Neural Tube Defects: Screening and Prevention

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Objectives

• After attending this presentation, the learner should be able to:
  – Define the most common types of neural tube defects.
  – Describe current prenatal screening for neural tube defects.
  – Explain the impact of folic acid supplementation on neural tube defect incidence.
Outline- Questions to Answer

• How does the neural tube normally develop?
• What are neural tube defects (NTDs)?
• How can we screen for NTDs?
• How can we prevent NTDs?
• What are some areas for future research?
How does the neural tube normally develop?
Normal Development

- Nervous system development begins in third week of pregnancy
- Neural plate appears

Figures for next three slides accessed at:
https://people.creighton.edu/~idc24708/Genes/Behavioral%20Genetics/3-step%20neurulation.png
Normal Development

- Edges of neural plate elevate to form neural folds
Normal Development

- Neural folds continue to raise and eventually join to create the neural tube
Neural Tube Animation

From Wesleyan University, Middletown CT

http://learningobjects.wesleyan.edu/neurulation/animation.php
Normal Development

• Neural tube closure is complete by 27 days

• This is so early, many pregnancies are not recognized at this point!
What are neural tube defects (NTDs)?
Neural Tube Defects

• Caused by problems in closing of the neural tube during development
• May affect any part of the brain or spinal cord
• Many different types
  – Spina bifida = most common
  – Anencephaly
  – Many other variants
Spina Bifida

• Also called “open spine”
• Affects vertebrae and spinal cord
• CDC estimate- About 1 in 2,500 US babies affected yearly
• Main types
  – Spina bifida occulta
  – Spina bifida cystica / aperta
    • Meningocele
    • Myelomeningocele
Spina bifida occulta

- Cannot be detected by screening
- Patients do not have symptoms
- Does not require treatment
Spina bifida occulta
Meningocele – Cross Section

- Fluid-filled cyst
- Bony defect
- Spinal cord and nerves
Meningocele - Side View

- Fluid-filled cyst
- Spinal cord and nerves
Meningocele

- Cyst must be surgically removed
- Patients usually have normal development
Meningomyelocele

Meningomyelocele

Meningomyelocele

• Must be closed surgically
• Thin cover = high infection risk if not treated
• Patients often have leg paralysis or bowel/bladder control problems
• Seizure disorders, kidney problems also seen
Anencephaly

- CDC Estimate- about 1 in 4,000 US babies affected yearly
- Severe problem with brain and skull development
- Top part of head and brain does not form
- Patients are blind, deaf, unconscious
- Patients do not usually survive longer than days
Anencephaly
Risk Factors

• NTDs more common in North America and UK
• NTDs less common in Asian countries
• Independent risk factors
  – Prior affected pregnancy
  – Drugs that affect folic acid metabolism
  – Maternal diabetes
  – Maternal obesity
Risk Factors

• However…
  – About 90% of cases of NTDs occur in children of women with no risk factors!
How can we screen for NTDs?
Alpha Fetoprotein (AFP)

- Glycoprotein (70,000 Da)
- Made by fetal liver
  - Small contributions from yolk sac and other fetal organs
- Concentrations
  - Highest in fetal serum
  - Moderate in amniotic fluid
  - Lowest (but still detectable) in maternal serum
Implications for screening

• There are three samples we could use to screen
  – Fetal serum- cordocentesis
  – Amniotic fluid- amniocentesis
  – Maternal serum- maternal blood draw

• The last option is by far the least invasive and least risky, so this is where we start
Figure 54-12, Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 4th ed., p. 2182.
A Brief History of Screening

- **1972- Brock et al.**
  - Amniotic fluid AFP ↑

- **1973- Three groups (Brock, Hino, Leek)**
  - Maternal serum AFP ↑

- **1977- Wald et al.**
  - Population screening with maternal serum AFP
A Brief History of Screening

• 1980s- maternal serum AFP screening standard of care in US
• Maternal serum screening now also uses additional markers to describe risk of Down syndrome and Trisomy 18
How we measure risk

• Best time for screening - 16 -18 weeks
• Why?
  – At this time in pregnancy, we can reliably see a difference between NTD and normal groups
How we measure risk

• Many factors affect maternal serum AFP
  – Number of fetuses ↑
  – Weeks gestation ↑
  – Maternal size ↓
  – Ethnic background ↑ in African-Americans
  – Maternal diabetes ↓
  – Open neural tube defects ↑

• We cannot just measure AFP without correcting for variation
How we measure risk

• AFP measured with sandwich immunoassay

• To correct, we use Multiples of the Median (MoM)
  – Median values for week of gestation calculated in performing lab
  – MoM calculation
    • Maternal test result / median for gestational age
  – Additional corrective factors are used to account for other sources of AFP variation
FP - 1.5-2.5%

Open SB - 80-85%

Anencephaly - 90-95%

Unaffected

Open Spina Bifida

Anencephaly

Maternal Serum AFP (MoM)
What happens if the screen is positive?

• Some recommend to re-test AFP (if <3.0 MoM)

• Level II (targeted) ultrasound
  – Confirms gestational age and number of fetuses
  – Specifically looks at fetal head and spinal cord
Meningocele
“Lemon Sign”

Lemon Shaped Skull

http://www.cpdx.com/images/ultrasounds/lemon%20skull2.jpg
“Banana Sign”

Anencephaly
What happens if the screen is positive?

• Amniotic fluid AFP
  – May be false positive (up to 2-3%) if there is fetal blood contamination

• Amniotic fluid acetylcholinesterase (AChE)

• Genetic counseling

• Chromosomes (karyotype) may also be useful
How can we prevent NTDs?
What are folates?

• Definitions
  – Folate and folic acid- general terms for a family of compounds
  – Foods naturally high in folates include
    • Leafy greens
    • Legumes
    • Liver
What are folates?

- Folates important for
  - Amino acids
    - Methionine synthesis
    - Histidine metabolism
    - Serine-glycine metabolism
  - DNA
    - Thymidylate synthesis
    - Purine synthesis

Figure 13-21, Robbins and Cotran Pathologic Basis of Disease, 7th ed. p. 641
What is the role of folates?

• We are not entirely sure
  – There is definitely an association between folic acid supplementation and decreased rates of NTDs
  – The exact biochemical mechanism for this is unclear
Definitions

• Fortification
  – Addition of folic acid to food products during manufacturing

• Supplementation
  – Addition of folic acid to diet by taking vitamin pills
History

- 1960s – possibility of folic acid to prevent NTDs suggested

- 1980s – small studies of folic acid supplementation in pregnant women appeared to decrease NTD risk
History

- **MRC Vitamin Study – 1991**
  - International, multicenter trial
  - 1817 high risk women (previous child with NTD)
  - 4 treatment groups
    - Folic acid only
    - Other vitamins only (A, D, B1, B2, B6, C, nicotinamide)
    - Folic acid + other vitamins (both)
    - Placebo (neither)
History

• MRC Vitamin Study Conclusions
  – Decrease in NTDs in two groups treated with folic acid
  – 72% of NTDs were prevented with treatment
  – Recommended supplementation for high risk women
  – Normal risk women thought to benefit from supplements as well
History

• 1992 - US Public Health Service recommended that all women of childbearing age ingest 400 μg folic acid daily

• January 1, 1998 – US FDA mandated grain fortification
  – 140 μg folic acid / 100 g grain
Current Recommendations

- Women of childbearing age - 400 μg/day
- High risk women - 4000 μg/day
- Use of supplements does not mean we do not need to screen for NTDs

Complete list at
http://www.cdc.gov/nccdppd/folicacid/cereals.html
Has fortification made a difference?

  - Spina bifida - 2,490
  - Anencephaly – 1,640
  - Total – 4,130
- Postfortification (1999-2000)
  - Spina bifida – 1,640
  - Anencephaly – 1,380
  - Total – 3,020
- Approximately 27% decline in NTDs

Has fortification made a difference?

- Boulet et al., 2008
  - Prevalence of neural tube defects per 10,000 births in US
  - Three time periods
    - 1999-2000
    - 2001-2002
    - 2003-2004
Has fortification made a difference?

<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Prevalence</td>
<td>5.98</td>
<td>5.37</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>3.51</td>
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<tr>
<td>Anencephaly</td>
<td>2.47</td>
<td>1.98</td>
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<tr>
<td>Hispanic</td>
<td>7.48</td>
<td>6.91</td>
</tr>
</tbody>
</table>

Has fortification made a difference?

  – Review of all live births and stillbirths in 7 Canadian provinces
  – Total number of births = 1,909,741
  – Found 46% decrease in NTD prevalence after fortification
Are we fortifying enough?

FIGURE. Percentage of wheat flour processed in roller mills that was fortified — worldwide and by World Health Organization (WHO) region, 2004 and 2007

2004 - 18%
2007 - 24%

CDC. Trends in wheat-flour fortification with folic acid and iron – worldwide, 2004 and 2007. MMWR. 57(1); 8-10.
Are we fortifying enough?

- Changes from 2004-2007 in fortification
  - Number of countries increased from 33 to 54
  - 540 million additional persons had access to fortified flour in 2007

CDC. Trends in wheat-flour fortification with folic acid and iron – worldwide, 2004 and 2007. MMWR. 57(1); 8-10.
Are women using supplements?

• CDC national study, 2007
  – Surveyed 2,003 women 18-45 years
  – 40% of all women using folic acid supplement
  – Non-Caucasian women had lower rates of supplement use

Are women using supplements?

• Women 18-24 years (1/3 of all births in US, most unplanned pregnancies)
  – Aware of need for folic acid use – 61%
  – Know when to take folic acid – 6%
  – Use daily folic acid supplement – 30%
  – Lowest awareness, knowledge and use of all age subgroups in survey

Inequalities in folic acid use

• Bentley et al., 2006
  – Consumption of folate by age and race
  – 15-44 year old women consuming \( \geq 400 \, \mu g/d \)
    • Whites - 39%
    • Blacks - 26%
    • Hispanics – 28%
Inequalities in NTD prevalence

• Grewal J et al., 2008
  – Frequency of NTD in low socio-economic status individuals and neighborhoods
    • About 2-fold increased risk in mothers with less than high school education

• Increased prevalence in Hispanics, as mentioned previously
Is flour fortification cost effective?

• Yes!
  – Annual cost to fortify approximately $3 million
  – Estimated annual economic benefit in US $425 million
  – Bottom line- although there are costs to fortify, they are less than the costs to care for patients with NTDs

What are some areas for future research?
Future Directions

- Is fortification sufficient to prevent folate-related NTDs?
- Do we need to add a higher level of folate to the food supply?
- What role, if any, does Vitamin B12 play?
Disclaimer

• The following represents some interesting new research
  – Not yet definitive!

• To all women of childbearing age in the audience:
  – Please keep taking your folic acid supplements!
Do women still need supplements?

• Mosley et al., 2009
  – No decrease in NTDs in patients using folic acid supplement compared with non-users
  – Reported use of supplements similar between NTD affected and unaffected pregnancies
  – Have we prevented all folate-related NTDs with fortification?
Arguments for more folic acid in flour

• Some claim that the reduction we have seen in NTDs since fortification is not as great as theoretically possible reduction
• Would increasing fortification to 350 μg/100g grain prevent more NTDs?
• Would it be harmful to ingest a higher dose of folic acid?
Vitamin B12

- Molloy et al., 2009
  - Low vitamin B12 level is an independent risk factor for NTD
  - Also seems to have additive effect with folate
    - Women with low B12 and folate had higher risk of NTDs than low level of either alone
  - More work remains
    - Is B12 fortification safe?
    - What dose is needed to offer adequate risk reduction?
Conclusions

• NTDs result from failure of the neural tube to close during development
• Maternal serum AFP + follow-up testing allows us to screen for NTDs
• Folic acid fortification and supplementation can reduce the number of NTDs
• Further work remains to discover how folic acid prevents NTDs, best dose of folic acid, role of B12, and how to eliminate inequalities
Folic Acid

What Should You Know?
If a woman has enough folic acid in her body before and during pregnancy, it can help prevent major birth defects of the baby's brain and spine. Women need 400 micrograms (mcg) of folic acid every day.

More folic acid facts »

Information For...
Healthcare Providers
Partners
Media
Policy Makers

Data and Statistics

Use of Supplements Containing Folic Acid Among Women of Childbearing Age—United States, 2007

More Data and Statistics »

Popular Links

Test Your Knowledge
How much do you know about folic acid?

Listen to This Podcast
Folic Acid: Helping to Ensure a Healthy Pregnancy

Pregnancy Information
Learn how to be healthy before, during, and after pregnancy.
Acknowledgements

• Wanda Kern
• Danielle LaGrave
• Dr. Ed Ashwood
• Dr. Patricia Slev
• Dr. Alan Rockwood
• Jeanne Panlener
References

• Ashwood ER. “Maternal Serum Screening.” Lecture, 7/9/07.
• CDC. Trends in wheat-flour fortification with folic acid and iron – worldwide, 2004 and 2007. *MMWR*. 57(1); 8-10.
References