Neural Tube Closure and Associated Defects

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Disclosures

• I have no relevant financial relationships to disclose
Learning Objectives

At the end of this activity learners should be able to:

• Describe the process of neural tube closure
• Explain the mechanisms of neural tube closure defects
• Categorize different types of neural tube closure defects
DEFINITIONS

Cranial
- Anencephaly
- Encephalocele
- Iniencephaly
- Cranial meningocele
- Acalvaria
- Craniorachischisis

Spinal
- Spina Bifida occulta
- Spina Bifida cystica
- Myelomeningocele
- Myelocele
- Meningocele
- Myelocystocele
- Rachischisis
- Tethered cord
Neural crest emigration

Mesodermal expansion

Neuroepithelial proliferation

Dorsolateral bending

Contraction of sub-apical actin microfilaments

Programmed cell death


Roellig et al, Developmental Cell, 2022
Hindbrain neuropore
Anterior neuropore
Posterior neuropore
Closure 1
Closure 2
Hindbrain neuropore
Craniorachischisis
Lumbosacral spina bifida
Spina bifida occulta
Exencephaly
Normal

Closed defect

Open defects

Meningocele

Myelomeningocele

Myeloschisis

Avagliano et al, Birth Defects Res 2019
Table 1:

Modifiable risk factors for NTDs

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Action</th>
<th>Risk</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal diabetes</td>
<td>Teratogenic effect due to embryonic exposure to high glucose concentrations leading to increased cell death in the neuroepithelium.</td>
<td>2-10-fold increase</td>
<td>(Ray, 2001; Shaw et al., 2003; Yazdy, Mitchell, Liu, &amp; Werler, 2011)</td>
</tr>
<tr>
<td>Maternal obesity</td>
<td>Teratogenic effect due to embryonic exposure to hyperinsulinemia, metabolic syndrome, and oxidative stress related to adiposity.</td>
<td>1.5-3.5-fold increase. The risk increases with increased maternal body mass index</td>
<td>(Anderson et al., 2005; Cammichael, Rasmussen, Lammer, Ma, &amp; Shaw, 2010; Dietl, 2005; Hendricks, Nuno, Suarez, &amp; Larsen, 2001; Shaw, Velie, &amp; Schaffer, 1996; Werler, Loutik, Shapiro, &amp; Mitchell, 1996)</td>
</tr>
<tr>
<td>Maternal Hyperthermia (sauna, hot water tube, fever)</td>
<td>Teratogenic effect due to embryonic exposure to heat stress.</td>
<td>2-fold increase</td>
<td>(Moretti, Bar-Oz, Fried, &amp; Koren, 2005; Suarez, Felkner, &amp; Hendricks, 2004; Waller et al., 2017)</td>
</tr>
<tr>
<td>Drugs (particularly valproate)</td>
<td>Teratogenic effect due to embryonic exposure to valproate action as inhibitor of histone deacetylases, disturbing the balance of protein acetylation and deacetylation, leading to neurulation failure.</td>
<td>10-fold increase</td>
<td>(Kanai, Sawa, Chen, Leeds, &amp; Chuang, 2004; Lammer, Sever, &amp; Oakley, 1987; Meador et al., 2006; Pai et al., 2015; Yildirim et al., 2003)</td>
</tr>
<tr>
<td>Inadequate maternal nutritional status</td>
<td>Teratogenic effect due to embryonic exposure to low folate intake, low methionine intake, low zinc intake, low serum vitamin B12 level, low vitamin C level, caffeine abuse, alcohol use, smoking, all conditions disturbing the folate-related metabolism</td>
<td>Undetermined</td>
<td>(Grewal, Cammichael, Ma, Lammer, &amp; Shaw, 2008; Kirke et al., 1993; Ray &amp; Blom, 2003; Schmidt et al., 2009; Suarez, Hendricks, Felkner, &amp; Gunter, 2003; Velie et al., 1999)</td>
</tr>
</tbody>
</table>
**Table 2:**

Differential diagnosis between meningocele, myelomeningocele and myelocele

<table>
<thead>
<tr>
<th>Type of defect</th>
<th>Meningocele Closed</th>
<th>Myelomeningocele Open</th>
<th>Myelocele Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound aspects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior anechoic cystic mass (sac-like protrusion) from the spine</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Presence of septa in the sac</td>
<td>-</td>
<td>+</td>
<td>//</td>
</tr>
<tr>
<td>Abnormality of vertebral bones (absence of the arches)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Abnormal shape of skull (lemon sign)</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Abnormal shape of cerebellum (banana sign)</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Association with Chiari type II malformation</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Association with hydrocephalus</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Association with clubfoot</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Macroscopic aspects of the lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence of vertebral arches</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Meningeal herniation though the bones defect</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Presence of neural tissues in the meningeal sac (medulla and/or nerves)</td>
<td>-</td>
<td>+</td>
<td>//</td>
</tr>
<tr>
<td>External exposition of placode</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Covered by skin</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Lee and Gleeson, Trends in Neurosci 2020

Greene and Copp, Annu Rev Neurosci 2014
Coding/noncoding variant
- De novo mutation
- Inherited variant
- Genetic modifier
- Somatic mosaic
- Combinations

Structural variant

Chromosomal aneuploidy
- Epigenetic dysregulation
- Environmental factors
  - Folate and nutrition
  - Maternal diabetes/obesity
  - Drugs

Neural tube defect

Lee and Gleeson, Trends in Neurosci 2020
Figure 8
Thank you and any question?