Neural Tube Disorders (s. Dysraphism)

Last updated: January 16, 2021

NEURAL TUBE DISORDERS (s. NEURULATION defects, s. DYSRAPHIA) – most common CNS malformations!

CLASSIFICATION

→ see p. Dev1 >>

ETIOPATHOPHYSIOLOGY

EMBRYOLOGY → see p. A13 (1) >>

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 (*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!

*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 (esp. *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. Dev1 >>

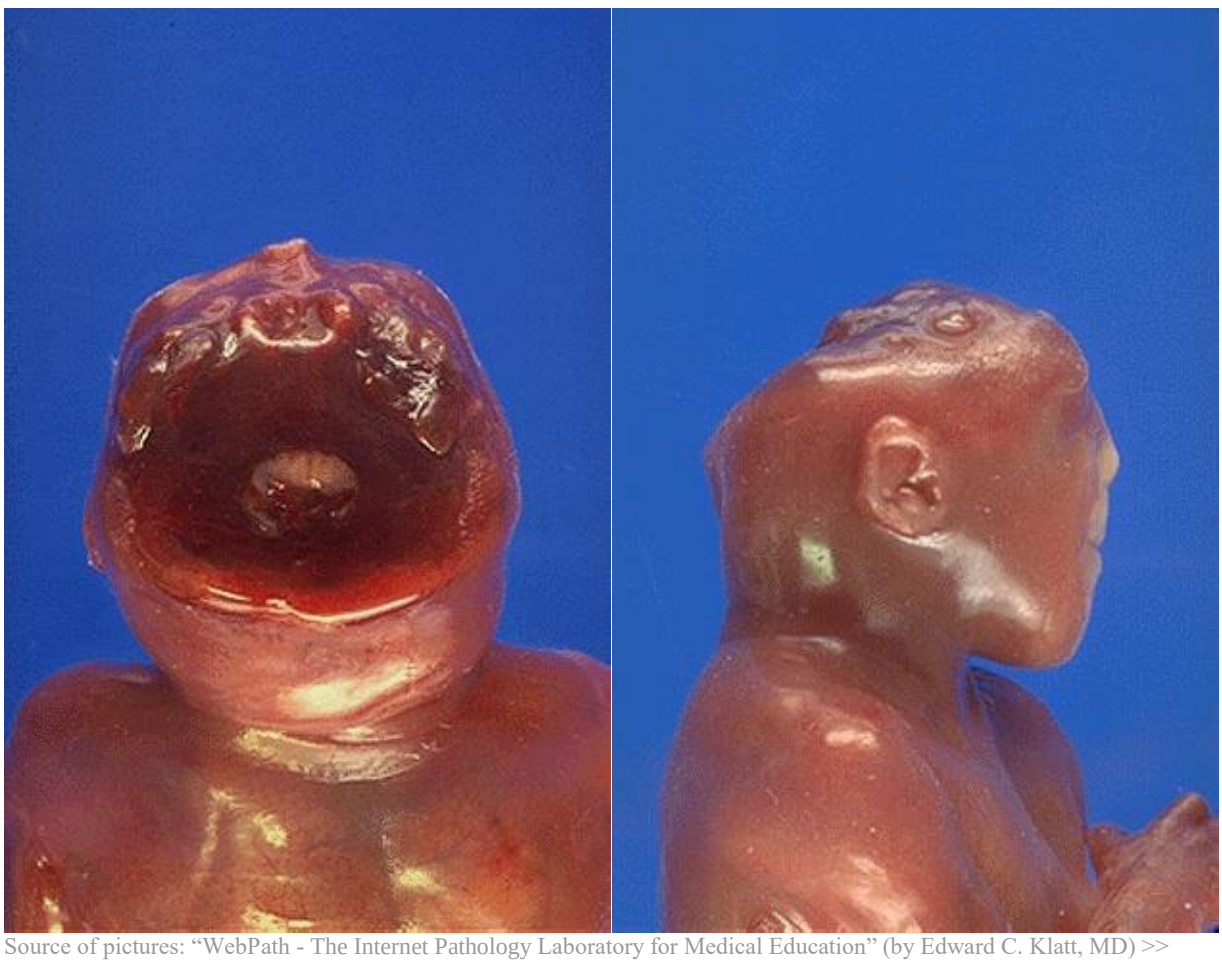
CRANIOSCHISIS

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 (*area cerebrovasculosa*).

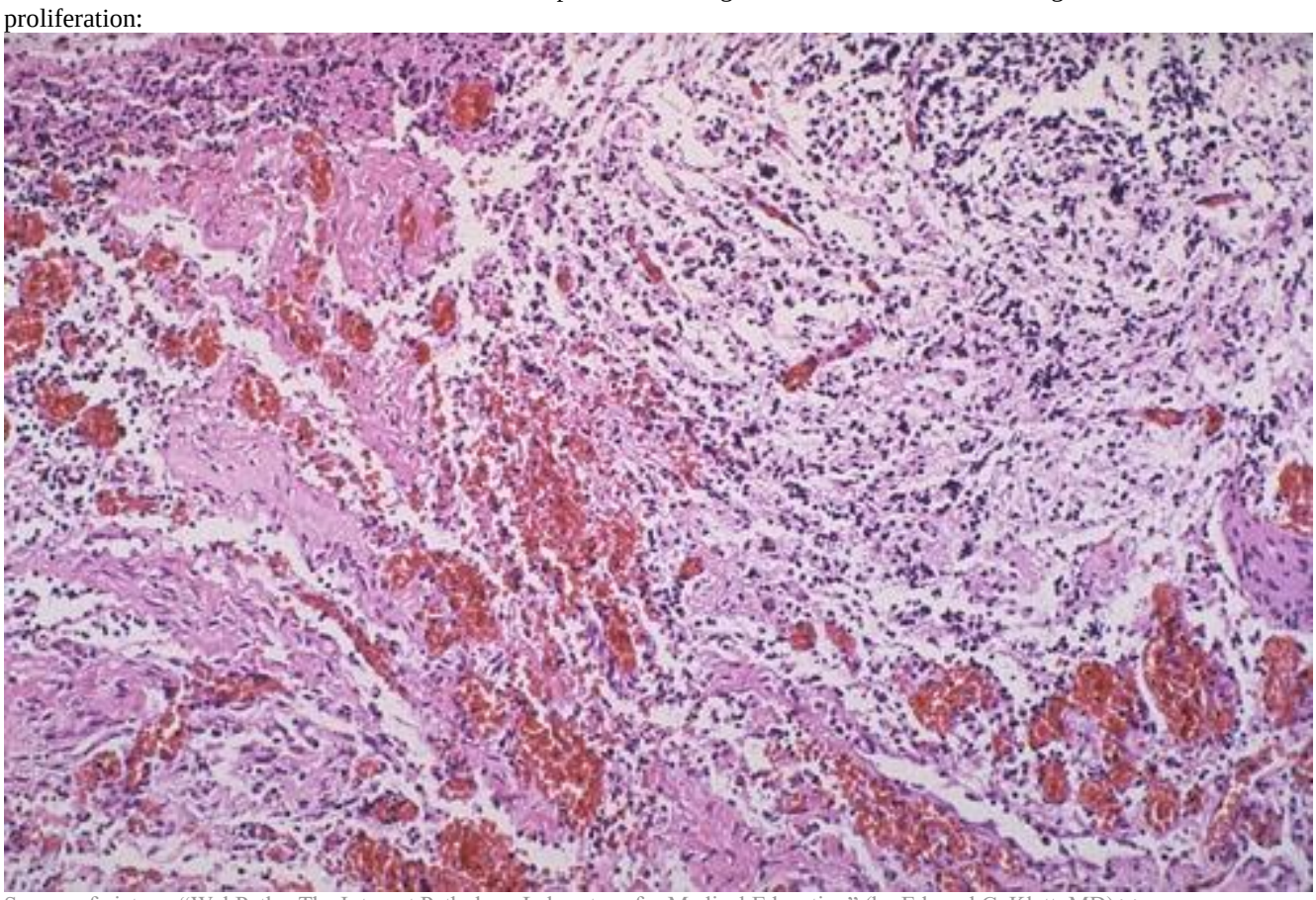
Clinical Signs

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).



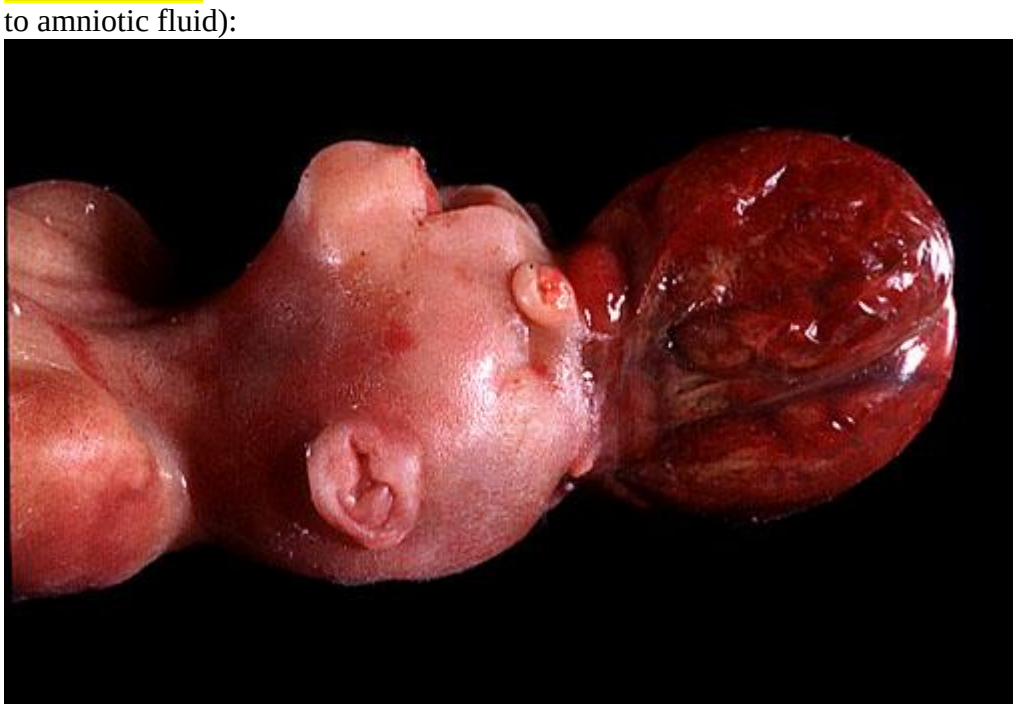
Source of pictures: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

"Area cerebrovasculosa" from skull base - scattered primitive neuroglial tissue elements within irregular vascular proliferation:



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

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



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

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

- ***transillumination*** of sac may indicate presence of neural tissue within.
- incidence - 1:5 ratio to MMC.

ENCEPHALOCELE (S. CEPHALOCELE)

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

a) **MECKEL-GRUBER 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

PARIETAL encephaloceles – less common.

SPHENOIDAL encephaloceles – endocrine dysfunction.

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. sincipital** (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-orbital: defect in the antero-inferior portion of medial orbital wall.
4. **Basal** (1.5% of encephaloceles; the only group that does not produce 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. transethmoidal: protrudes into nasal cavity through defect in cribriform plate
    b. spheno-ethmoidal: protrudes into posterior nasal cavity
    c. transsphenoidal: protrudes into sphenoid sinus or nasopharynx through patent craniopharyngeal canal (foramen cecum)
    d. fronto-sphenoidal or spheno-orbital: protrudes into orbit through superior orbital fissure.
5. **Posterior fossa**: usually contains cerebellar tissue and ventricular component.

Clinical Features

1) **protuberant mass** that may be pulsatile (except basal encephaloceles); **size** of encephalocele varies: barely visible bulge* ÷ larger than infant's head.
*may resemble cephalhematoma
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) → **seizures**.
4) frequently associated with *other intracranial abnormalities* (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 neoplasm!; better term - **NASAL GLIAL HETEROTOPIA**) - 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, hypothalamic dysfunction.
- requires immediate imaging and prophylactic antibiotics → surgical repair.

A nasal polypoid mass in a newborn is an encephalocele until proven otherwise!

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).

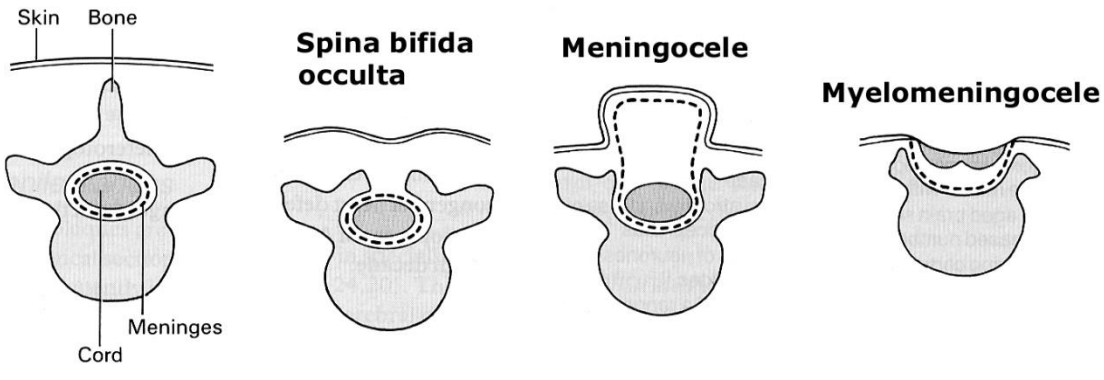
A. **SPINA BIFIDA OCCULTA** - defect in vertebral arch without any other associated defect (i.e. without involvement of cord or meninges; skin is intact over malformation).
- most commonly - L_5 & S_1 (up to 24% of population!), C_1, Th_1.
- defect is nearly always narrow and asymmetric.
- **asymptomatic** 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 (S. APERTA, CYSTICA)** - defect in vertebral arch plus:

A) **MENINGOCELE** - 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.

ATYPICAL MENINGOCELES (differentiate from dural ectasias in spondyloarthropathies):
1) **ANTERIOR SACRAL MENINGOCELE** – presacral cystic mass projecting into pelvis through anterior eccentric defect in sacrum* → constipation, bladder dysfunction, anomalies of female genital tract (e.g. rectovaginal fistula, vaginal septa).
*pathognomonic scimitar [riestas rytietiškas kardas] appearance on plain X-ray
2) **INTRASACRAL MENINGOCELE** – sacral canal is expanded by meningocele which lies below normal level of termination of thecal sac.
3) **LATERAL THORACIC MENINGOCELE** – intrathoracic posterior mediastinal mass through eroded intervertebral foramen; occurs (70-85%) in association with neurofibromatosis.
4) **ANTERIOR THORACIC MENINGOCELE** 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) **MYELOMENINGOCELE** (most common derangement of neurulation!) - involves meninges and underlying spinal cord; no skin covering over defect.



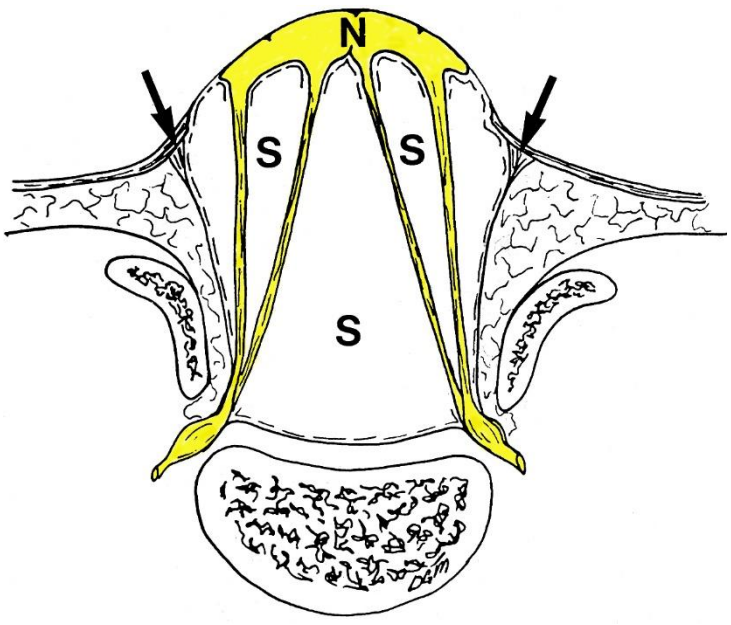
MYELOMENINGOCELE

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 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):



Source of picture: David C. Sabiston "Sabiston Textbook of Surgery: the Biological Basis of Modern Surgical Practice", 15th ed. (1997); W.B. Saunders Company; ISBN-13: 978-0721658872 >>

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:

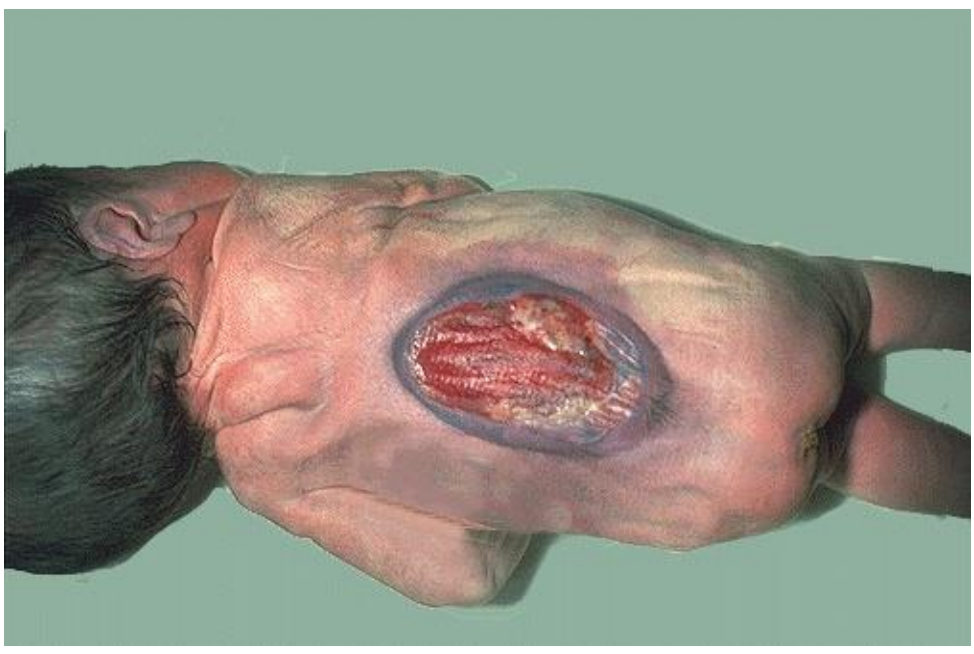
1. Saclike **cystic structure** covered by thin layer of partially epithelialized tissue.
   - remnants of neural tissue are visible beneath membrane, which may occasionally rupture and leak CSF.
2. **Spinal cord dysfunction**:
   1) **flaccid paralysis & sensory deficits** below level of lesion:
      defects above L_3 - deficits preclude ambulation (wheelchair dependent);
      defects between S_1 and L_3 - assisting devices may allow ambulation;
      defects below S_1 - 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, pachygyria.
   6) **diastematomyelia**, diplomyelia.
   7) **skeletal deformities** (kyphosis, scoliosis, dislocated hips, clubfeet, Klippel-Feil syndrome) – esp. in defects above L_3 – 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 myelomeningoceles:

1. Scoliosis (esp. with lesions above L_3)
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.



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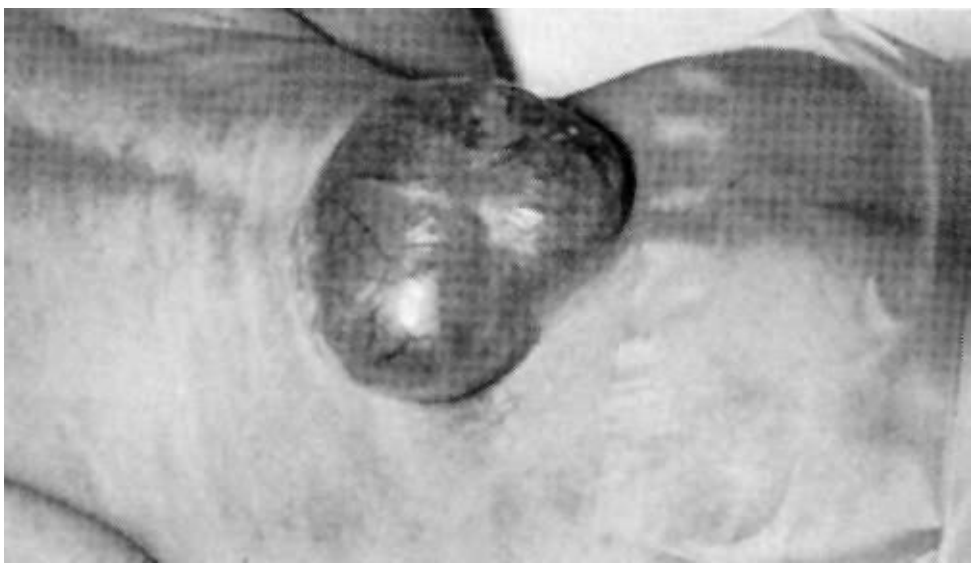
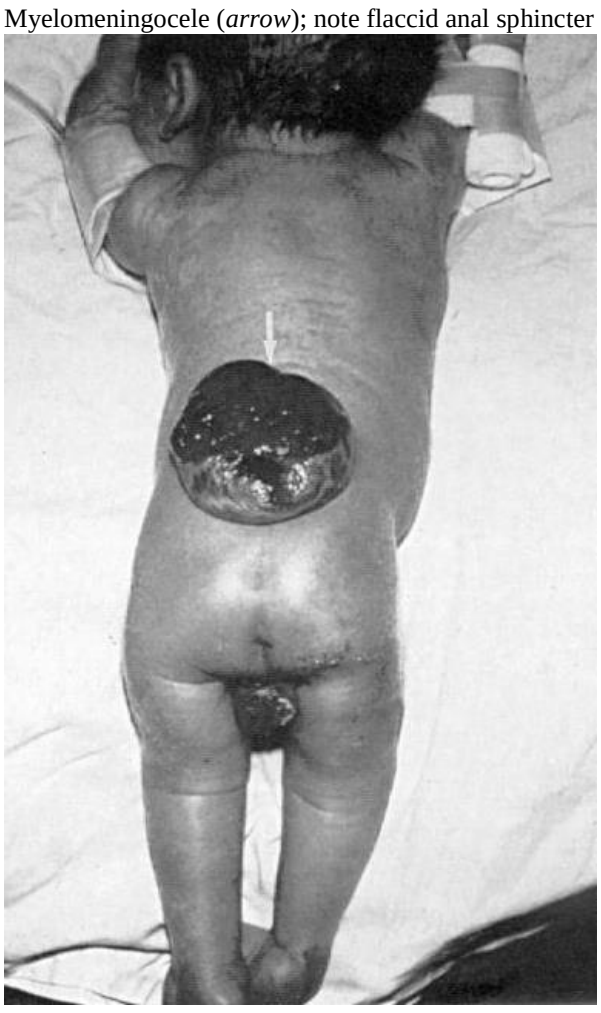
Lumbar myelomeningocele covered by thin layer of skin:



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.

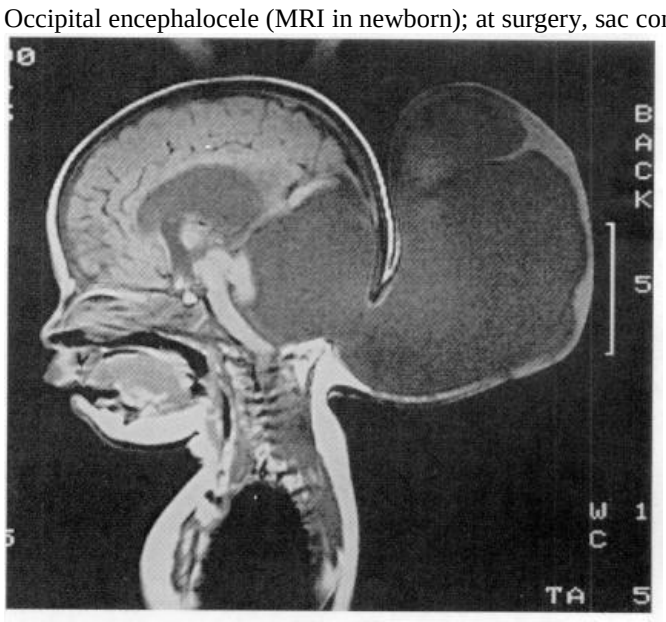
POSTNATAL DIAGNOSIS

- 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:



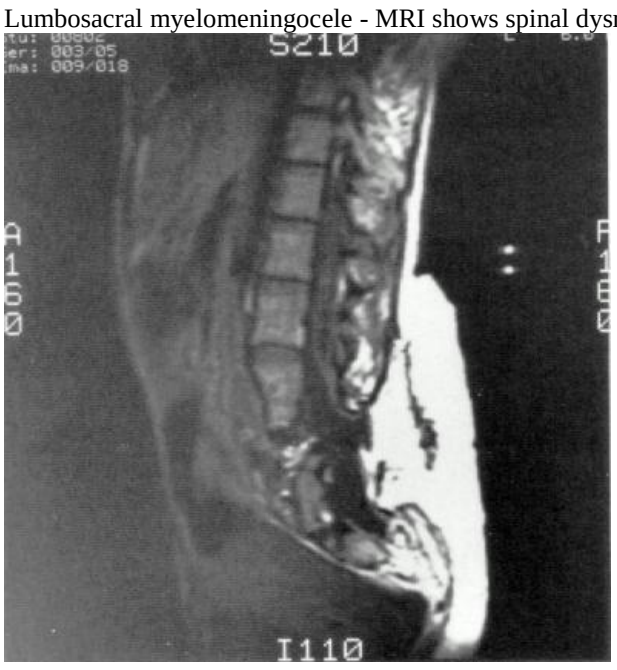
SPINA BIFIDA

- **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:



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: 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.

- CSF leak → urgent surgery within 12-24 hours (to prevent meningitis).
- surgical PROGNOSIS is best in sporadic frontal encephaloceles; occipital encephaloceles are more commonly associated with hydrocephalus → worse cognitive outcome.
  - 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**.

MENINGOCELE

Surgical repair – for cosmetic reasons: amputation of herniating sac, and closing dura; remainder of wound is closed in layers.

- prior to surgery, patient must be thoroughly imaged (MRI) for neural tissue involvement, if any, and associated anomalies.
- if CSF is leaking → immediate surgery (to prevent meningitis).

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*

MORTALITY RATE:

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

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.

U.S. Public Health Service 1992 recommendation:

1) all women of childbearing age capable of becoming pregnant must take **0.4 mg folate** daily (dose should not exceed 1.0 mg/d to avoid secondary vit. B_{12} 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).

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

3. **Change** VALPROATE to another anticonvulsant.

BIBLIOGRAPHY for ch. "Developmental Anomalies" → follow this LINK >>