Pathogenesis of Rubella and Congenital Rubella

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Pathogenesis of Primary Infection

- Spread by droplet from URT (7 d before – 7-10 d after onset of rash).
- High concs of virus.
- Incubation period 14 days (range 12-21)
- Virus replication in buccal mucosa and lymphoid tissue.
- Spread via lymphatic system leading to viraemia and systemic infection.
Relation between clinical and virological features of postnatally acquired rubella.
Rubella rash
Rubella rash

• First on face and spreads down
• Maculo-papular, lesions may coalesce.
• Usually lasts $\leq 3$ days and may be fleeting.
• Pinpoint enanthem on soft palate sometimes
Pathogenesis of rubella rash

• Not fully understood.
• Rubella virus (RV) is present in the skin.
• Immune mechanisms may be responsible.
Joint symptoms (1)

- Most common in post-pubertal females (≤ 70%)
- Arthralgia or arthritis for 3-4 days, occasionally up to 1 month.
- RV may persist in the synovium.
- RV antibodies detected in synovial fluid.
- Immune complexes may be responsible (CIC in serum from vaccinees).
Joint symptoms (2)

• Hormonal factors – high incidence in females and assoc with menstrual cycle.
• No convincing evidence for association with chronic joint disease.
Immune responses

- IgG and IgM used for diagnosis.
- IgG (predom IgG1), IgM, IgA and sec IgA.
- CMI – lymphoproliferative responses a few days after rash. Mixed Th1/Th2 response.
- Mild, transient immunosuppression.
Child with a Congenital Rubella Cataract

- This child is 9 months old.
- A cataract in the other eye was surgically removed.
- Cataracts may develop following maternal rubella in 1st 12 weeks of pregnancy.
• Thrombocytopenic purpura in congenital rubella.
(1964, USA. From Banatvala & Best).
Some Common Manifestations of Congenital Rubella (1)

Permanent
- Cataract
- Retinopathy
- Sensorineural deafness
- Heart defects
- Microphthalmia
- Microcephaly

Transient
- Low birth weight
- Hepatosplenomegaly
- Meningoencephalitis
- Thrombocytopenic purpura
- Bone lesions
Some Common Manifestations of Congenital Rubella (2)

- Developmental
- Sensorineural deafness
- Peripheral pulmonary stenosis
- Mental retardation
- Central language defects
- Diabetes mellitus
Pathogenesis of Congenital Rubella

• Most damage is during the period of organogenesis.
• Persistence of RV → delayed manifestations
Histological studies
(Töndury & Smith 1966)

- Foci of damage in the chorion, desquamated cells enter the fetal circulation.
- Damage to endothelial cells → haemorrhages → tissue necrosis.
- Obstructive lesions in arteries.
- Tissue necrosis
- No inflammatory response
# Congenitally-acquired Rubella Persistence of Virus

<table>
<thead>
<tr>
<th>Site</th>
<th>Age (yrs)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Lens</td>
<td>3</td>
<td>Menser et al. 1967</td>
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<tr>
<td>Thyroid*</td>
<td>5</td>
<td>Ziring et al. 1977</td>
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<tr>
<td>Brain†</td>
<td>12</td>
<td>Weil et al. 1975</td>
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<td>Cremer et al. 1975</td>
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* Hashimoto’s disease
† Cases of panencephalitis
Congenital rubella: immune responses

- Impairment of CMI responses – allows clones of RV to persist.
- Specific IgG, IgA and IgM are produced, but antibody titres may fall rapidly in some affected children.
- May lack antibodies to C, have weak response to E2 and weak response to E1 compared with adults.
- T-cell lines fail to respond to certain RV E1 peptides.
- Suggests selective immune tolerance to E1.
RV-induced changes observed in cell cultures (1)

• Retardation in cell division – mitotic inhibition – may be due to disruption of actin filaments (cytoskeleton).

• Apoptosis
Rubella Virus CPE in RK13 Cells is due to Apoptosis.
Pathogenesis of Congenital Rubella

- Apoptosis of essential cells.
- No apoptosis in fetal fibroblasts, may allow RV to persist.
RV-induced changes observed in cell cultures (2)

- RV may disrupt normal cell growth: NSP p90 interacts with pRB & pCK.
- Disturbance of signalling pathways that control cell differentiation, proliferation and survival.
- RV replication may be limited by interferon &/or DI RNAs.
CRS and IDDM (1)

- RV isolated from pancreas of infants with CRS.
- RV-induced damage to islet cells, but not cytolytic.
- Depression of immunoreactive secreted insulin.
- RV capsid shares epitopes with β-cell protein.
- Autoantibodies to islet cells in 20% patients in 2\textsuperscript{nd} decade.
- Genetic susceptibility (↑ HLA DR3 ↓ DR2).
Conclusions

• IDDM may be caused by an autoimmune reaction or direct damage caused by persisting virus.

• The mechanisms by which RV interferes with normal cell growth are of considerable interest.

• More research is required to elucidate the mechanisms by which RV causes fetal damage.
Rubella

Cell mediated immune responses (1)

- Decrease in total leucocytes, neutrophils and T cells.
- Transient depression of lymphocyte responsiveness and DTH to mitogens and antigens.
- Specific lymphoproliferative responses develop rapidly and persist for many years.
Rubella

Cell mediated immune responses (2)

- Proliferative responses in adults are influenced by selected HLA-DR antigens.
- CD4+ MHC class II restricted and CD8+ class I restricted T-cell responses are observed.
Interference with the cell cycle

• NSP P90 interacts with pRB and pCK.
• pRB, retinoblastoma protein is a cell cycle regulatory protein.
• pCK, citron-K kinase protein, a cytokinesis regulatory protein.
Cell survival signaling pathways

- Studies in RK13 cells.
- Inhibition of PI3K-Akt signaling reduced cell viability and increased Rv apoptosis.
- Inhibition of Ras-Raf-MEK-ERK pathway impaired RV replication and growth.