CONGENITAL RUBELLA SYNDROME IN SINGAPORE CHILDREN

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It is well-known that rubella infection of the mother in the early months of pregnancy have resulted in mental deficiency, microcephaly and congenital heart disease in the infant. Studies over the past few years in different parts of the world have resulted in a re-evaluation of the concepts of the clinical features and pathogenesis of congenital rubella.

Gregg in 1941 recorded 78 infants with congenital rubella syndrome in which he had 13 of his own cases and 65 from other parts of Australia, where the majority of the cases gave a history of rubella in the early months of pregnancy, and the infants were born with bilateral cataract, congenital heart disease and mental deficiency. Gregg's observations were soon confirmed by Swan and his associates in South Australia. On 101 cases of congenital malformation following maternal rubella in early pregnancy they found the following malformations:- Microcephaly (62%), cardiac disease (52%), deaf-mutism and deafness (48%), cataract (18%) and mental deficiency (5%).

In 1962 and 1963 rubella appeared in epidemic form in Great Britain and in the eastern United States, and it was described by Cooper and Krugman as a very extensive one; with many pregnant and susceptible women exposed to the infection, an increased number of congenital malformations were recognised at different centres in the United States, and further new manifestations with involvement of other systems were recognised. The exact number of infants affected is not known, but it was estimated that between 10,000 and 20,000 infants with congenital rubella manifestations were born in the United States between 1964 and 1966 (Cooper and Krugman 1966). In 1967, Dudgeon gave a review of 120 cases of congenital rubella syndrome from Great Ormond Street Childrens' Hospital, London, where he gave a frequency of the defects encountered in congenital rubella in the following order:-

1. Intrauterine growth retardation, resulting in low birth weight and retarded growth.
2. Defects in the heart, resulting in patent ductus arteriosus, septal defects, pulmonary stenosis and myocardial damage.
3. Defects in the eye, resulting in cataract, retinopathy, microphthalmia, glaucoma and cloudy cornea.
4. In the ear, perceptive deafness.
5. In the central nervous system, a full fontanelle microcephaly, raised cells, and protein in c.s.f. and retarded development.
6. In the blood, thrombocytopaenic purpura with anaemia.
7. In the liver, hepatitis, jaundice and hepatosplenomegaly.
8. Other lesions include adenopathy, hypogamma globulinaemia, pneumonitis and splenic fibrosis.

In Singapore so far, although we are aware of the congenital rubella syndrome, there has been no report of collected series of cases of congenital rubella syndrome; this report points out not only of the existence of this condition but also shows that in Asians a history of rubella is often lacking because it is difficult to see the rash on a dark skin and in subclinical infections of rubella the clinical manifestations of rubella may be minimal. Awareness of the existence of this condition is important, because these children when infected are constantly excreting the virus in their urine and secretions, and there is a danger of persons being infected with the rubella virus. The following are some cases of congenital rubella syndrome encountered during a study of mentally defective children in Singapore.

Case 1

G.T.C., was a seven-year old boy, who was referred because of delayed milestones and retarded mental development. The patient was the youngest of nine children, and the mother gave a history of having attempted abortion at the second month of pregnancy. The patient was born at the end of a normal gestational period, but with a birth weight of only 4 lbs. and was jaundiced for 2 weeks after birth. He was stunted in growth, measuring 3 feet 9 inches, and weighing only 45 lbs. The circumference of the head was only eighteen inches, indicating that the child had a severe microcephaly, and his intelligence was severely subnormal. (see Figs. 1 (a) & (b)). He had bilateral cataract for which

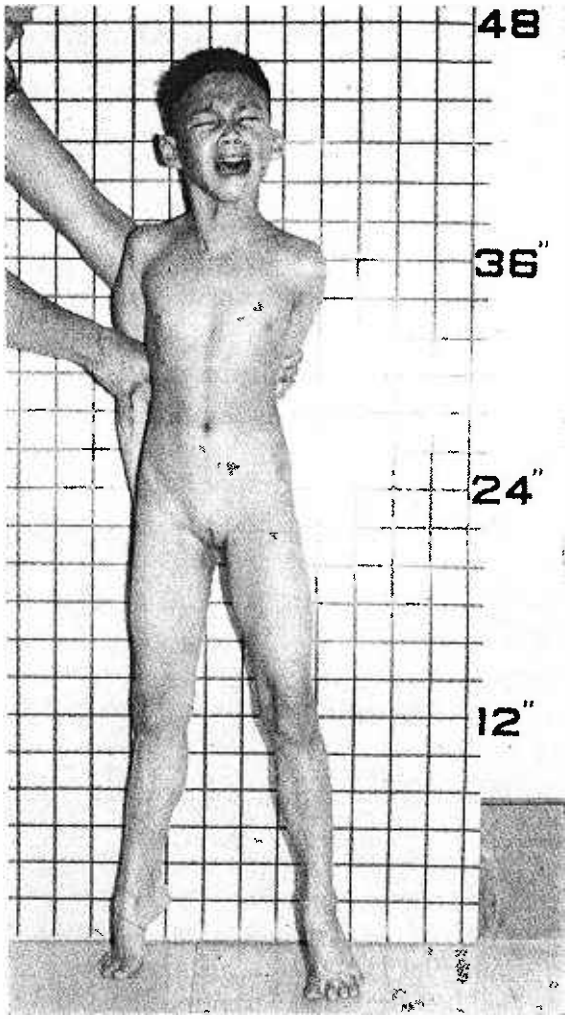

Fig. 1(a). Note the seven-year old mentally retarded child with microcephaly.

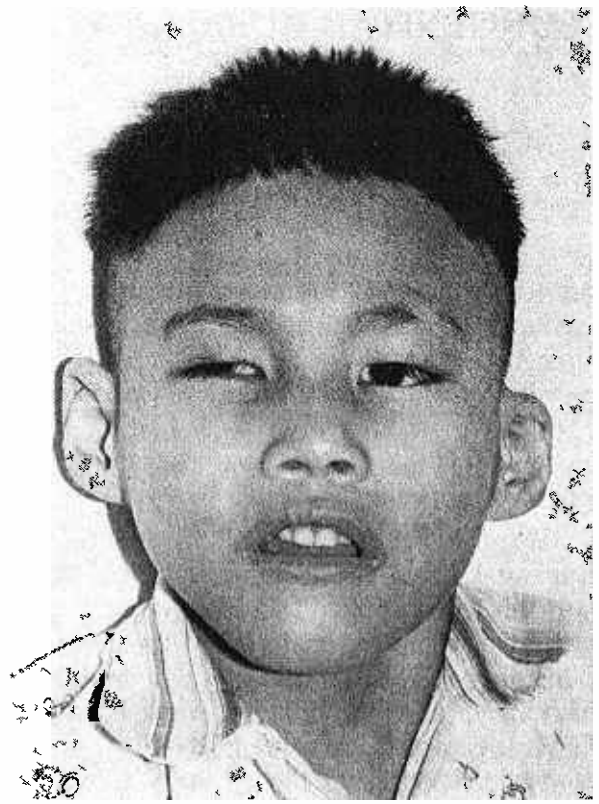

Fig. 1(b). Note the microcephaly and microphthalmus. This child had bilateral cataract operated on at birth.

he was operated on at birth. On auscultation of the heart, a loud machinery murmur was audible indicating that the child had a patent ductus arteriosus. The neutralising antibody titre was only 1 in 8 (low titre) but the rubella haemagglutination antibody titre was 1/256, indicating that the child had an antibody level consistent with that found in congenital rubella syndrome. Although a history of rubella infection was lacking in the mother, the child fitted clinically and radiologically with the diagnosis of congenital rubella syndrome.

Case 2

T.K.Y. was a 21-month old female, who was referred because of inability to speak. The mother admitted that during the first three months of pregnancy she had a fever and rash, which could have been German measles. The physical milestones of the child were completely delayed, and she was able to sit up at only one year, and walk at eighteen months of age. Physical examination of the child revealed a backward child whose circumference of the head was below normal levels, measuring only $17\frac{3}{4}$ inches (see Fig. 2 (a)). The patient was completely deaf and could not respond even to the loudest noise. The left eye displaced a rubella retinitis with pigmentary changes at the macula. (see Fig. 2 (b)). At the same time she had a congenital heart defect in the form of a ventricular septal defect. The haemagglutination test for rubella was strongly positive, being 512. The conglomeration of clinical characteristics, namely cataract, microcephaly, deafness and congenital heart disease together with the strongly positive haemagglutination test makes it clear that this is a case of congenital rubella syndrome. Further, the history of fever and rash in the early months of pregnancy might have been due to German measles.

Case 3

K.B.K. was a seven-month old Malay child who was admitted to the ward for bronchopneumonia. The patient was the youngest of 7 children and the pregnancy was reported to be quite healthy. The delivery was normal, and the birth weight was low, being $4\frac{1}{2}$ lbs. There was no history of jaundice in the neonatal period. Physical examination revealed an obvious microcephalic child (see Figs. 3 (a) & (b)) whose circumference was $14\frac{3}{4}$ inches. There was bilateral cataract, with microcornea and bilateral nystagmus (Fig. 3c). Clinically there was no evidence of congenital heart disease. All the limbs were

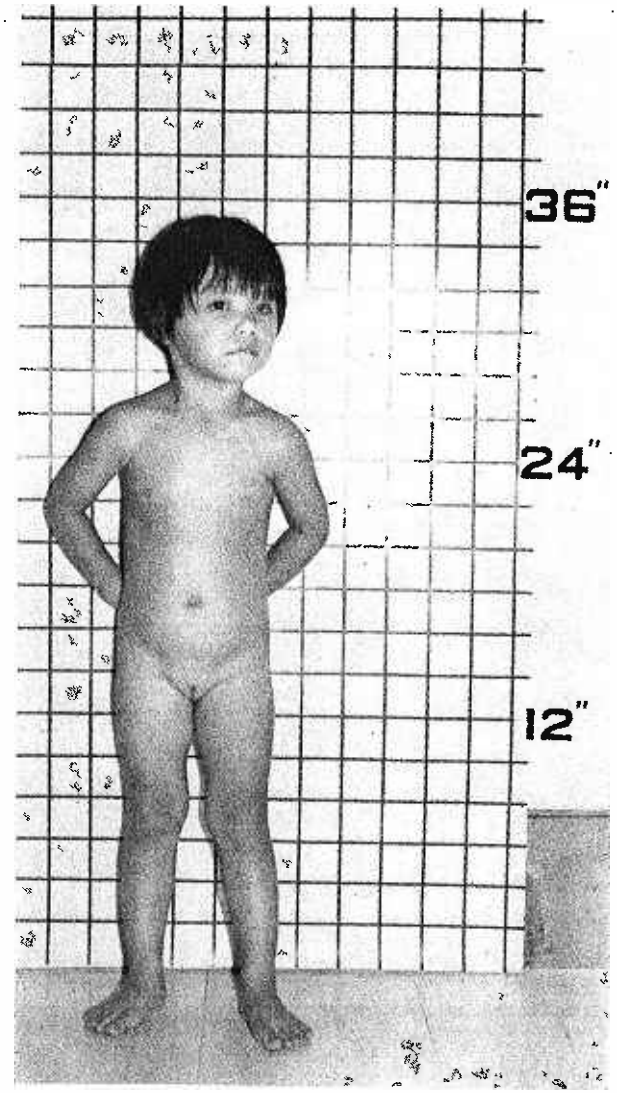

Fig. 2(a). To show the stunting of growth, and microcephaly, the circumference of the head measuring 17¾ inches.

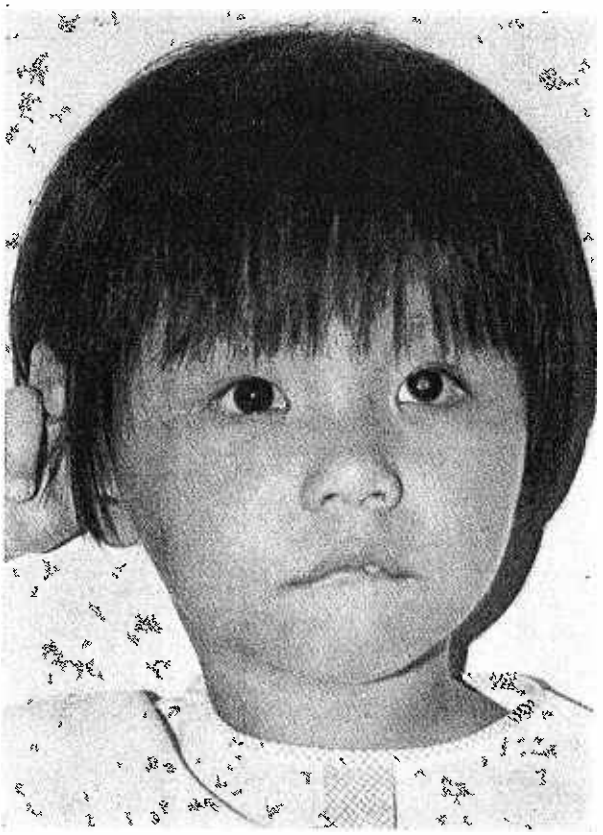

Fig. 2(b). Note the abnormality of the (L) eye, showing a dilated pupil. This eye showed rubella retinitis with pigmentary changes at the macula.

hypotonic and the child has been followed up for 2 years, but is of severe subnormal intelligence. Radiographs of the long bones and knees did not reveal any abnormality. The titre of the rubella neutralisation test at the age of 2 years was 64, and this is suggestive of an intrauterine rubella infection.

Case 4

L.C.S. was a seven-day old baby admitted for severe jaundice developing on the 3rd and 4th day of life. The mother was quite healthy during pregnancy and did not take any herbs, nor did she give a history of rubella infection. Both mother and baby were of the same blood group B, and the blood for glucose-six-phosphate dehydrogenase was normal. The indirect serum bilirubin was 21 mgms% and the child required an exchange transfusion. The birth weight of the baby was 4½ lbs. and the liver was 2 finger breadths and the spleen 1 finger breadth. Because of hepatosplenomegaly it was decided to do a platelet count and this was 45,000 cmm; the haemoglobin was 14.6 gm%, the bleeding-time 4½ minutes, clotting-time 4 minutes and prothrombin time 16 seconds (control 16 seconds). Radiographs of the knees at the lower end of the femora show a horizontal radiolucent area (see Fig. 4) so characteristic of rubella infection. The haemagglutination titre of the baby was 16, while that of the mother was 14, and the neutralising anti-body titre was 32. In addition there was a very high level of IgM (19S) and IgA (7S) indicating passive transfer of antibodies from mother to child. The IgG was 1480 mgms/100 c.c. of blood. It has been shown in infants with congenital rubella at or soon after birth that the blood will contain IgM (19S) and IgG (7S) antibody passively acquired from the mother. The IgM antibody persists but the IgG declines during the first few months of life and is then replaced by the infants own IgG antibody. Clinically, radiologically and serologically therefore there is no doubt that this is a case of congenital rubella syndrome.

Case 5

S.F.A. was a 4-week old Chinese boy, born on 15.8.67. The gestational period of the mother was 41 weeks and the baby was 9 lb. 9 ozs. at birth. The patient was the youngest of 12 child-

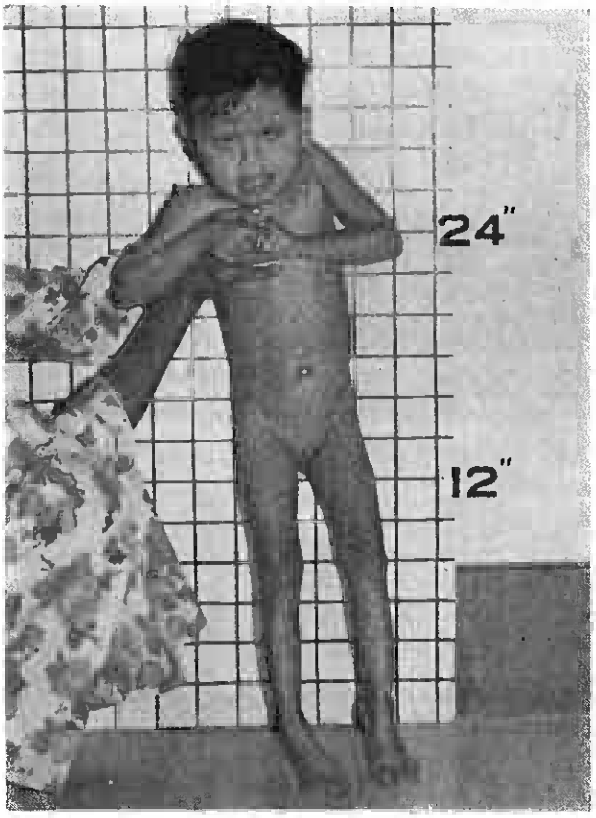

Fig. 3 (a).

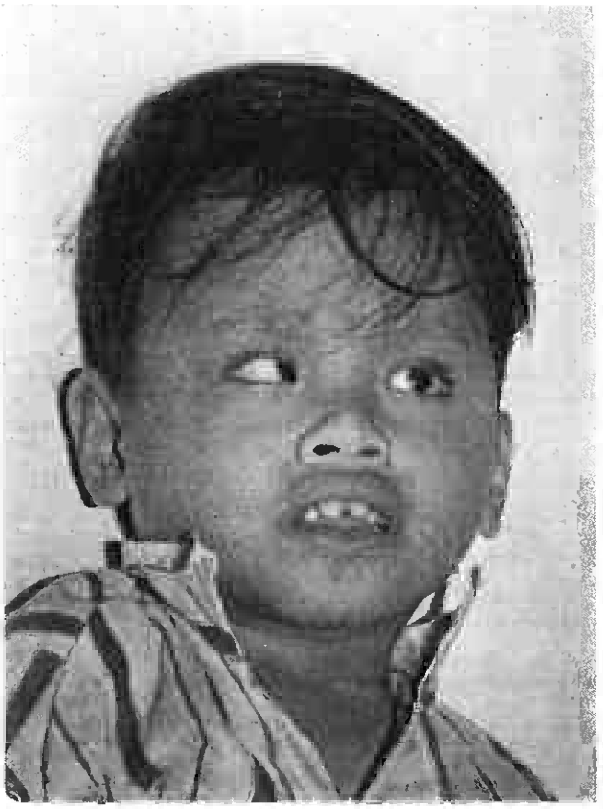

Fig. 3 (b).

Figs. 3 (a) and (b) reveal an obvious microcephalic child of low grade intelligence with squint.

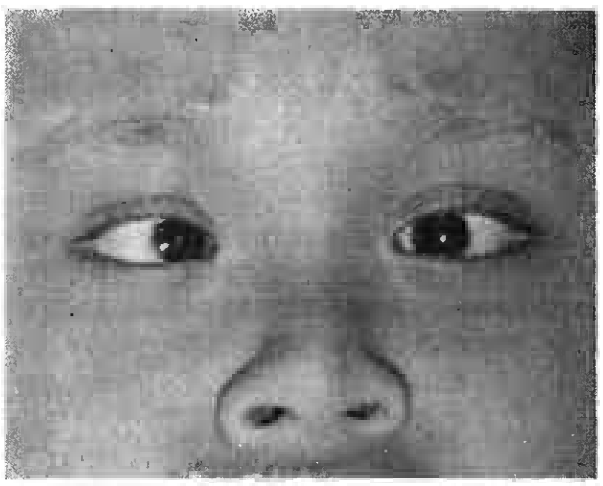

Fig. 3 (c). A close-up of the eyes to show the squint. There was bilateral cataract, microcornea and bilateral nystagmus.

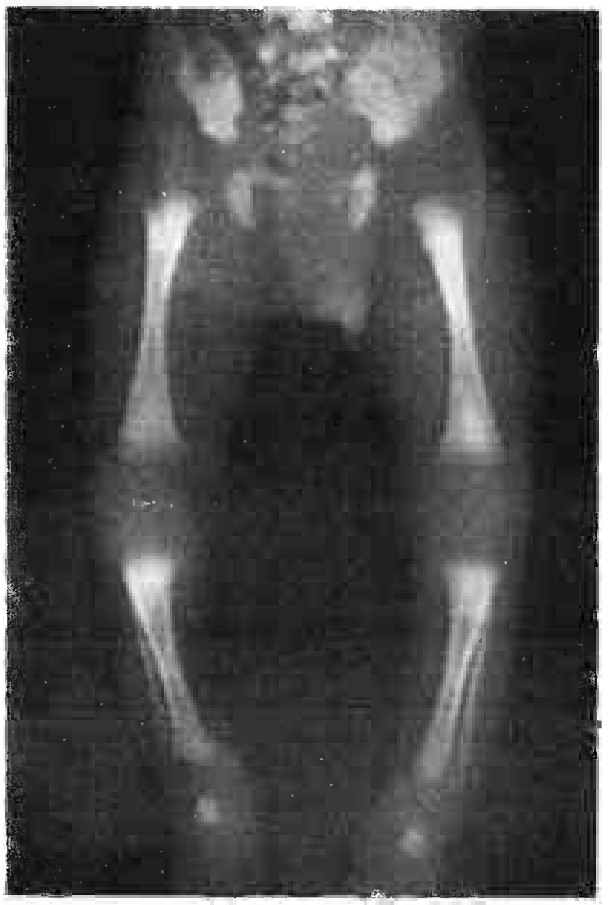

Fig. 4. A radiolucent area across the lower end of the femora in Case 4 so characteristic of congenital rubella.

ren, and all 12 children were perfectly healthy. The mother was aged 36 years old, and the mother's pregnancy was perfectly healthy. Physical examination of the child revealed an obvious Mongol with characteristic bilateral simian creases and an umbilical hernia. There was bilateral congenital cataract with marked horizontal nystagmus. Clinically there was no bruit over the heart and the lungs were clinically clear. The liver was 2 f.b. and the spleen not palpable. On the 6th day of life there was a bilateral purulent discharge from both eyes and umbilical bleeding. The total white cell count was elevated, being 22,500 cmm. The differential count showed polymorphs in the region of 91%, lymphocytes 7%, monocytes, 1% and eosinophils 1%. The platelet count was 130,000 cmm. The reticulocyte count was 1%, the bleeding time being 3 minutes and the clotting time 9 minutes, the prothrombin time was 65 seconds, the control being 13 seconds. The Kahn test of the mother was negative. Radiographs of the knees revealed a radiolucent area at the lower end of both femora. The rubella haemagglutination test was strongly positive being 1024; in view of the child's age of four weeks, it is a bit early to say whether this is maternal or foetal, and the test would be repeated later at the age of six months.

Case 6

W.N.L. was a nine-year old Chinese female, referred by the Eye Department for inability to cope with her lessons at school. She was the youngest of five children and was born at Kandang Kerbau Hospital weighing 6 lbs. The pregnancy was healthy. There was no history of German measles during pregnancy. The physical milestones of the child were normal. Physical examination revealed a stunted school girl of educational subnormal intelligence level with marked horizontal nystagmus. (Figs. 5 (a) & (b)). The cataract had been operated on at the age of one year. She also had a congenital heart defect in the form of a ventricular septal defect. Blood was taken for complement fixation test and for neutralising tests and although the neutralisation test was low 1 in 8, the rubella haemagglutination antibody titre was high being 256.

Case 7

G.T.K. was a premature baby weighing only $3\frac{1}{2}$ lbs. The patient was the 11th of 15 children, and the gestational period was 38 weeks. This is one of the few instances where the mother gave a history of having had German measles during the 4th month of pregnancy. The child

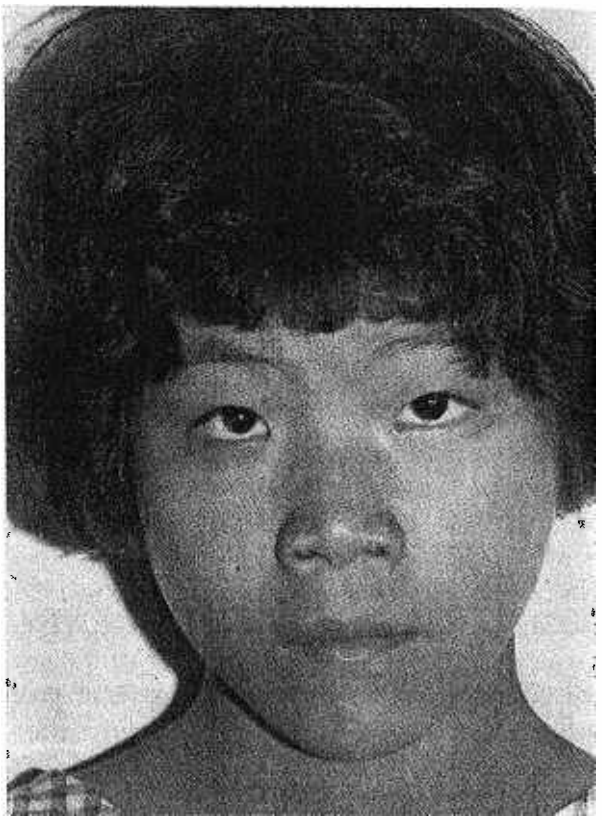

Fig. 5 (a). To show the nine year old school-girl of subnormal intelligence.

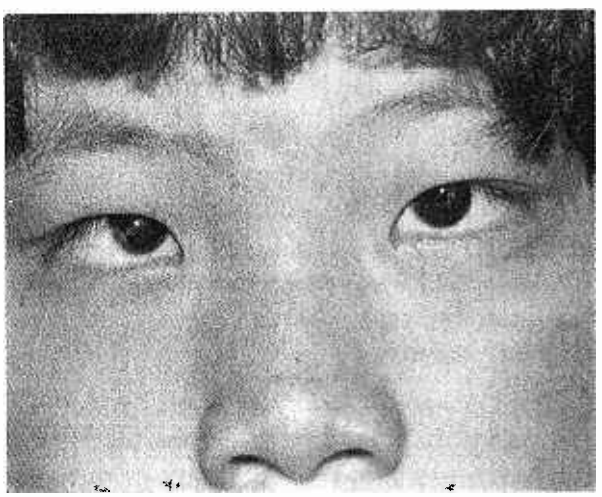

Fig. 5 (b). A close-up of the eyes. This child had marked horizontal nystagmus.

now at the age of 10 years is mentally retarded and has a microcephaly, measuring only $18\frac{3}{4}$ inches, a ventricular septal defect, and is stunted measuring only 3 feet 6 inches, and weighing 32 lbs. No abnormality was detected in the eyes. The results of the haemagglutination inhibition tests was 2048, while the rubella complement fixation test was 12, both of which show a very high titre.

DISCUSSION

Rubella has a world-wide distribution and has its highest incidence in older children and

young adults, and is uncommon in infants and pre-school children. Antibody studies by Dudgeon 1965; Sever, Shiff, Bell, Kapiluan and Huebner show from antibody studies that 15% to 18% of women of child-bearing age are still susceptible to rubella. Viraemia occurs at an early age in the disease process, the foetus being infected at the time of the rash. It has also been said that rubella can occur without a rash (Krugman, Ward, Jacobs, and Lazer 1953), and it is only within the past few years that the importance of subclinical infection has come to be recognised and that patients with subclinical infection are infectious. Laboratory studies have now revealed a stage when they can usefully be employed in the diagnosis of suspected cases of rubella in pregnant women and of cases with whom they have been in contact (Plotkin 1964). McCarthy et al (1963) and Dudgeon (1964) have cultured the virus in a number of different cell culture systems e.g. primary African green monkey kidney (AGMK) and R.K. 13 transferred line of rabbit kidney cells. Dudgeon states that the virus is present in the nasopharynx and urine and faeces for a week before and after the onset of a rash, and virus can be recovered in about 85% to 90% of cases of rubella. A number of serological tests are also used to determine the patients immune status to rubella.

(1) Neutralising antibody:

McCarthy (1963) and Dudgeon (1964) have also found neutralising antibodies within a few days of the rash, increasing rapidly by the end of the first week, and reaching a plateau 21 to 28 days after the rash. The titre remains unaltered for many years.

(2) Complement fixing antibodies:

Complement fixing antibodies in rubella appear slightly later than neutralising antibodies and may not reach a peak titre till about one month after the rash. Complement fixing antibodies in rubella appear slightly later than neutralising antibodies and may not reach a peak titre till about one month after the onset of the rash. It is more reliable than neutralising antibodies and the titre declines after two to five years. If a rising titre to both neutralising and complement fixing antibodies is present. the diagnosis of rubella is certain (Dudgeon 1967). Recent infection can be considered highly probable if a high titre to both neutralising and complement fixing antibody is found. The presence of a neutralising antibody without any rise of complement fixation titre suggests a past infection. Infants with congenital rubella have also serum neutralising antibodies comparable to those observed in the mothers. The predominant antibody appears to be IgM (19S) up to 7 months of age; by the end of the first year, IgG (7S) antibody may be dominant. Detectable levels of neutralising antibodies appear to persist for many years.

Isolation of patients

The new discoveries in the rubella syndrome have led to the importance of isolating these contagious babies to prevent the spread of infection to susceptible women in the early months of pregnancy. Infants with rubella should be admitted to a separate room (Cooper & Krugman 1966). Ideally staff members should be screened for rubella neutralising antibodies and only immune persons should be assigned to the rubella unit. Cooper & Krugman (1966) have outlined the management of the congenital rubella syndrome in the neonatal period. One of the early signs is purpura and this may be extensive, but spontaneous haemorrhage may be rare in spite of the severity of the thrombocytopaenia. Examination of the eyes would reveal rubella retinopathy and the small rubella cataract is a central lenticular opacity while rubella retinopathy is a black patchy pigmentation variable in size and location. Hepatosplenomegaly may be minimal at birth, but progressive enlargement occurs occasionally during the neonatal period. Hearing loss may be difficult to bear until the child is about 4 or 5 years old. Rubella associated deafness is usually not complete and therefore hearing aids are indicated (Cooper & Krugman 1966).

Preventive Measures of Rubella

Dudgeon (1967) states that McDonald and Peckham (1967) have studied the effect of gamma-globulin given to 30,746 pregnant women exposed to rubella during pregnancy in the period of 1956 to 1962. The attack rate in the family was 1.95%. The incidence of heart disease and deafness in the offspring of 610 women who contacted rubella was 18%. They found 13% of women in the first eight weeks of pregnancy contacted rubella. Gamma-globulin given before exposure will reduce the clinical rate and thereby reduce the risk of foetal infection. Dudgeon (1967) states that the only answer to the prevention of foetal malformation lies in inducing a state of active immunity to rubella before pregnancy, and this can only be done by active immunisation with vaccines. Dudgeon (1967) states that Parkman, Meyer and Panos (1966) have administered high passage levels of attenu-

TABLE I

CONGENITAL RUBELLA SYNDROME IN SINGAPORE CHILDREN

No.	Sex Age	B.W.	Pregnancy Birth History	Jaundice	Haemoglobin	Petechiae	Liver	Spleen	Eye Changes
Case 1	M/7 yrs.	4 lbs.	No rubella	Yes for 3 months	13 gm%	Nil	Np	Np	Microphthalmus with cataract
Case 2	F/2 yrs.	5 lbs.	No rubella	No	12 gm%	Nil	Np	Np	Rt. eye rubella retinitis with pigmentary changes in macular (L) eye cataract
Case 3	M/4 wks.	9 lbs. 9 oz.	No rubella	Yes	—	130,000	2 f.b.	Np	Bilateral cataract
Case 4	F/1 yr.	4 lbs.	No rubella	No	11.8 gm%	No	2 f.b.	Np	1. Nystagmus 2. Microcornea 3. Cataract
Case 5	M/3mths	4 lbs 8 oz.	No rubella	Yes, 7th day of life	13.8 gm%	No Platelet 45,000	2 f.b.	2 f.b.	Nil. X-ray changes in knees
Case 6	F/9 yrs.	6 lbs.	No rubella	No	13.8 gm%	Not done	Np	Np	Nystagmus
Case 7	M/10 yrs.	3 lbs. 8 oz.	Yes, at 4 mths.	Yes, 7 days after birth	Not done	Not done	Np	Np	Nystagmus

TABLE 1 (Contd.)

	Mentality	Heart	Deafness	Neutralising Antibodies	Haemagglutination Antibodies
Case 1	Microcephaly	P.D.A.	No	8 (low titre)	1 in 256
Case 2	E.S.N. level	V.S.D.	Total deafness	Not done	512 (+ve)
Case 3	Mongol	C.H.D.	Too young to be tested	Not done	1024 (+ve)
Case 4	Microcephaly	Normal	No	64 (+ve) Intrauterine Infection	Not done
Case 5	Too young to assess	N.a.d.	Too young to assess	32	16 — Baby 14 — Mother
Case 6	Educationally subnormal	V.S.D.	No		
Case 7	Low grade Microcephaly	Normal	No	C.F.T. — 12	HAI 2048 (high)

ated virus in 34 institutionalised children. None of them developed any illness and all developed neutralising antibodies. It is hoped that in the next few years vaccination of pregnant women against rubella will prevent this dreadful complication.

SUMMARY

1. Seven cases of rubella syndrome occurring in Singapore children are described.
2. The features common to those children are seen in Table 1, namely mental deficiency, microcephaly, congenital heart disease and cataract.
3. A review of the present day literature pertaining to rubella infection is given.
4. It is hoped in the near future with suitable vaccines that this dreaded complication occurring to infected foetuses will be prevented by vaccination to pregnant women.

ACKNOWLEDGEMENT

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