Epidemiology of Microcephaly in Brazil

Workshop
March, 2016
A new congenital syndrome? Zika virus infection?

- Clusters of new phenotype of neonatal syndrome
- Timeline
- Microcephaly
  - Causality, Correlation vs Coincidence
- Ongoing studies
  - Case control
  - Cohort studies
History of disease reporting in the US
Medical mystery with a global reach ...
Search to Explain Birth Defects in Brazil Led to Zika Virus

Primary Microcephaly-causes

Causes
Genetic
Environmental
  Toxic exposures
  Foetal alcohol syndrome
Radiation
Clinical/Infections

TORCH Infections:
Toxoplasmosis,
Other (Syphilis, Varicella-zoster,
  Parvovirus B19),
Rubella,
Cytomegalovirus (CMV), and
Herpes infections.

Calcifications suggest infectious origin
Microcephaly

Definition
• Reduced head circumference of <32 cm
• Morphological abnormalities

Known Causes
Genetic
Toxic-Metabolic
Including Fetal Alcohol Syndrome
Environmental
Infectious

Congenital infection?
• Cerebral abnormalities (dysgenesis, calcifications)
• High number of microcephaly cases within few weeks/short time
• Geographical spread
• Cluster
≠ transmission mechanisms of ToRCHes (Toxoplasmosis, Rubeola, CMV, Herpes, Syphilis)

Arboviruses?
• Dengue
• Chikungunya
• Zika???

Perinatal transmission → neonatal infection?
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1947</td>
<td>Zika virus isolated in a Rhesus monkey at Zika forest in Uganda.</td>
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<td>Arbovirus - Flavivirus family.</td>
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<td>1952</td>
<td>First human case of Zika</td>
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<td>1960</td>
<td>Sporadic human cases in Asia and Africa</td>
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<td>2007</td>
<td>First outbreak in Micronesia/ Pacific, with Exanthema, conjunctivitis</td>
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<td>and arthralgia</td>
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<td>2013-14</td>
<td>Outbreaks in French Polynesia, associated with cases of Guillan</td>
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<td></td>
<td>Barré syndrome</td>
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Zika virus: following Dengue and Chikungunya?

Emergence 2005–15

The Lancet. Volume 386, Issue 9990, Pages 243-244 (July 2015)
DOI: 10.1016/S0140-6736(15)61273-9
Pubmed: ‘Dengue’ vs ‘Zika’ (past 10 yrs)
Global research priorities for infections that affect the nervous system

Chandy C. John¹, Hélène Carabin², Silvia M. Montano³, Paul Bangirana⁴, Joseph R. Zunt⁵ & Phillip K. Peterson⁶

Nature. 2015 Nov 19;527(7578):S178-86. doi: 10.1038/nature16033
Timeline – microcephaly in live births in Metropolitan Recife, 2015

2015

Aug – Sep
Increased awareness of neonates with microcephaly

October
SES-PE receives notifications from doctors
Picture suggestive of congenital infection
Beginning of investigation of SES-PE\(^1\), SVS/MS\(^2\) and OPAS

11\(^{th}\) November
Declaration of National Public Health Emergency

1\(^{st}\) February 2016
Public Health Emergency of International Concern (PHEIC)
WHO

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\(^1\) Health Secretary of Pernambuco State
\(^2\) Health Surveillance Secretary of the Ministry of Health
\(^3\) Pan-American Health Organization (PAHO)
Rapid communication

Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014

3 mothers with their children RT-PCR positive

www.eurosurveillance.org

Article published: 3 April 2014, Besnard et al
Evidence

- Increase in occurrence of suspected cases of infectious microcephaly
- Period of major Zika circulation in the North-East corresponded to first gestational months of the women
- Nervous system alteration of the children, compatible with infectious disease
- Neurotropism of Zika virus and other Flaviviruses in literature
- Virus detection in amniotic fluid of pregnant women and one still birth
Distribution of notifications of suspected cases of microcephaly in Brazil - Feb 13, 2016

By The New York Times | Source: Brazil's Ministry of Health
Microcephaly in live births – Pernambuco State, 1/08/2015 - 12/12/2015
Microcephaly in live births –
Pernambuco State, 1/08/2015 – 12/12/2015
Spatial distribution of suspected microcephaly in Pernambuco State, November 2015
ZIKV neurotropism:
• ZIKV crosses blood-brain barrier - intraperitoneally injected mice: Dick, 1952
• Progression of disease in directly infected mice brains: Bell, 1972

ZIKV cell pathomechanism - autophagy:
• Autophagy: cell-protective mechanism against unwanted material, but:
  • ZIKV “hijacks” for viral replication➔“Virus factories” intracytoplasmatic inclusions

Pathogenesis of microcephaly – centrosomes:
• Abnormal function & amplification of centrosomes
  (mitosis, regulatory functions, vesicle trafficking): Thornton, 2009; Marthiens, 2013

➔ Microcephaly in fetal ZIKV infection due to ?link autophagy & centromes

Tetro JA. Zika and microcephaly: causation, correlation, or coincidence? Microbes and Infection, Institut Pasteur, 2016, p 1-2.
Projects by Microcephaly Epidemic Research Group (MERIC)

Case series

Case-control

Cohort

Pregnant women with rash

Neonates with congenital abnormalities

Research
# Publications of MERG – online shortly

<table>
<thead>
<tr>
<th>Title</th>
<th>Journal/Publication Details</th>
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<tr>
<td>Microcephaly in Pernambuco State – Epidemiological characteristics</td>
<td>Cadernos de Saude Publica (Reports in Public Health), 2016 (accepted)</td>
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<td>and evaluation of diagnostic criteria</td>
<td></td>
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<tr>
<td>Head computed tomography findings in infants with congenital microcephaly due to prenatal Zika virus infection</td>
<td>Submitted 2016 (under review)</td>
</tr>
<tr>
<td>The epidemic of Microcephaly in Brazil: description of 104 cases, 2016</td>
<td>Submitted, 2016 (under review)</td>
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Acknowledgments

MERG Team

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Mother-Child Institute Pernambuco (IMIP) and other state and municipal hospitals
Ministry of Health, Brazil
Pan-American Health Organization, Brazil
PAHO, Washington
Epidemiology and Population Health, London
School of Hygiene & Tropical Medicine, London

MERG Protocols (other publications & updates soon…)
http://scf.cpqam.fiocruz.br/merg/index.php/documentos/3-protocolos
Tetro JA. Zika and microcephaly: causation, correlation, or coincidence? Microbes and Infection, Institut Pasteur, 2016, p 1-2.