELE

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).

Location (usually midline):

 OCCIPITAL encephaloceles (85% in North America) - often large and have variable contents
   a) MECKEL-GRIEBER syndrome - rare autosomal recessive condition: occipital encephalocele, microcephaly, microphthalmia, cleft lip / palate, abnormal genitalia, polycystic kidneys, polydactyly.
   b) WALKER-WARBURG syndrome - autosomal recessive congenital muscular dystrophy. see p. Mus5.

ANTERIOR encephaloceles:

a) most common isolated malformation in southeast Asia.
   b) Robert's syndrome
   CEREBELLAR encephaloceles – less common.

SPHENOIDAL encephaloceles – endocrine dysfunction.

Clinical Features:

1) protuberant mass that may be pulsatile; size of encephalocele varies: barely visible bulge ≥ larger than infant's head.

Source of pictures: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

"Area cerebrovasculosa" from skull base - scattered primitive neuroglial tissue elements within irregular vascular proliferations.

Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>
MYELOMENINGOCELE

*may resemble cephalohematoma

2) neurological deficits correlate with extent of cysts that is herniated into celo: motor deficits, visual defects, psychomotor developmental delay.

3) malformed corne (within / adjacent to celo) → seizures.

4) frequently associated with other intracranial abnormalities (e.g. hydrocephalus, agenesis of corpus callousm, Dandy-Walker malformations, holoprosencephaly).

5) prognostic is good for many patients.

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

NASAL GLOMUS (misleading term - not neoplasm!): form of frontonasal encephalocele with no clear bony defect - may not be immediately obvious on external examination.

m present us intramesal abnormalities (CSF thinitcortex following removal of nasal polypl, pharyngeal obstruction, or recurrent meningitis."

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

– requires immediate imaging and prophylactic antibiotics → 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 - 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 to S (up to 24% of population!); C7, Th1:

• defect is nearly always narrow and asymmetric.

• 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 (APERTA, CYSTICAL) - defect in vertebral arch plus:

A) MENINGOCOELE - involves meninges alone (i.e. POSTNEURULATION DISORDER - neural elements are intact)

• transilluminating protruding / herniating meningeal sac is covered by skin; may be asymptomatic?

• meningocele distends with crying.

APPENDE MENGOCOELE (differentiate from dural eacts in spondyloarthropathies):

1) ANTERIOR SACRAL MENGOCOELE - presacral cystic mass projecting into pelvis through anterior eentric defect in sacrum* → constipation, bladder dysfunction, anomalies of female genital tract (e.g. rectovaginal fistula, vaginal septa).

*pathognomonic sign: "hump" on anterioiliac spine on plain X-ray

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

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

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

B) MYELOMENINGOCOELE (most common derangement of neurlitation): involves meninges and underlying spinal cord; no skin covering over defect.

MYELOMENINGOCOELE

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 neural elements

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B) MYELOMENINGOCOELE (most common derangement of neurlitation): involves meninges and underlying spinal cord; no skin covering over defect.
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. Sacral 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 L3 - defects 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 mésoderm:
   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 myelomeningocele in lumbosacral region - ventricular outlet obstruction and obliteration of posterior fossa subarachnoid cisterns are likely causes.
   3) LUCKENSHADIA! (> 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, pachygyria.
   6) diastematomyelia, diplomyelia.
   7) skeletal deformities (kyphosis, scoliosis, dislocated hips, clubfeet, Klippel-Feil syndrome) – esp. in defects above L3 – due to intrauterine paralysis.

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 myelomeningocele:

1. Scoliosis (esp. with lesions above L3)
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.
NCNEURAL TUBE DISORDERS

Diagnosis

Prenatal Diagnosis

1. Serum chemistry - through routine screening programs: see p. 71-72 (3). [1]
   - Serum α-fetoprotein (AFP)↑: specificity is much lower than amniotic fluid peak; 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:

**MENINGOCELE**
- US - subcutaneous cystic mass in continuity with spinal canal through bone defect.

**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:
  1. Encephalocele contents:
     a) relocation into cranium
     b) resection
  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.
- CSF leak → urgent surgery within 12-24 hours (to prevent meningitis).
- surgical PROGNOSIS is best in sporadic frontal encephaloceles; occipital encephaloceles are more commonly ascended with hydrocephalus → worse cognitive outcome.

**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.

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

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

**PROPHYLAXIS**
- Folate supplementation 4 mg/day before conception* and during early pregnancy (until 12th week).
- *general diet fortification with folate in case of unplanned pregnancy
- esp. for women who have had infant / fetus with neural tube defect.
- folate mechanisms are poorly understood.

U.S. Public Health Service 1992 recommendation:

1. all women of childbearing age capable of becoming pregnant must take 0.4 mg folate daily
2. may decrease with time
3. *goal of surgery here - to simply improve caregiving for such infant.
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).

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

3. Change VALPROATE to another anticonvulsant.

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