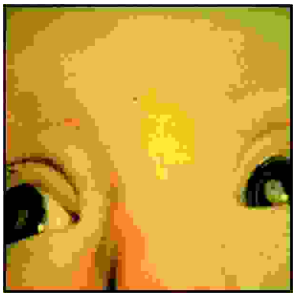
REVIEW PROF-987

CONGENITAL RUBELLA SYNDROME



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ABSTRACT... nageen1704@hotmail.com Rubella is a major public health problem which is usually a mild rash illness in children and adults. However, its seriousness and public health importance stems from the ability of Rubella virus to cross the placental barrier and infect fetal tissue, which may result in congenital rubella syndrome. The mechanism by which Rubella virus causes fetal damage is not well understood. Congenital rubella syndrome is an under-recognized public health problem in Pakistan and can be reduced by vaccinating all seronegative women.

INTRODUCTION

Rubella is a mild exanthematous, and moderately contagious disease caused by Rubella virus, which is the sole member of the Rubivirus genus of the Togavirus family. The only known hosts for Rubella virus are humans and only one serotype has been identified[1]. The word Rubella means “little red”. Rubella is commonly called German measles or 3-day measles and it is the third of the six viral exanthems of childhood[2]. The name most likely comes from the Latin term germanus meaning "similar" and indeed, rubella and measles share some characteristics, but they are caused by different viruses[3,4].

In 1752 and 1758, the German physicians de Bergen and Orlow first described rubella as unique entity who called it Rothëlin, however, they considered it to be a modified form of measles or scarlet fever. In 1866, Henry Veale introduced the name “Rubella”, believing that the name of a disease should be short for the sake of convenience in writing and euphonious for ease in pronunciation[5]. Rubella was thought to be a benign disease until 1941, when the Australian ophthalmologist Norman McAlister Gregg first described the congenital defects of infants of mothers who had developed rubella early in pregnancy[5,6]. The increasing recognition of congenital rubella syndrome during and after the pandemic of 1962 to 1965 emphasized the need for the development of an efficacious vaccine. In 1969, three strains of live attenuated rubella vaccines were licensed in various countries but RA27/3 vaccine has been used exclusively in the United States.

TERATOGENICITY

Rubella virus can also act as a teratogen, inducing Congenital Rubella Syndrome when spread from mother to fetus in the first trimester of pregnancy. Teratogens are non-genetic factors that interfere with normal embryonic, fetal differention and morphogenesis. They are not mutagens. The effects of teratogens are the congenital defects[4].

Cellular damage seen during early gestation of Rubella virus-infected fetuses is unlikely to involve the immune system, since no fetal immune response can be detected at this early stage. Although the presence of immunoglobulin such as immunoglobulins IgM, IgG, and IgA, T cells, natural killer cells, and interferon can be detected by mid-gestation in infected fetuses, the extent to which they limit or contribute to further fetal damage has yet to be determined[3].

PATHOGENICITY

Rubella occurs worldwide with a seasonal distribution[1]. The peak incidence of infection is in late winter or early spring[3]. Rubella virus enters the cell via endocytic pathway[1]. Rubella viral replication continues in localized areas of the nasopharynx and regional lymph nodes for 7-9 days and is followed by viremic spread to multiple sites throughout the body. Maximal viremia and viruria occur 10 to 17 days after infection, and heavy viral shedding from the nasopharynx continues from 10 to 24 days postexposure. Rash develops 16-18 days after infection and at the same time antibody begins to be detected (Figure-I)[6]. Incubation period varies from 14-21 days. There are three distinctive features of Rubella virus replication, which may impact on normal host cell function, notably, mitochondrial abnormalities, disruption of the host cell cytoskeleton and more recent work has investigated the ability of Rubella virus to induce apoptosis[4,5].

In a pregnant female, viremia may result in infection of the developing fetus and infection can occur by invasion of the fetal tissue. Infected circulating cells such as monocytes may enter the fetal blood stream directly[6].

Vertical transmission may occur during gestation, when virus crosses the placenta, during birth or by passage of virus from mother to child in breast milk or through close contact[3]. Development of congenital rubella infection probably depends upon gestational age (Table-I)[1]. Miscarriages and still births are also common among women who get rubella while they are pregnant[1,5,6].

Fig-I

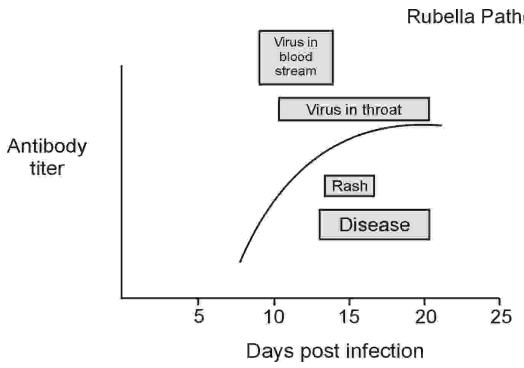

Table-I Incidence of defects in rubella infection is closely linked to stage of pregnancy when the infection is acquired.

Stage of pregnancy	Incidence of defects
1-12 month	40-60%
3 months	30-35%
4 months	10%
5 months	6%
6 months or onwards	Very low

There is no true carrier state of rubella but infants infected with rubella before birth often shed the virus for as long as 12 months after birth, or, rarely, longer[3]. In Colombo South Teaching Hospital, during the period of February 1999 to February 2001, of the 500 antenatal blood samples 82% were positive for rubella specific IgG. 373(75%) women gave a history of vaccination against rubella before their present pregnancy. Out of 127 unvaccinated women, 12(9%) gave a history of past infection with rubella and of this 3(25%) were seronegative for rubella specific IgG. 18% of pregnant women at 16 weeks of gestation were at risk of giving birth to a baby with congenital rubella syndrome[7].

CLINICAL FEATURES

Transient sequelae include many of the transient clinical manifestations of congenital rubella were recognized during the large pandemic of 1962 to 1965[5]. These manifestations resolve over a period of weeks. They include dermal erythema ("blueberry muffin rash"), chronic rash, thrombocytopenic purpura, hemolytic anemia, generalized lymph-adenopathy, interstitial pneumonitis, hepatitis, hepatosplenomegaly, nephritis, myositis, myocarditis, bone radiolucencies and meningoencephalitis. Among the more common of these findings are rash, hepatosplenomegaly, jaundice, pulmonary involvement, meningoencephalitis and radiographic abnormalities. The majority of such infants are intrauterine growth restricted at delivery[8].

Permanent manifestations include sensorineural hearing loss is the most common permanent manifestation of congenital rubella, with deafness occurring in 80% of congenitally infected patients. Additional permanent sequelae of congenital rubella include cardiovascular anomalies, ophthalmologic findings, and neurological impairment.

Structural defects of the cardiovascular system occur in the majority of infants whose mother acquired rubella during the first two months of gestation[8]. Patent ductus arteriosus is the most common of these cardiovascular sequelae, followed by pulmonary artery stenosis and pulmonary valvular stenosis (Figure-II)[9].

Ophthalmologic findings include cataracts, retinopathy, and microphthalmia. The retinopathy results from pigmentary defects in the retina and usually does not interfere with vision. In contrast, a small number of patients have congenital glaucoma, which, if undetected, can result in visual impairment[10].

Permanent neurologic impairment can result from the active replication of *Rubella virus* in the CNS both in utero and following delivery. Indeed, neurologic sequelae such as mental retardation and motor disabilities correlate with the severity and persistence of the acute meningoencephalitis that is present at delivery in 10 to 20% of infants with CRS. Movement and behavioral disorders can also been seen in surviving patients[8,11].

Delayed manifestations include sequelae of congenital rubella that develop in childhood or adulthood but are not present in infancy include endocrinopathies, deafness, ocular damage, vascular effects, and progressive panencephalitis. Of these, the development of insulin-dependent diabetes mellitus occurs most frequently, with approximately 20% of patients being diagnosed by the time they reach adulthood. Autoimmune-mediated thyroid dysfunction can also be seen[8].

Fig-II

Rubella syndrome

Microcephaly PDA Cataracts

HISTOPATHOLOGY

Direct cellular destruction by Rubella virus accounts for some of the tissue damage seen in congenital rubella syndrome[1]. Vascular injury and resulting insufficiency are more important in the pathogenesis of congenital defects. In addition, Rubella virus infection in vitro disrupts actin microfilaments and mitotic arrest has been demonstrated in vivo. Such disruption and arrest may account for the decreased number of cells in many organs of congenitally infected infants, resulting in their generalized intrauterine growth restriction[3].

In general, affected organs are hypoplastic, cellular and tissue necrosis can also be demonstrated in affected organs. The pathological findings of the placenta include edema, fibrosis, and necrosis of the villi resulting in small placenta[3]. Examination of Rubella virus- induced cataractous eye lenses from first trimester fetuses revealed pyknotic nuclei, cytoplasmic vacuoles and inclusion bodies in primary lens cells. Lens is the

predominant site of necrosis and lens development is found to be retarded; iris and retina can also be affected. Cataract is responsible for about 10% blindness among children in India. Similarly, examination of Rubella virus infected fetuses' revealed cellular damage to the epithelium of the cochlear duct[10].

Viral meningoencephalitis is occasionally caused by rubella. Neurological damage is caused by direct invasion and destruction of neural tissues by actively multiplying viruses or by a host reaction to viral antigens[12]. The CSF contains from a few to several thousand cells per cubic millimeter, protein concentration tends to be normal, and there is absence of microorganisms on gram stain and routine bacterial culture.

Progressive rubella panencephalitis is a rare form of chronic encephalitis associated with persistent Rubella virus infection of the brain. This was first recognized in 1974[5]. There are insidious changes in behavior and deteriorating school performance. Subsequently frank dementia, seizures, cerebral ataxia and spastic weakness. Furthermore, there is progression to coma, spasticity, brain stem involvement and death in 2-5 years. Such patients pose no substantial risk of infection to others[8,12].

HOST DEFENCES

In maternal rubella infection, transplacental transfer of maternal IgG is minimal during the first half of pregnancy but increases considerably beginning around 16 to 20 weeks gestation[3]. As a consequence, until the middle of the second trimester, the amount of maternal rubella specific IgG present in fetal circulation is only 5 to 10% of that present in the maternal circulation. At the same time, the transplacental transport of rubella specific IgG is increasing at mid gestation, the fetal humoral system is beginning to produce detectable quantities of fetal immunoglobulin[12,13]. The predominant class of fetal antibody produced in the latter half of pregnancy is IgM, although fetal IgG and IgA are also produced. Nevertheless, rubella specific IgG is more abundant overall, due to the combined amounts of both maternal and fetal antibody of this class. As the concentrations of maternal IgG decline following birth, rubella specific IgM will predominate for a period of several months before declining to levels that are lower than those of the increasing neonatal IgG. Virtually, all congenitally infected infants have detectable IgM during 3-6 months of life; and about one-third have detectable IgM from 6 months to 2 years of age. Over that first several years of life, the amounts of rubella specific IgG can decrease and some children can lose detectable IgG altogether. Low avidity IgG can persist even after disappearance of Rubella virus specific IgM[14].

Rubella virus specific cell mediated immune responses in infants with congenital rubella are diminished, compared to those in children following post natally acquired disease. Additionally, abnormal delayed-type hypersensitivity skin reactions can occur in congenitally infected persons[14].

LABORATORY DIAGNOSIS

Laboratory tests that can be performed for the diagnosis of rubella infection are [15,16]

* Viral cell cultures
* Enzyme Linked Immunosorbent Assay
* Latex Agglutination
* Hemagglutination Inhibition Test
* Immunofluorescent Assay
* Western blotting
* Complement Fixation
* Polymerase chain reaction
* Immunoblot

Prenatal diagnosis of rubella is of value when maternal infection occurs after first trimester[17.]

1) Isolation of virus from the amniotic fluid but the reliability of this technique has not yet been demonstrated[14,16].

2) Detection of Rubella virus RNA, protein in chorionic villus sampling and amniotic fluid has been currently demonstrated[16].

VACCINATION

Rubella vaccine dose is usually given in combination with the measles and mumps vaccines referred to as MMR, to decrease the cost and number of injections needed. MMR vaccination results in IgG antibody production in more than 98% of vaccine recipients. The child should not receive the first dose of MMR before 12 months of age. Before that, the baby still has some of its mother's antibodies, which can interfere with the vaccine and keep it from working (Table-II). Vaccination of teenage or adult groups in colleges, workplaces, hospitals (staff and volunteers) or military bases helps prevent outbreaks[18].

Table-II

Type of vaccine	Live attenuated viral vaccine
Number of doses	One given by the intra muscular or subcutaneous route as monovalent. MR or MMR
Schedule	9-11 months in countries where the disease is highly endemic, later in countries with high levels of control
Booster	Not required
Contraindications	Reaction to previous dose, pregnancy (in practice, rubella vaccine given inadvertently to pregnancy women has not resulted in abnormalities, indicating that termination would not be appropriate in such cases)
Adverse reactions	Malaise, fever, rash 5-12 days later, rarely arthritis, anaphylaxis
Special precautions	None

Susceptible women of childbearing age also should consider being vaccinated before traveling abroad, as rubella is widespread in many countries.[1,3,18]Postpubertal females who are not known to be immunized to rubella should be immunized. They should not receive the vaccine if they are pregnant, and they should be warned not to get pregnant within 3 months of vaccination. Breast feeding is not a contraindication to such immunization[18].

IMMUNIZATION POLICIES

In 1992, a study showed that in Abbasi Shaheed Hospital of Karachi, 355 pregnant women were tested for IgM and IgG type of antibodies by Enzyme immunoassay. Of 212 pregnant women with abortion, 39(18%) and 80(38%) were seropositive and of 143 pregnant women with normal reproductive performance, 7(5%) and 23 (16%) were positive for IgM and IgG respectively. Premarital screening and vaccination of seronegative girls are recommended to reduce morbidity and mortality related to Rubella virus[19]. In short, the observed frequency of rubella antibodies in Pakistan is higher than those reported from the other countries of the world. The reason is that MMR vaccine is available in Pakistan but the cost of this vaccine is relatively high. If we can provide these vaccinations in childhood then one can prevent the spread of diseases and often the death of small children due to this disease.

The World Health Organization regional office for Europe held a technical consultation on rubella surveillance issues in March 2003. Participants identified the following needs for applied research with regard to surveillance for CRS[20.]

1. Frequency, etiology and sensitivity of methods for detection of rash, fever in pregnancy need to be assessed[20].
2. Optimal methods (sensitivity and cost) need to be defined for identification of cases of CRS.
3. Optimal definitions to identify circulation of Rubella virus in the community are needed.
4. Ethical and legal implications of serologic testing for susceptibility to rubella in antenatal care

In September 2003, the 44th Directing Council of the Pan

American Health Organization adopted a goal to eliminate rubella and congenital rubella syndrome by 2010. One of the main objectives of this initiative is improving women's health, consistent with achieving the Millennium Development Goals[21].

TREATMENT

There is no antiviral therapy.[1] Patients with congenital rubella require supportive care not only in the neonatal period but also throughout life for such permanent impairments as deafness and heart defects[1,4]

Interferon and amantadine have been used in individual cases of CRS. Interferon has also been used in the treatment of chronic arthritis secondary to postnatal rubella infection, again with indeterminate results[19] Isoprinosine has been administered to patients with progressive rubella panencephalitis but has no apparent therapeutic benefit[11]

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