Neonatal Rubella Myocarditis

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Teratogenicity of the rubella virus for the developing organ systems of the human embryo has been recognized since Gregg's (1941) clinical description of the congenital rubella syndrome and the retrospective epidemiological investigation of the 1940 Australian rubella epidemic by Swan *et al.* (1943). Pathogenesis, however, remained speculative, as rubella was only of presumed viral aetiology. Subsequent retrospective and prospective studies established the congenital rubella syndrome as a well-defined clinical entity (Greenberg, Pellitteri, and Barton, 1957; Ingalls, 1957; Lundström, 1962; Michaels and Mellin, 1960; Tartakow, 1965; Wesselhoeft, 1949).

Laboratory identification and propagation of the rubella virus was reported simultaneously by Weller and Neva (1962) and by Parkman, Buescher, and Artenstein (1962). The viral aetiology of rubella had been confirmed. Selzer (1963) demonstrated this virus in the placenta, amniotic fluid, and foetal tissues of an infected human abortus, thereby confirming that teratogenicity of this virus was the result of infection of tissues during the vital period of organogenesis.

This was a fortuitous sequence of events, because rubella occurred in almost pandemic proportions in the United States of America during 1964. The epidemic originated in the New England States and then swept south and west to the Rocky Mountains where it stopped, sparing the Intermountain and Pacific Coast States. A large number of afflicted infants were born and numerous groups throughout the United States reported their experience with the congenital rubella syndrome during this epidemic. In addition to extending the clinical description of the syndrome, three observations of extreme im-

portance were made. (1) Rubella virus persists in the tissues of the afflicted newborn infant after birth, and may be isolated from the nasopharynx, urine, and tissues. Infants may shed virus for as long as a year after birth (Sever and Monif, 1965). (2) The afflicted infant is contagious to susceptible subjects (Schiff and Dine, 1965). (3) The rubella virus is not only a teratogenic agent, but is also a cause of continuing clinical disease in the newborn infant.

It is the purpose of this report to describe the clinical course, electrocardiographic, radiological, virological, and post-mortem findings of 10 infants with stigmata of the congenital rubella syndrome who had active myocardial disease during the neonatal period.

SUBJECTS AND METHODS

Forty-six newborn infants with stigmata of the congenital rubella syndrome were admitted to the nurseries of the City of Memphis Hospitals between October 1964 and April 1965. As soon as the clinical diagnosis was established, these infants were enrolled on a study protocol. Each infant was examined daily by one of the authors, and electrocardiograms were taken at least twice each week. Chest radiographs were taken at birth and, thereafter, whenever the patient's clinical condition changed. Cultures for virus isolation were taken from the throat, rectum, and urine of all patients during life, and from multiple tissues of the necropsied patients.

The details of the isolation of the virus have been published elsewhere (Sever, Schiff, and Traub, 1962; Korones *et al.*, 1965).

The first infant (Case 1) to come to our attention was a Negro girl, born at term, with a birth weight of only 1680 g. Congestive heart failure and physical findings of persistence of the ductus arteriosus were manifest on the tenth day of life. An electrocardiogram recorded shortly after the onset of congestive heart failure was similar to that sometimes seen with anomalous origin of the left coronary artery from the pulmonary artery (Fig. 1). Q waves were present in leads I and aVL. S-T

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FIG. 1.—Electrocardiogram of Case 1. There are abnormal Q waves; S-T elevations in leads I, II, and aVF and depressions in aVR and the right precordial leads. T wave inversion is present in the left precordial leads.

segment elevation with blending of the T wave was present in leads I, II, aVL, aVF; S-T segment depression was present in lead aVR and in the right precordial leads. This infant was critically ill; response to digitalization was poor. The diagnoses of persistence of the ductus arteriosus and anomalous origin of the left coronary artery led

to exploratory thoracotomy. A large ductus arteriosus was ligated and divided. Although both coronary arteries originated from the aorta, gross areas of the myocardium had the appearance of infarction. The infant died shortly after operation and permission for necropsy was not granted. An interview with the patient's mother revealed that she had been exposed to rubella during the first trimester of pregnancy, though she did not have clinically apparent disease. If this infant is included in the total series, 10 of 47, or 21 per cent had myocardial disease.

Sex, length of gestation, birth weight, and the external stigmata of the congenital rubella syndrome of the 10 infants are recorded in the Table: 8 were girls; the male: female ratio in this series was 16:30. All except 3 infants had low birth weights in relation to gestational age.

Rubella virus was isolated from each infant during life with the exception of Case 9, who had many of the clinical stigmata of the congenital rubella syndrome. The virus was isolated from several tissues obtained at necropsy from Cases 2 and 3, but virus was not isolated from the myocardium.

Three clinical courses were observed.

Course I. Three infants (Cases 1, 2, and 3) developed severe left ventricular failure on the tenth (Case 1) and fifth days (Cases 2 and 3) of life. Response to intensive medical management, including intravenous epinephrine administration (Rudolph, Mesel, and Levy, 1963), was minimal. Their electrocardiograms were so similar as to be almost interchangeable. Fig. 2 is the electrocardiogram recorded from Case 3. The electrocardiographic abnormalities persisted on serial tracings until death at 31, 27, and 47 days of age, respectively. Each infant had cardiomegaly and radiological evidence of pulmonary oedema (Fig. 3). Each had from one to four periods of cardiac arrest before death.

A similar clinical course was observed in Case 4, though the electrocardiogram of this infant did not show any evidence of myocardial damage until the day before death (at 120 days), when minor S-T segment

TABLE
CLINICAL DATA ON 10 INFANTS WITH CONGENITAL RUBELLA SYNDROME

Case No. and sex	Estimated gestational age (wk.)	Birth weight (g.)	Stigmata of the congenital rubella syndrome
1 F	37	1680	Possible rubella exposure; persistence of ductus arteriosus
2 M	38-40	2220	Maternal rubella; congenital cataracts; thrombocytopenic purpura; hepatosplenomegaly; persistence of ductus arteriosus
3 F	41	2155	Microphthalmia; congenital cataracts; persistence of ductus arteriosus; brain anomalies
4 F	37	1616	Lytic bone lesions; thrombocytopenic purpura; microphthalmia; hepatosplenomegaly; persistence of ductus arteriosus
5 F	38	1660	Maternal rubella; thrombocytopenic purpura; persistence of ductus arteriosus; congenital cataracts; brain anomalies
6 F	41	2290	Maternal rubella; microphthalmia; microcephaly; multiple neurological abnormalities; peripheral pulmonary stenoses
7 F	41	2650	Maternal rubella; microphthalmia; microcephaly; neurological abnormalities; multiple peripheral pulmonary stenoses
8 F	30 (?)	2400	Maternal rubella; microcephaly; cataract, right eye; neurological abnormalities; multiple peripheral pulmonary stenoses
9 F	36	3430	Maternal rubella; microcephaly; congenital heart disease; unilateral cataract
10 M	41	2725	Maternal rubella; thrombocytopenic purpura; congenital heart disease; congenital cataracts

FIG. 2.—Electrocardiogram of Case 3. There are pathological Q waves in leads I, aVL, and V6. S-T elevation is present in these leads and the R wave amplitude is small. S-T depression is apparent in lead aVR and in the right præcordial leads.

and T wave changes appeared. This infant had complete transposition of the great vessels; microscopical sections of the myocardium showed areas of myocardial necrosis.

FIG. 3.—Chest radiograph of Case 3. The heart is massively enlarged and there is pulmonary oedema.

Necropsies on Cases 2, 3, and 4 revealed that the only congenital cardiovascular anomaly in Case 2 was persistence of the ductus arteriosus; in Case 3 there was persistence of the ductus arteriosus and a membranous ventricular septal defect; and in all patients there were gross myocardial lesions. There was a slightly depressed, brownish plaque, 2.0×3.0 cm., over the anterior aspect of the right ventricle of Case 2; the heart of Case 3 contained several greyish-pink patches over the free wall of the left ventricle and in the posterior portion of the interventricular septum.

The microscopical appearance of the myocardium was similar in all infants; Case 2 had the most severe and extensive changes; Case 4, the least extensive. Rarely were normal areas of myocardium seen in sections from Case 2; in some areas changes were so extensive that it was difficult to identify the tissue as myocardium. These changes were: loss of cross-striation of the myofibrils, remarkable swelling of the fibres, and nuclear pleomorphism. The myofibrils were finely to coarsely granular and contained vacuoles of varying size, some so large as to extend across the width of several fibres. Nuclear pyknosis and vacuolization were extensive. In some nuclei margined chromatin surrounded a single large nuclear vacuole. No inclusion bodies were present, nor was there an interstitial inflammatory response (Fig. 4 and 5). The epicardium and endocardium were normal. In less severely involved regions of the myocardium there was slight (though constant) loss of cross-striation and swelling of the fibres. Nuclear pleomorphism, though mild, was invariably present.

Course II. Three infants (Cases 5, 6, and 7) pursued a similar clinical course with similar electrocardiographic changes initially. After the onset of congestive heart failure (between 7 and 14 days of age), S-T segment and T wave changes were apparent. Within a week to 10 days, the T waves became more or less symmetrically inverted in I, aVL, and in the left præcordial leads. During the following 6 weeks, the S-T segments returned to the isoelectric line and the inverted T waves gradually became isoelectric or upright (Fig. 6), so that the final S-T segment and T wave changes were indistinguishable from those that may be associated with administration of digitalis glycosides. Simultaneously with these S-T segment and T wave changes there was a progressive increase in R wave amplitude in the left præcordial leads. This change has been noted during the recovery phase of "acute aseptic myocarditis", though interpretation of its significance in these infants is complicated by the presence of a left-to-right shunt with consequent left atrial and left ventricular overloading. This sequence of electrocardiographic changes also mimics the serial changes observed in adults who have had acute myocardial infarction with subsequent healing and recovery.

With regression of S-T segment displacements and improvement in T wave morphology, the clinical status of these infants improved. The signs of heart failure regressed; the heart size decreased; and they gained weight. None has died; their hearts are now only moderately enlarged (Fig. 7) and each is receiving maintenance doses of digoxin.

FIG. 4.—Low-power photomicrograph of the myocardium of Case 3. This shows the general lack of cross-striation, swelling of myocardial fibres, nuclear pleomorphism, and fatty degeneration and replacement of the necrotic myocardium. ($\times 350$.)

FIG. 5.—High-power photomicrograph of an area of myocardial necrosis of Case 3. ($\times 1200$.)

FIG. 6.—The electrocardiogram of Case 6 at approximately 4 months of age. The initial electrocardiogram was similar to those of Cases 1 and 3. S-T segment and T wave changes now apparent cannot be distinguished from those secondary to tachycardia, digitalis, or changes produced by the underlying congenital heart disease. R wave amplitude in the left præcordial leads has increased greatly.

Course III. Electrocardiograms of 3 infants (Cases 8, 9, and 10) recorded shortly after birth, had changes that,

FIG. 7.—Chest radiograph of Case 6. The cardiac silhouette is moderately enlarged, perhaps due primarily to the congenital anomalies known to be present (persistence of the ductus arteriosus and multiple peripheral pulmonary stenoses).

in the adult, would be compatible with healed anterolateral myocardial infarction. Fig. 8 is an electrocardiogram from one of these infants. In leads I and aVL an abnormal Q wave is inscribed on the downstroke of the QS deflection. Small amplitude R waves are inscribed in the vertical vector leads (II, III, and aVF) and in the left præcordial leads. No S-T segment changes are apparent, and T wave morphology is "normal". None of these infants had an abnormal neonatal course so far as the cardiovascular system was concerned, and chest radiographs showed hearts of normal size (Fig. 9). These electrocardiograms suggested that *in utero* myocardial disease had healed by the time of birth.

DISCUSSION

Active viral disease in newborn infants with the congenital rubella syndrome was not described before these observations. After exerting its teratogenic effect, it was felt that the rubella virus had completed its work. In the 1964 epidemic, evidence of continuing disease in the postnatal period was observed in the brain (Kenny, Michaels, and Davis, 1965), bones (Korones *et al.*, 1965; Rudolph *et al.*, 1965), lung (Korones *et al.*, 1965), and liver (Korones *et al.*, 1965).

The discovery of myocardial disease in our patients resulted from the knowledge that rubella virus was

FIG. 8.—Electrocardiogram of Case 10 recorded six days after birth. Pathological Q waves are present in leads I, aVL, V6, and V7. No S-T segment or T wave changes are apparent and the R wave amplitude in the left præcordial leads is small.

present in the infants' tissues, that viral myocarditis is a necrotizing disease, and that myocardial necrosis is reflected by the observed electrocardiographic changes. Thereafter, infants with the congenital rubella syndrome were studied closely for evidence of myocardial disease and 8 additional infants with evidence of myocardial disease were subsequently discovered.

Infants with myocardial involvement had an

FIG. 9.—Chest radiograph of Case 10. The heart is small and there are no signs of pulmonary congestion.

extremely high mortality rate (4 of 10) and the survivors have had an extremely high morbidity rate. Some infants spent as long as 3 months in hospital, and all except 3 (Cases 8, 9, and 10) have been readmitted on several occasions with congestive heart failure or pneumonia.

Microscopical pathology revealed extensive myocardial necrosis, as predicted by the electrocardiograms. Of interest is the fact that virus was not isolated from the myocardium of the infants brought to necropsy, though virus was isolated from many other tissues. Isolation of rubella virus from the myocardium has been reported in only a few instances (Sever and Monif, 1965). Necrosis was extensive, but there was no evidence of an interstitial inflammatory response or cellular infiltration. Saphir and Cohen (1957) believe that such changes are characteristic of viral myocarditis.

Rubella myocarditis, in the newborn infant, like other viral myocarditides, is a necrotizing cardiomyopathy. Though the infection is acquired congenitally, it may not become clinically obvious until a few days or weeks after birth. On the other hand, the myocarditis may heal completely *in utero*, and in these circumstances myocardial damage is only detected by electrocardiographic changes similar to those associated with healed myocardial infarction in adults.

SUMMARY

Of 47 infants with the congenital rubella syndrome, 10 had electrocardiographic evidence compatible with myocardial death, injury, and ischaemia. Changes were present at birth or appeared within the first 10 days of life. Seven infants had active myocardial disease in the neonatal period and four died. The post-mortem observations of myocardial necrosis were compatible with myocarditis of viral aetiology. Three infants survived; serial electrocardiograms of these infants showed evolutionary changes similar to those observed in adults who have had myocardial infarction with subsequent healing. Three additional infants had electrocardiographic changes at birth, compatible with healed infarction, suggesting that active myocarditis had occurred with healing *in utero*.

From these observations it can be concluded that damage to the heart and great vessels caused by the rubella virus is confined not only to the first trimester of pregnancy with production of congenital anomalies, but also that the virus may persist in the myocardium for varying periods of time after birth, producing active destruction of tissue.

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REFERENCES

- Greenberg, M., Pellitteri, O., and Barton, J. (1957). Frequency of defects in infants whose mothers had rubella during pregnancy. *J. Amer. med. Ass.*, **165**, 675.
- Gregg, N. McAlister (1941). Congenital cataract following German measles in the mother. *Trans. ophthal. Soc. Aust.*, **3**, 35.
- Ingalls, T. H. (1957). German measles and German measles in pregnancy. *Amer. J. Dis. Child.*, **93**, 555.
- Kenny, F. M., Michaels, R. H., and Davis, K. S. (1965). Rubella encephalopathy. *Amer. J. Dis. Child.*, **110**, 374.
- Korones, S. B., Ainger, L. E., Monif, G. R. G., Roane, J., Sever, J. L., and Fuste, F. (1965). Congenital rubella syndrome: New clinical aspects with recovery of virus from affected infants. *J. Pediat.*, **67**, 166.
- Lundström, R. (1962). Rubella during pregnancy: A follow-up study of children born after an epidemic of rubella in Sweden, 1951, with additional investigations on prophylaxis and treatment of maternal rubella. *Acta paediat. (Uppsala)*, **51**, Suppl. 133.
- Michaels, R. H., and Mellin, G. W. (1960). Prospective experience with maternal rubella and the associated congenital malformations. *Pediatrics*, **26**, 200.
- Parkman, P. D., Buescher, E. L., and Artenstein, M. S. (1962). Recovery of rubella virus from army recruits. *Proc. Soc. exp. Biol. (N.Y.)*, **111**, 225.
- Rudolph, A. J., Singleton, E. B., Rosenberg, H. S., Singer, D. B., and Phillips, C. A. (1965). Osseous manifestations of the congenital rubella syndrome. *Amer. J. Dis. Child.*, **110**, 428.
- Rudolph, A. M., Mesel, E., and Levy, J. M. (1963). Epinephrine in the treatment of cardiac failure due to shunts. *Circulation*, **28**, 3.
- Saphir, O., and Cohen, N. A. (1957). Myocarditis in infancy. *Arch. Path.*, **64**, 446.
- Schiff, G. M., and Dine, M. S. (1965). Transmission of rubella from newborns: A controlled study among young adult women and report of an unusual case. *Amer. J. Dis. Child.*, **110**, 447.
- Selzer, G. (1963). Virus isolation, inclusion bodies, and chromosomes in rubella-infected human embryo. *Lancet*, **2**, 336.
- Sever, J. L., and Monif, G. (1965). Limited persistence of virus in congenital rubella. *Amer. J. Dis. Child.*, **110**, 452.
- , Schiff, G. M., and Traub, R. G. (1962). Rubella virus. *J. Amer. med. Ass.*, **182**, 663.
- Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B. (1943). Congenital defects in infants following infectious diseases during pregnancy. *Med. J. Aust.*, **2**, 201.
- Tartakow, I. J. (1965). The teratogenicity of maternal rubella. *J. Pediat.*, **66**, 380.
- Weller, T. H., and Neva, F. A. (1962). Propagation in tissue culture of cytopathic agents from patients with rubella-like illness. *Proc. Soc. exp. Biol. (N.Y.)*, **111**, 215.
- Wesselhoeft, C. (1949). Rubella (German measles) and congenital deformities. *New Engl. J. Med.*, **240**, 258.