Congenital Rubella Infection and Hearing Loss

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9.1 Introduction

Rubella is generally mild, self-limited, and vaccine-preventable contagious viral infection, mainly affecting children aged 2–12 years. Rubella virus infection is specified with maculopapular rash, lymphadenopathy, and sometimes fever. Arthritis might accompany rubella, especially in women, but is observed less in men and children. Although rare, encephalitis can also develop during rubella infection, more commonly in adults [1].

Many postnatal rubella infections are subclinical and asymptomatic. However, pregnant women in their first trimester with rubella infection might experience miscarriage, stillbirth, and even congenital disabilities of the fetus, known as congenital rubella syndrome (CRS) [2].

Congenital rubella syndrome was first recognized in 1941 and could have various symptoms, such as mild to severe sensorineural hearing loss (SNHL), cataracts, mental retardation, and congenital heart disease [1, 3, 4]. During pregnancy,

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maternal rubella infection causes roughly 105,000 children to be born with CRS annually worldwide [5], a potentially fatal condition that could be prevented with vaccination. After reinfection, a few confirmed CRS cases have been observed, and this event is rarely teratogenic [4, 6].

In 1969, after the license of the rubella vaccine, rubella and congenital rubella cases decreased rapidly in countries employing national immunization programs. Nevertheless, CRS and rubella remain a significant public health threat in countries lacking rubella immunization programs worldwide [7].

9.2 Etiology

In 1962, Weller and Neva [8] and Parkman et al. found a positive-sense, enveloped, and single-stranded ribonucleic acid (RNA) virus called rubella virus [9, 10]. Rubella virus is considered in the Rubivirus genus the sole member within the Togavirus family. Only one serotype of the rubella virus has been recognized, and humans are the only identified reservoirs [7, 8].

Three structural polypeptides are observed in the rubella virüs; a single nonglycosylated core protein, C, surrounding the virion's RNA, and two envelope glycoproteins of E1 and E2. The rubella virus E1 prevailing exterior molecule is the primary target of the humoral reaction, and it is responsible for viral attachment, fusion, hemagglutination, and neutralization. The E2 glycoprotein is embedded into the envelope [7, 11].

9.3 Pathogenesis

The rubella virus enters the target cell by binding the E1 protein on its surface to the host cell's myelin oligodendrocyte glycoprotein (MOG), mainly identified in human central nervous system (CNS) cells and the placenta [12, 13]. The rubella virus is transmitted to the fetus by the placental route and infects all fetal organs. When a maternal infection develops in the first trimester of pregnancy, the risk of fetal defects is as high as 85–90%, as organogenesis occurs during this period [7]. The risk decreases to 50% with maternal infection at 13–16 weeks and 25% at 15–16 weeks [7]. Although fetal defect risk is infrequent in maternal infections that develop after the 16th week, hearing loss (HL) may develop with maternal infection as late as 20 weeks [7, 14]. Whether rubella reinfection during pregnancy is transmitted to the fetus is controversial [7, 14, 15].

The pathogenesis of congenital rubella infection remains unclear. A few studies demonstrated the histopathological changes related to the CRS in multiple organs. Cytopathic damage occurs in blood vessels, and ischemia develops in affected organs [16]. Noninflammatory necrosis was detected in infected fetuses' eye, ear, heart, brain, and liver structures [8, 17]. Lachrymal glands in the eye and the direct viral infection in epithelial cells of the ciliary body, pycnotic nuclei, inclusion bodies, and cytoplasmic vacuoles detected in primary lens cells could play an influential

role in developing cataracts [18]. Histopathological analysis of rubella virus-infected fetuses showed cellular damage in the cochlear duct and/or stria vascularis epithelium. These findings may explain the cause of deafness in CRS [17, 18].

Tropism of the rubella virus to the fetal endothelial cells was detected [19]. Vascular pathologies such as thrombosis and surrounding tissue necrosis in CRS result from persistent rubella virus infection of the endothelium [7, 19]. Vascular necrotic changes cause cellular destruction, leading to ischemic damage to the myocardium and brain [6, 17] and significant histopathological changes in the liver [18]. Necrotizing and inflammatory changes were presented in the liver of the infected fetus [18].

9.4 Epidemiology

Rubella was a more common disease before the rubella vaccine's global use, which occurs most often during spring, mainly among young children. Epidemics occur every 6–9 years, and large-scale epidemics arise for up to 30 years [1]. In the pre-vaccine era, in the United States of America (USA), 62 CRS and 57,600 rubella cases were reported every year [20]. The last major American epidemic occurred in 1964–1965. There was a report of 12.5 million rubella cases and approximately 20,000 CRS cases in this epidemic [1, 2]. After national vaccination campaigns in the USA, rubella incidence has decreased by more than 99% and declined by 86% worldwide [21]. After 2004, rubella and CRS elimination were declared from the USA [7, 22]. However, rubella is still commonly circulated in different parts of the world, and an estimated 100,000 infants are born with CRS yearly [7]. As a result of the failure to manage vaccination programs, large rubella outbreaks were reported in low- and middle-income countries such as Ethiopia, Oman, Uzbekistan, Romania, Argentina, Brazil, and some other Latin American countries [23].

In 2021, the World Health Organization (WHO) reported that the current rubella vaccine global coverage was 69%, with 90% in America, 95% in Europe, 45% in Eastern Mediterranea, 32% in Africa, 83% in South-East Asia, and 94% Western Pacific [5]. Twelve and a half million disability-adjusted life years (DALYs) and 131,000 deaths because of CRS could be prevented from 2001 to 2030 with expanded coverage for the rubella vaccine. Eighty-one of 194 (42%) member states in WHO regions confirmed eradicating rubella until September 2019 [5].

9.5 Clinical Manifestations of Congenital Rubella Syndrome

During pregnancy, and especially in the first trimester, CRS is the most severe consequence of rubella virus infection. Manifestations of CRS vary depending on the timing of maternal infection. The defect risk is quite high if maternal rubella infection develops in the first trimester. The risk is considerably reduced after 18–20 weeks of pregnancy [7, 24, 25].

Congenital rubella syndrome presents different manifestations during intrauterine, early (neonatal), and later periods. Congenital disabilities and death in the affected fetus and premature birth may develop. A literature review evaluating articles between 1991 and 2014 reported that 17 of 32 fetuses showed 56 various disabilities detected before labor [24]. Amniotic fluid anomalies (40%), cardiac malformation (34.3%), brain anomalies (12.5%), and ocular abnormalities (6.25%) were identified. Placentomegaly, hepatosplenomegaly, hyperechogenic bowel, ascites, short femur, micrognathia, hyperechogenic scrotal mass, and single umbilical artery were among the other ultrasound findings [24].

9.5.1 Early Manifestations

In 1970, abnormalities were reported in a systematic review of 1109 children having CRS [24]. Early manifestations of CRS include intrauterine growth retardation, low birth weight, blueberry muffin lesions, generalized lymphadenopathy, hepatosplenomegaly, hepatitis, jaundice, diarrhea, bleeding underneath the skin, hemolytic anemia, congenital heart disease, pneumonitis, meningoencephalitis, cataract, microphthalmia, retinopathy, bony radiolucencies, cryptorchidism, and inguinal hernia. Some manifestations may be temporary, while others may be permanent (Table 9.1) [1, 2, 26]. In a study following the 1964 rubella epidemic in the USA, 68% of newborns with CRS were subclinical, and 71% of subclinical patients developed clinical signs in the first 5 years [27].

9.5.2 Cardiac Defects

Patent ductus arteriosus (PDA), pulmonary valvular stenosis, pulmonary artery stenosis, pulmonary hypertension, coarctation of the aorta, aortic stenosis, atrial septal defect (ASD), and ventricular septal defect (VSD) are the cardiac defects detected in 38–70% of CRS patients [2]. The most common cardiac finding is PDA in newborns with CRS. In evaluating 36 children having CRS using echocardiography, PDA was found in 67%, ASD in 19%, pulmonary stenosis in 8%, VSD in 3%, and atrioventricular septal defect in 3% [28]. In another study evaluating more patients with CRS, similar to previous studies, the most frequently detected defect was PDA (87%), tricuspid regurgitation (65%), ASD/patent foramen ovale (50%), pulmonary hypertension (44%), mitral regurgitation (26%), pulmonary stenosis (23%), pulmonary regurgitation (15%), aortic stenosis (14%), VSD (9%), aortic regurgitation (7%), coarctation of the aorta (4%), and atrioventricular septal defect (1%) [2]. Affected newborns may also develop myocarditis, which can result in death. In addition to cardiac defects, vascular problems may also occur in children with CRS. Many vessels, such as coronary, cerebral, and peripheral arteries, with obstructive lesions were reported [29].

Table 9.1 Clinical manifestations of congenital rubella syndrome[a]

	Temporary	Permanent
General	Low birth weight	
Skin effects	Dermal erythropoiesis	Chronic rash
		Dimples
Ocular effects	Cloudy cornea	Cataracts
	Iridocyclitis	Microphthalmos
		Glaucoma
		Pigmentary retinopathy
		Hypoplasia of the iris
		Severe myopia
Auditory effects		Central hearing impairment
Cardiovascular effects	Myocarditis	Pulmonary arterial stenosis
		Aortic stenosis
		Coarctation of aorta
		Atrial/ventricular septal defects
		Patent ductus arteriosus
		Tetralogy of Fallot
		Pulmonary hypertension
Pulmonary effects	Interstitial pneumonitis	Interstitial pneumonitis
		Tracheoesophageal fistula
Gastrointestinal effects	Hepatosplenomegaly	
	Hepatitis	Duodenal stenosis
	Jaundice	Jejunal or rectal atresia
	Chronic diarrhea	
Central nervous system	Meningoencephalitis	Microcephaly
	Large anterior fontanel	Spastic diplegia
	Hyperirritability (tremors)	Brain calcification
	Seizures	Cerebral arterial stenosis
	Hypotonia	
Hematologic effects	Hemolytic anemia	
	Hypoplastic anemia	
	Thrombocytopenia with/without purpura	
Urogenital anomalies	Vesicoureteral reflux	Hypospadias
		Cryptorchidism
		Vesicoureteral reflux
		Inguinal hernia
Orthopedic effects	Radiolucent bone disease	Clubfoot
	Pathologic fractures	
	Myositis	
Immunologic effects		Thymic hypoplasia
		Asplenia

[a] Adapted and modified from Ref. [1, 2, 26]

9.5.3 Congenital Rubella Infection and Hearing Loss

The most characteristic manifestation of CRS is congenital SNHL due to disease, damage, and other causes impacting the inner ear (e.g., the cochlea) and the auditory nerve (eighth cranial nerve). Few histopathological studies examining the placenta have shown emboli in the placental vessels [7, 17]. This causes thrombosis and surrounding tissue necrosis that will affect the development of fetal organs. Cytopathic action, mitotic inhibition, and increased chromosomal breaks have been identified in congenitally infected human embryonic cells and fetuses [17]. Reduced cell numbers and hypoplasia may occur in infected organs [6].

Histopathological evaluations showed cellular damage in rubella virus-infected fetuses' cochlear duct and stria vascularis epithelium. These findings may explain the cause of HL in infants with CRS [14, 18].

Temporal bone studies have been performed to explain the HL that develops in CRS. Data on temporal bone pathology in infants with CRS were reported. Six sets of temporal bones were examined in Baltimore and Houston studies, and a cochleosaccular change was detected in most of the bones [17]. No pathological changes were reported in the utricle, spiral ganglia, or semicircular canals. The collapse of the sacculi and a few changes in the organ of Corti were observed in bones. Ward et al. [30] and Alford showed atrophy and destruction of the stria vascularis [17].

In studies, pathologies in the middle ear were also investigated to explain the cause of HL in CRS. Only moderate perivascular infiltration was recognized in the middle ear mucous membrane in a small number of bones [17]. However, there are still unanswered questions about the pathogenesis of HL related to CRS.

Hearing loss may be the only manifestation of CRS. Previous studies have reported that 66–90% of children with CRS have a hearing impairment after maternal infection in the 18th to 20th pregnancy weeks [2]. Although CRS-related HL is usually detected in early childhood, progressive hearing problems beginning in later years have also been reported [12].

Congenital rubella syndrome was reported as the cause in 32–41% of children with hearing impairment [31, 32]. The HL in CRS generally is bilateral (%61), and sensorineural but can be unilateral [26, 33]. The severity of HL in children with CRS ranges from mild to severe and may progress over time. Fifty-seven percent of infants with rubella virus isolated have SNHL; however, 41.5% of cases were confirmed serologically [34]. In a recent study from China, among 720 children with HL, CRS was detected as the cause in 42 (5.83%) [35].

In studies investigating the causes of HL after the widespread application of the rubella vaccine, rubella was found to be a significantly less common cause of SNHL. This result is related to the overall decline in rubella prevalence following universal childhood vaccination programs [36].

Hearing loss in children with CRS may be overlooked in infancy. Children with HL may be mistakenly evaluated as developmentally delayed. Furthermore, progressive hearing impairment beginning several years after birth may also develop [37]. Experiencing HL in the first years of life could lead to cognitive, language, speech, and developmental delays. Early diagnosis of SNHL due to CRS is the most

critical management aspect. Special rehabilitative measures and education programs prevent the development of weak language skills and speech delays. Otoacoustic emissions (OAEs) and automated brainstem auditory evoked responses (BAERs) should be tested in infants of mothers with rubella experienced during pregnancy at regular intervals until age 5 to assess HL [38].

9.5.4 Ophthalmological Manifestations

N. McAlister Gregg, an Australian ophthalmologist, first reported that maternal rubella infection could cause congenital disabilities [3]. Every part of the fetal eye is impacted via transmission of the rubella virus by the bloodstream and rarely lymphatic fluid [4]. The rubella virus may remain in the crystalline lens for more than one year [27]. Fifty-three to 78% of patients with CRS had ocular defects [2]. Cataracts, microphthalmia, pigmentary retinopathy, chorioretinitis, myopia, hyperopia, strabismus, and nystagmus are among the ocular findings found in newborns with CRS [2, 4, 24]. Ocular defects may progress postpartum.

Congenital rubella syndrome's most common ocular manifestation is "salt and pepper" pigmentary retinopathy. It is seen in 24–60% of cases with CRS [2]. Cataract, usually unilateral, is also a common sequela of CRS (17–63%) [2] due to partial arrest in cell development and lens maturation [4]. Microphthalmia, another frequently seen complication of CRS and often associated with cataracts, may be unilateral or bilateral [39].

9.5.5 Delayed Manifestations

Some delayed manifestations of CRS resulting from directly or indirectly damaging the embryo by the rubella virus occur later in life. Although the exact relationship between late-onset findings and CRS is not conclusively proven, endocrine, cardiovascular, ocular, neurological, and psychosocial problems have been observed as delayed manifestations among CRS children [40].

Delayed manifestations of CRS are summarized in Table 9.2 [1, 26, 40]. None of these delayed manifestations seen in patients with CRS are reported as the results of studies using control groups. Contrary, some studies concluded that CRS does not cause a higher risk for these diseases [40].

9.5.5.1 Endocrine Abnormalities

Diabetes, thyroid disorders, early menopause, osteoporosis, and possible growth hormone deficiency are endocrine problems as delayed manifestations of CRS. The relationship between endocrine problems and autoimmunity is vital in these patients. It is thought that diabetes develops in CRS patients due to damage to pancreatic cells by the rubella virus. In a study from Japan, diabetes prevalence was 1% in patients with CRS, higher than in Japanese society [40].

Table 9.2 Delayed manifestations of congenital rubella syndrome[a]

Auditory effects	Sensorineural hearing impairment
Ocular effects	Keratic precipitates Keratoconus Corneal hydrops Lens absorption
Endocrine effects	Diabetes mellitus Hypothyroidism Thyrotoxicosis Idiopathic hypothyroidism Hyperthyroidism Thyroiditis Growth hormone deficiency Addison's disease Early menopause Osteoporosis
Cardiovascular effects	Hypertension Mild aortic valve sclerosis
Neurological and psychosocial problems	Progressive rubella panencephalitis Learning disorder Psychomotor developmental delay Ataxia Cerebral palsy Psychosi Intellectual disability Autism spectrum disorder Behavior problems

[a] Adapted and modified from Ref. [1, 2, 40]

Hypothyroidism, hyperthyroidism, and thyroiditis are also seen in cases with CRS as delayed health issues. In a study of adolescents with CRS having HL, thyroid disorders were found in 19.6% [26]. Autoimmune mechanisms are considered effective in the pathogenesis of endocrine abnormalities.

Early menopause and osteoporosis are other delayed manifestations of CRS. A study evaluated patients with CRS 60 years after intrauterine infection [41]. Eight of the 11 women had early menopause, and 4 had osteoporosis. Endocrine abnormalities due to CRS may cause these conditions [42]. In 1977 growth hormone deficiency was reported in two boys with CRS [43]. However, this sole case report is insufficient to prove CRS's association with this disorder.

9.5.5.2 Cardiovascular Abnormalities

It is suggested that intimal fibromuscular proliferation and arterial sclerosis may develop in vascular structures in CRS [38]. These vascular sequelae may cause peripheral, cerebral, and coronary vascular disease in adulthood. Obstructive arterial lesions and systemic hypertension may develop secondary to renal disease [27, 42].

9.5.5.3 Ocular Abnormalities

Glaucoma and spontaneous lens absorption have been reported as delayed manifestations in patients with CRS [26, 44].

9.5.5.4 Neurologic and Psychosocial Abnormalities

Chronic progressive encephalopathy simulating measles-related subacute sclerosing panencephalitis (SSPE) was observed in a few patients with CRS as a late-onset manifestation [26]. Psychiatric disorders, intellectual disability, and behavioral problems have also been reported [26, 42].

Children having CRS may develop mild to severe psychomotor disorders. Among these disorders, intellectual disability (41–42%), hyperactivity (18%), spastic diplegia (14%), seizure disorder (7%), autism (7.4%), spastic quadriplegia (2%), and hemiparesis in a few cases were reported [2, 45–48]. A prospective study detected communication or language disorders in children evaluated with the Denver test and Ages and Stages Questionnaire (ASQ) [48]. Ninety-five percent of children with CRS having intellectual disabilities experienced hearing or visual disorders simultaneously [48]. Hearing and vision defects are important causes of these disorders [48]. Twelve to 15% of children with CRS were evaluated with a Modified Checklist for Autism in Toddlers, and the Diagnostic and Statistical Manual of Mental Disorders-V was diagnosed for autism spectrum disorder [2, 48].

9.6 Diagnosis and Laboratory Findings

In newborns whose mothers have a rubella history during pregnancy, microcephaly, generalized lymphadenopathy, hepatosplenomegaly, ocular abnormalities, or thrombocytopenia suggest congenital rubella infection, and the neonate should be evaluated for CRS. Serological and molecular tests are used in the diagnosis of rubella infection. Viral isolation or reverse-transcriptase polymerase chain reaction (RT-PCR) is the best method to diagnose CRS definitively. A positive test for viral RNA on cerebrospinal fluid, amniotic fluid, urine, nose swabs, or the throat is beneficial for diagnosing congenital rubella infection [49].

In the neonatal period, antibodies to the rubella virus should be investigated in infant and maternal sera for serologic diagnosis of rubella infection. Congenital rubella syndrome is diagnosed in newborns with rubella immune globülin (Ig) M positivity in serum or cord blood [1, 7]. Rubella IgG antibodies detected in a newborn passed from the mother will drop over time [26]. Continuation or rising rubella IgG antibody levels over several months is also diagnostic for CRS [49]. Congenital rubella syndrome can be diagnosed when a woman has a rubella infection during pregnancy by detecting rubella virus RNA in the amniotic fluid [4].

9.7 Treatment

There is no specific treatment for CRS. Infants with suspected CRS should have pediatric, cardiac, auditory, ophthalmological, and neurological evaluations. Appropriate treatments should be planned according to the affected system. The introduction and maintenance of physical, speech, behavioral, and occupational therapies at an early age are essential. A multidisciplinary team should evaluate the need for hearing aids, cochlear implants, cardiac interventions, ophthalmological surgeries, glasses or contact lenses, and appropriate treatments [1, 7].

9.8 Prevention and Control

Isolation of patients with rubella should be done 7 days after the rash onset. Standard and droplet precautions are suggested, especially for hospitalized patients. Infants with CRS are contagious via urine and nasopharyngeal secretions until one year of age. Contact isolation should be applied to children with suspected or proven CRS until the rubella PCR test is negative in two clinical samples taken 1 month apart after the 3rd month. And also, isolation measures should be applied in hospitalized children smaller than 3 years old for congenital cataract surgery [1, 49].

Immunoglobulin administration is not recommended for rubella-exposed pregnant women because studies have reported that this approach failed to prevent anomalies related to congenital rubella infection in the fetus [50].

The best protection against rubella infection is provided by vaccination. Rubella vaccine is a live virus vaccine administered by subcutaneous injection. The rubella vaccine is combined with the measles and mumps (MMR), or measles, mumps, and varicella (MMRV) vaccines. The Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommend the first dose of rubella-containing vaccination at 12–15 months, followed by the second dose at the age of 4–6 [50–52]. In postpubertal women without a record of rubella immunization, the rubella vaccine should be administered before planning a pregnancy. It is recommended not to become pregnant for 28 days after vaccination [50].

9.9 Conclusion

Rubella is an infectious disease transferred primarily via droplet or direct contact from nasopharyngeal secretions. Rubella in pregnancy may cause CRS leading to severe medical problems. Sensorineural HL is one of the most prevalent complications of CRS. Vaccination is the best protection against rubella, CRS, and related SNHL. After the widespread implementation of the rubella vaccine, rubella and CRS cases have decreased globally.

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