Appendix

Infectious causes of microcephaly: Epidemiology, Pathogenesis, Diagnosis, and Management


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Supplementary Table 1. Clinical features of the major congenital infections

<table>
<thead>
<tr>
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<th>CMV</th>
<th>HSV</th>
<th>Rubella</th>
<th><em>T. gondii</em></th>
<th>ZIKV</th>
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<tr>
<td><strong>Overall</strong></td>
<td>12.7% symptomatic at birth</td>
<td>16-58% long term sequelae</td>
<td>10-15% of initially asymptomatic develop</td>
<td>90% have defects if infection occurs in the first 10 weeks of pregnancy</td>
<td>24% of live born infected infants symptomatic at birth</td>
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<td>10-15% of initially asymptomatic develop neurological sequelae</td>
<td>Only 5% of cases of neonatal HSV are attributable to <em>in utero</em> transmission</td>
<td>27-42% of congenital rubella syndrome</td>
<td>24% of live born infected infants symptomatic at birth</td>
<td>Congenital infection estimated as 29% in a preliminary analysis of a cohort in Brazil</td>
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<td>12% of initially asymptomatic develop SNHL</td>
<td>90% have defects if infection occurs in the first 10 weeks of pregnancy</td>
<td>5-10% of symptomatic cases</td>
<td>Currently uncertain risk. Modelling based on data from French Polynesia estimated a risk of 1% (95% CI 0.3, 1.9%) infected the first trimester developed microcephaly.</td>
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<td><strong>Microcephaly</strong></td>
<td>35% of symptomatic children with congenital CMV identified through screening</td>
<td>16% of cases of <em>in utero</em> transmission</td>
<td>27-42% of congenital rubella syndrome</td>
<td>5-10% of symptomatic cases</td>
<td>Currently uncertain risk. Modelling based on data from French Polynesia estimated a risk of 1% (95% CI 0.3, 1.9%) infected the first trimester developed microcephaly.</td>
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<td>Central nervous system findings</td>
<td>71% of symptomatic children identified through screening CT abnormal and 48% had calcification. Lissencephaly and polygyria also reported.</td>
<td>Calcification in up to 30% of cases of in utero transmission. Other structural abnormalities including porencephaly, ventriculomegaly also described.</td>
<td>Evidence from case series: subcortical anterior temporal cysts, periventricular and basal ganglia calcification and white matter hyperintensities in the periventricular and subcortical regions.</td>
<td>13% intracranial abnormality (calcification, ventricular dilatation), higher rates the earlier infection occurs in pregnancy.</td>
<td>Case studies of 23 infants with microcephaly show that all had calcifications in the cortical-subcortical junction and a range of other malformations including cortical gyral abnormalities (pachygyria, polymicrogyria and lissencephaly), brain stem abnormalities, ventriculomegaly, and myelination changes. Hypertonicity, hyperreflexia.</td>
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<td>Skin and musculoskeletal</td>
<td>Petechiae 55%, purpura 3% of symptomatic children identified through screening.</td>
<td>95% of cases of in utero transmission have skin lesions, 17% have limb and bone abnormalities.</td>
<td>Purpura 17%</td>
<td>Up to 25% have a rash. Skin findings may include petechiae, ecchymoses, purpura, and blue-red &quot;blueberry muffin&quot; lesions.</td>
<td>Arthrogryposis No skin lesions reported but excessive scalp skin noted.</td>
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<td>Eyes</td>
<td>Visual impairment 22-58% of symptomatic children identified through screening. Chorioretinitis in 9% of symptomatic children identified through screening.</td>
<td>39% of cases of in utero transmission have ophthalmologic abnormalities.</td>
<td>78% ocular involvement (pigmentary retinopathy, cataracts, microphthalmia) and 86% visual loss. 25% cataracts, 5% retinopathy.</td>
<td>18% ocular involvement (retinochoroiditis, microphthalmia). Can develop as a late manifestation throughout childhood and adolescence.</td>
<td>A study of 29 infants with microcephaly showed ocular abnormalities were present in 35%: focal pigment mottling of the retina and chorioretinal atrophy, optic nerve abnormalities, iris.</td>
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<td>Haematology</td>
<td>Thrombocytopenia 38% of symptomatic children identified through screening</td>
<td>No data available</td>
<td>Thrombocytopenia is reported to occur</td>
<td>Thrombocytopenia up to 40%</td>
<td>Not known</td>
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<td>Neurodisability</td>
<td>Cognitive defects 35% of symptomatic 2 Neurological sequelae (inc SNHL in 35-45% symptomatic 29) 6·5% of asymptomatic develop cognitive/ neurological impairment 1 25% IQ &lt;70, 16% motor deficit in symptomatic children identified through screening 7 Normal development at 1 year predicts normal neurological outcome 30,31</td>
<td>Minimal data, High rate of developmental delay when reported in surviving children 8</td>
<td>62% psychomotor retardation 13-41% mental retardation 9,11</td>
<td>Difficult to estimate as early fetal infection often results in termination where available. Modern case series involving treated children demonstrate very good neurodevelopmental outcomes with low risk of serious neurological sequelae 32 Higher rates of severe neurological outcome have been reported in other series 33</td>
<td>Suspected seizures and swallowing difficulty 34 Developmental delays 14</td>
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<td>Hearing loss</td>
<td>SNHL 35% of symptomatic, 36% of symptomatic through screening 17 SNHL in 7-10% asymptomatic 2 In developed countries 21% SNHL at birth, 24% at 4 years.</td>
<td>Rare reports of SNHL 35</td>
<td>Hearing loss is common in congenital rubella syndrome and is the most common single defect. Estimates range from 60-95% 9-11</td>
<td>Very rare in modern case series Up to 10% in historic series 12</td>
<td>SNHL. One study showed 4 out of 69 (5.8%) infants with ZIKV related microcephaly had hearing loss. 36</td>
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<td>Cardiac</td>
<td>Not commonly reported</td>
<td>Not commonly reported</td>
<td>Estimates vary from 45-66%, Main cardiac defects are patent ductus arteriosus and pulmonary stenosis 9-11</td>
<td>Extensive heart calcification may occur</td>
<td>Cardiac dysautonomia has been reported 37</td>
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<td>Liver</td>
<td>Jaundice in 40%, hepatosplenomegally in 17%, Transaminitis 55% of symptomatic children identified through screening 7</td>
<td>28% of cases of in utero transmission have liver impairment 8</td>
<td>Hepatosplenomegaly 19% 11</td>
<td>Can lead to hepatomegaly and cholestatic jaundice and occasionally liver calcifications</td>
<td>Hepatomegaly not reported 25</td>
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<td>Death</td>
<td>4% of symptomatic 2 0-5% of all infections identified through screening 1</td>
<td>45% of cases of in utero transmission 8</td>
<td>3-4% if infected in the first trimester 4</td>
<td>Rare in modern case series – mainly therapeutic termination (&lt;2%) 5,33</td>
<td>Unknown but fetal deaths have been reported 38,39</td>
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SNHL: Sensorineural hearing loss

References