Congenital Rubella Syndrome After Maternal Reinfection

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Introduction

Morgan-Capner,1 in 1986, reviewed 12 reports of maternal rubella reinfection with fetal consequences in contrast to the overall opinion that reinfection did not harm the fetus.2 Since then numerous other cases have been described.3,4,5 We here offer a case report and review the literature published since 1986.

Patient Report

The male patient was born in another hospital at 38 weeks' gestation. Pregnancy was complicated by intrauterine growth retardation (IUGR) detected from 24 weeks onward. The Apgar scores were 8 at one minute and five minutes. Birth weight was 2,040 g (tenth percentile (p10) = 2,700 g), length 43 cm, and head circumference 32.5 cm (p10=33 cm). Besides the symmetrical IUGR a systolic heart murmur 2/6 was found, but no other clinical anomalies were mentioned. On the fifth day the infant was found to be pale, and on physical examination a slightly enlarged liver was noted.

Laboratory investigations at that time revealed a mild anemia (hemoglobin 13 g/dL) and a low platelet count (29×10^3/mm^3). The baby was observed without any treatment and he was discharged home with his mother 1 week later. Mild thrombocytopenia persisted for a few weeks, reaching a normal level at the age of 1 month. On day 24 he was readmitted because of poor feeding. Rotavirus enteritis was detected. The anemia was more prominent (Hb 7.7 g/dL). Specific immunoglobulin M (IgM) for Cytomegalovirus and Toxoplasma gondii in the infant's serum were negative. At the age of 2 months he was operated on for an incarcerated inguinal hernia. Two hours after surgery his respirations became labored and he went into acute respiratory failure. After resuscitation and endotracheal intubation and ventilation, he was transferred to our university hospital.

On admission the infant was comatose with bilateral mydriasis. Cerebral dysfunction with tetrapsasticity was evident. Hepatomegaly and a systolic murmur were confirmed. Splenomegaly was noted. Head circumference was 3 cm below the tenth percentile. Ultrasound and computed axial tomography (CAT) scan of the brain showed both periventricular leukomalacia and calcifications with subcortical atrophy (Figure 1). Echocardiography showed an open ductus arteriosus but no other structural anomalies.

Because congenital infection was strongly suspected, maternal vaccination status and course of the pregnancy were reviewed. The mother had been vaccinated...
against rubella at the age of 12 years. The mother had not experienced any rubella-like symptoms during pregnancy, but she remembered having contact with an ill child in the third month of pregnancy, who might have had rubella. We were not able to prove rubella infection in that child because of interfering vaccination. Assay of the mother’s serum at the start of the second month of pregnancy revealed a rubella-specific IgG concentration of 16 IU/mL (more than 15 international units is considered immune in our hospital) and IgM negative. Although we could not rule out infection with a wild strain in the first month of pregnancy, she was considered to have a protective antibody level against rubella. Rubella-specific antibodies in the serum of our patient were IgM positive and IgG 65 IU/mL on day 68, and on day 81, IgM was still positive with a rubella-specific IgG serum level of 235 IU/mL. Rubella virus was isolated from nasopharyngeal secretions in primary cultures of African Green Monkey Kidney cells, grown in Minimal Essential Medium (Life Technologies, Rockville, MD) containing 10% fetal calf serum. The virus was detected by interference with the cytopathic effects of echovirus type 11 as a challenge virus. Maternal IgM remained negative, but 2 months after delivery her serum rubella-specific IgG level was 360 IU/mL.

Respiratory distress persisted and serial attempts to extubate failed. More prominent clinical signs of patent ductus were present and ducal ligation was performed. Despite this intervention the infant died 2 months later from chronic respiratory failure. Postmortem examination showed features of bronchopulmonary dysplasia and confirmed the

periventricular cystic leukomalacia. The rubella virus was cultured as described above, from a liver specimen, but not from the lungs.

**Discussion**

Congenital rubella syndrome (CRS) is accepted as a definite diagnosis if the infant is born with a clinical picture consistent with CRS in addition to at least one of the following criteria: (1) isolation of rubella virus in a clinical specimen from the patient; (2) demonstration of rubella-specific IgM in the infant’s serum; (3) persistence of rubella antibody in the infant’s serum at a higher titer than expected from passive transfer of maternal antibody, and/or (4) serologically confirmed maternal rubella infection in the first trimester of pregnancy. Retrospective diagnosis of CRS in older children was also considered. Findings in our patient (hepatosplenomegaly, thrombocytopenia, and the cystic cerebral lesions with periventricular calcifications) were very suggestive for a congenital rubella infection. This assumption was confirmed by three of the four above-mentioned diagnostic criteria.

The maternal IgG serum concentration for specific antirubella antibodies of 16 IU/mL was considered protective, and therefore only anti-CMV and *Toxoplasma* titers were evaluated in the referring hospital. However, since one obtained a positive history of maternal vaccination and a significant specific antibody IgG titer early in pregnancy, the criteria for re-infection were met. Maternal re-infection is typically subclinical and specific IgM often remains negative. On the other hand, one may argue that the IgG titer found at 5 weeks’ gestation might reflect the early rise after prima.
Congenital Rubella Syndrome

acute infection and that an IgM titer was missed owing to the 9-month interval between the two samples. Indeed, immunity before the affected pregnancy was not confirmed in our patient, but the IgG level of 16 IU/mL at 5 weeks, together with the affirmative history of the mother and her mother about rubella vaccination, was accepted as immunity and thus protective by the gynecologist. This clinical situation is a frequent one in daily practice, for most women consult their gynecologist for the first time during pregnancy.

Reviewing the last 10 years of literature, we were unable to define a cutoff level of antirubella antibodies considered protective in case of renewed contact with the wild virus during pregnancy (Table 1). In eight of 16 cases of CRS after reinfection the maternal specific antirubella IgG was at least 15 IU/mL (equivalent to a hemagglutinin inhibition [HIA] assay IgG titer of 1:16) at the start of pregnancy, and even serum levels as high as 25 IU/mL seem to be not high enough for fetal protection.10 The question of repeating rubella vaccination remains open.

During 15 years of follow-up in Israel, Fogel et al15 confirmed 35 cases of rubella reinfection in pregnancy, despite extensive vaccination programs since 1975. Twenty of them occurred in the first trimester of pregnancy, and the remaining 15 beyond the 13th gestational week. However, all of the 19 children born to mothers following reinfection were healthy. The 16 other pregnancies were interrupted. In two of the four products of conception available for viral isolation, the virus could be isolated.13 Combining the results of three reports, the

| Table 1 |

REVIEW OF REPORTED CASES OF CRS AFTER MATERNAL RUBELLA REINFECTION OVER THE LAST 10 YEARS: NEONATAL AND MATERNAL RUBELLA-SPECIFIC IMMUNE STATUS BEFORE AND AFTER PREGNANCY

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(a) IU/mL by ELISA; (b) hemagglutination inhibition antibody titer equivalent to 15 IU/mL; (c) top = termination of pregnancy; ? = not tested or no information.
fetal risk for congenital infection after maternal reinfection during the first trimester of pregnancy has been estimated at 8% (95% confidence intervals: 2–22%). The CRS has not been reported after reinfection beyond 12 weeks' gestation. However, even in an immune person, symptomatic rubella reinfection after a contact with a rubella vaccine (RA 27/3 combined) recipient has been described.

Conclusion

Congenital rubella syndrome should still be considered in a neonate with a clinical picture suggestive of congenital infection, even if the mother shows preconceptional immunity for rubella either acquired by natural infection or by vaccination. Contact with rubella should be avoided throughout the first two trimesters of pregnancy even in "IgG-positive" pregnant women. More research is probably needed for the reassessment of a safe, if any, level of antirubella antibodies protective against fetal reinfection during pregnancy.

REFERENCES


