



The Many Expressions of Congenital Rubella

T. Tam

Since the start of the Canadian Paediatric Surveillance Program (CPSP) in 1996, nearly all reported cases of congenital rubella syndrome (CRS) have been children with multiple defects. There have been no reports of congenital rubella infection (CRI). The latter is defined as cases with no clinically compatible manifestations but with laboratory confirmation of infection. The aim of this report is to encourage general paediatricians and subspecialists to investigate and report CRS with less severe or late-onset manifestations and CRI.

Fetal infection with rubella varies from extensive involvement of multiple organs when infection occurs in the first trimester, to focal involvement of a few organs when fetal infection occurs after the 16th week of gestation. Unlike postnatal rubella infection, congenital infection is chronic, with persistence of the virus throughout fetal life and long after birth. Chronic infection or viral reactivation can lead to ongoing pathology during childhood and adulthood.

Newborns with CRS represent the tip of the iceberg of sequelae secondary to congenital rubella, as intrauterine infection more frequently results in normal-appearing infants. Many manifestations of congenital rubella are undetectable or are overlooked in the early months of life. Late-onset manifestations include endocrinopathies, deafness, ocular damage, chronic immunologic dysfunction, and vascular and central nervous system disease. Insulin-dependent diabetes mellitus is the most frequent of the endocrinopathies associated with congenital rubella, but thyroid and growth hormone abnormalities, precocious puberty and Addison's disease have also been documented. Sensorineural deafness is the most common manifestation of congenital rubella and may be progressive or may occur after years of normal acuity. Glaucoma has been reported in patients three to 22 years of age who did not have congenital glaucoma. Subretinal neovascularization may result in delayed-onset visual abnormalities. Mental retardation, autism, and other behavioral problems secondary to congenital rubella may be delayed or have a progressive course. Progressive panencephalitis is a rare sequelae that is usually manifested in the second decade of life.

Laboratory proof of congenital rubella infection is essential to ensure proper treatment, follow-up and long-term management. Irrespective of findings on clinical examination, all infants born to mothers who had documented or suspected rubella infection during pregnancy should be investigated. Infants with compatible clinical manifestations should also be investigated, irrespective of maternal history. Maternal infection without a rash in pregnancy can still lead to fetal disease. Congenital rubella after maternal reinfection has occasionally been documented, therefore a maternal history of rubella immunity before pregnancy must not preclude the investigation of an infant with compatible symptoms.

RESOURCES



Investigations during infancy should include viral isolation, testing of cord blood for rubella-specific IgM (RIgM) and serial RIgG. Viral excretion generally wanes after six months but may persist for a year or longer. The virus is most readily isolated from the nasopharynx, but can also be isolated from the urine, conjunctiva or cerebrospinal fluid. In general, detectable RIgM is a reliable indicator of congenital infection, but false positive results may occur depending on the techniques used and, very rarely, newborns infected later *in utero* may not have had adequate time to produce detectable levels of IgM. Maternally-derived RIgG usually declines by six months of age and persistence of RIgG at 12 months of age (prior to immunization), especially at high titres, is presumptive evidence for intrauterine infection. All serum samples should be tested in parallel.

Making a diagnosis in patients beyond infancy is not as easy and frequently a definitive retrospective diagnosis cannot be made. Referral to infectious diseases specialists or immunologists should be considered as there are useful diagnostic tools available, including: examination of cell mediated immune response to rubella antigen; IgG avidity testing; analysis of specific rubella antibody profiles and polymerase chain reaction. In older children and adults in whom virus shedding has ceased from other sites, virus may still be isolated from lens material at the time of cataract surgery. In children with encephalitis, virus may persist in the cerebral spinal fluid for several years.

Teaching Points

Which infants should be investigated for congenital rubella infection?

- Any infant born to a mother who had documented or suspected rubella infection at any time during pregnancy.
- Any infant with evidence of intrauterine growth retardation or any other manifestations consistent with congenital rubella (i.e., cataracts or congenital glaucoma, congenital heart defect, sensorineural hearing loss, pigmentary hearing loss, purpura, hepatosplenomegaly, jaundice, microcephaly, meningoencephalitis, radiolucent bone disease and progressive or late-onset manifestations such as mental retardation, diabetes mellitus and progressive

panencephalitis, and any other conditions possibly caused by the rubella virus), regardless of maternal history.

What investigations should be performed to document congenital rubella infection?

During infancy

- Isolation of the virus from nasopharynx, urine, conjunctiva or CSF.
- Cord blood or neonatal serum for IgM. Repeat at six months of age if negative.
- Serial IgG at three and six months of age and, if required, repeat at 12 months of age.

Beyond infancy

Consult infectious diseases specialists or immunologists.