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Review

Clinical manifestations of congenital rubella syndrome: A review of our experience in Vietnam

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ABSTRACT

Rubella vaccination programs have dramatically reduced the incidence of rubella and congenital rubella syndrome (CRS) in developed countries. However, CRS prevalence is still rising in developing countries where rubella-containing vaccines (RCV) are not included in the immunization program and even in some countries where a part of the population lacks immunity to rubella despite the presence of RCV in the regular immunization program. This review aimed to summarize the clinical features of CRS using data from our studies conducted between 2011 and 2015 in Vietnam, wherein we examined clinical manifestations in Vietnamese children with CRS who were born after the large rubella outbreak of 2011; a series of studies dealing with CRS in North America and Europe after the 1960s epidemic; and those from countries before introduction of RCVs.

This review shows that children with CRS have a variety of disabilities such as hearing, visual, developmental, behavioral, cardiac, and endocrine impairments, which have variable severity and may appear in different combinations. Some of these impairments can appear or worsen later in the lives of these children.

Physicians should thus complete pediatric, cardiac, auditory, ophthalmologic, and neurologic examinations along with laboratory diagnostic testing soon after birth. These assessments should be repeated during follow-up if congenital rubella infection is suspected in a neonate. Timely intervention for cardiac defects can be lifesaving. Early introduction and continuation of speech, occupational, physical, and behavior therapies and training with appropriate medical interventions by a multidisciplinary team approach are required to maximize quality of life.

Contents

Abbreviations: ASD, autism spectrum disorder; ASQ, the Ages and Stages Questionnaire; CARS2, Childhood Autism Rating Scale, second edition; CRS, congenital rubella syndrome; Denver II, the Denver Developmental Screening Test II; DSM, the Diagnostic and Statistical Manual of Mental Disorders; M-CHAT, Modified Checklist for Autism in Toddlers; PH, pulmonary hypertension; RCV, rubella-containing vaccine; SNHL, sensorineural hearing loss.

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1. Introduction

Rubella is usually a mild infectious disease often accompanied by rash; however, rubella infection in pregnant women can result in miscarriage, stillbirth and a series of disabilities known as congenital rubella syndrome (CRS), characterized by cataracts, hearing impairment, cardiac defects, and damage to the nervous system [1,2].

Rubella became a focus of major interest in 1944 when Gregg, an Australian ophthalmologist, showed an association between a syndrome including cataracts and heart disease with maternal rubella in early pregnancy [3]. Swan and colleagues expanded Gregg's findings and described the association between rubella and hearing impairment, cataracts, congenital heart disease, low birth weight, failure to thrive, microcephaly, and developmental delay [4].

A rubella pandemic started in Europe in 1962–1963 and spread to the United States in 1964 [5]. The extensive pandemic in the United States resulted in an estimated 20,000 children with CRS, leading to >11,000 spontaneous or therapeutic abortions and 2100 neonatal deaths [6]. This tragic experience expanded our understanding of CRS, adding numerous other transient or permanent abnormalities to its clinical spectrum. Clinical manifestations and the long-term prognosis of CRS have been well studied since the late 1960s to 1980s.

The first rubella vaccine entered into commercial use in 1969 and 1970 and it has been introduced into the national immunization program in many countries thereafter, which has led to a dramatic worldwide decrease in CRS. However, CRS remains a problem, especially in developing countries where rubella-containing vaccines (RCVs) are not included in the national immunization program, with estimates of more than 100,000 new CRS cases annually worldwide in 2010 [7]. Even in countries where RCVs are included in the national immunization program, CRS can emerge if a considerable portion of the population in the community remain susceptible to rubella. A rubella outbreak occurred in Japan between 2012 and 2013, resulting in the emergence of more than 40 CRS cases. This outbreak occurred because middle-aged males did not receive childhood RCVs and the RCV immunization rate among women of childbearing age was insufficient as mandatory immunization in a school setting was converted into immunization individually at private clinics [8,9]. In the United States, where endemic rubella was eliminated, several children with CRS were born to mothers from countries where RCVs are not included in the national immunization program and who were therefore presumably unimmunized [10]. The occurrence of CRS increased with the low coverage of regular RCV immunization during childhood, leading to an increase in the proportion of pregnant women susceptible to rubella in Greece in 1993 [11]. Hence, despite being vaccine-preventable, CRS remains non-negligible disease in some countries.

However, it is difficult to detect CRS in many cases. Many CRS-associated defects can be undetectable or overlooked in the early months of life and some manifestations may occur later in life; during childhood, adolescence, or early adulthood. It is difficult to recognize these manifestations and associate them with CRS not only in rubella-endemic countries where surveillance or screening for each defect in young children are scarce but also in countries where rubella is rarely seen because of the immunization program [12]. Therefore, there have been few studies that comprehensively examined clinical manifestations of CRS using recently established screening or assessment tools.

In the Khanh Hoa Province, south-central Vietnam, in 2009–2010, when RCVs were not a part of the national vaccination program, 29% (95% confidence interval, 27–31%) of pregnant women were susceptible to rubella [13]. In the following year, a large-scale rubella outbreak occurred throughout Vietnam between January and July 2011, and many CRS cases emerged [14]. To characterize the clinical manifestations of CRS, infants with CRS in the Khanh Hoa Province were examined and followed up prospectively for four years [15,16]. The first study [15] targeted infants <12 months of age who had manifestations suggesting CRS [17], from October 2011 to September 2012, at the only referral hospital in Khanh Hoa. In the second study [16], we followed up the children with CRS and assessed their developmental, ophthalmological, and otological status in 2013 and 2015 [16]. A retrospective survey of children with CRS was also performed, focusing on patent ductus arteriosus (PDA), by reviewing the medical records from 2011 to 2015 in a children's hospital in Ho Chi Minh City, Vietnam (Toizumi et al., under review).

The present paper reviews clinical manifestations of CRS using data from studies in Vietnam from 2011 to 2015 ([15,16]; Toizumi et al., under review), in which CRS patients were examined using currently available assessment tools. Moreover, data from previous studies examining a substantial number of patients born after a large rubella outbreak in Europe and North America in the 1960s, and from other studies from countries before RCV introduction or from those where RCVs have not been introduced yet were also reviewed.

2. Epidemiology of congenital rubella syndrome

Incidences of CRS per 1000 live births during rubella epidemics in countries without RCVs in the national immunization program were 0.6 in Trinidad and Tobago in 1982–83 [18], 0.7 in Oman in 1993 [19], 0.8 in Ghana in 1995–1996 [20], 0.9 in Sri Lanka in 1994–95 [21], 1.5 in Singapore in 1969 [22], 2.2 in Panama in 1986 [23], 3.5 in Russia in 1979–1997 [24], and 20 in the Ryukyu Islands (Okinawa, Japan) after a rubella epidemic in 1964–1965 when Okinawa was under the United States occupation [25] (Table 1). The incidence during non-epidemic periods varied from 0.1 to 0.2 per 1000 live births [26].

In Khanh Hoa province, Vietnam, 38 CRS cases aged less than 12 months were identified during a one-year period after the rubella outbreak in 2011 (our first CRS study, [15]). In this study, the incidence of CRS was 2.1 per 1000 live births, which peaked up to 7.8 per 1000 live births in the highest epidemic month. The incidence in Nha Trang City, the capital of Khanh Hoa province, was 3.0 per 1000 live births, which was assumed to be more accurate because the surveyed hospital was located in this city, where most of the infants were from.

Difference in seroprevalence among women of childbearing age could reflect variable CRS incidences among the studies (Table 1).

Table 1
Incidence of congenital rubella syndrome (CRS) and rubella susceptibility in women of childbearing age.

Country, city	Year	CRS incidence (per 1000 live births)	Reference	Proportion of women of childbearing age susceptible to rubella
Khanh Hoa, Vietnam	2012–2013	2.1	[15]	29% in 2009–2010 [13]
Vietnam (mathematical modeling)		2.3 (estimated)	[7,13]	29% in 2009–2010 [13]
Trinidad and Tobago	1982–1983	0.6	[18]	68% [75]
Oman	1993	0.7	[19]	8% in 1988–89 (4–30% by regions) [19]
Ghana	1995–1996	0.8	[20]	7% (postepidemic) [20]
Sri Lanka	1994–1995	0.9	[21]	43% [76]
Singapore	1969	1.5	[22]	47% [77]
Panama	1986	2.2	[23]	38% in urban and 64% in rural [75]
Russia	1979–1997	3.5	[24]	17% [24]
Ryukyu (Okinawa, Japan)	1964–1965	20	[25]	7–11% in the Ryukyus, 37% in Amami (islands close to the Ryukyus) (postoepidemic) [78]

Once a rubella outbreak occurs, drastic change in seroprevalence will follow. Difference in CRS incidence also could be influenced by methods detecting CRS (e.g., active/passive surveillance, availability of specific examinations, inclusion of cases of late-onset manifestations, and so on) and the definition of CRS. Therefore, it is difficult to interpret and compare those results directly. It is interesting to note that the finding in our study in Khanh Hoa was comparable to a CRS incidence of 2.3 (95% CI, 2.1–2.6) cases per 1000 live births in Vietnam that was estimated by mathematical modeling using rubella seroprevalence of pregnant women in Nha Trang between 2009 and 2010 [7,13].

The incidence of CRS determined in our study may have been underestimated because it did not include those who died in other small district hospitals soon after delivery, those who would develop or reveal CRS manifestations in later life, and those with abortions or stillbirths.

3. Clinical manifestations of congenital rubella syndrome

Clinical manifestations of CRS discussed below are summarized in Table 2.

3.1. Manifestations of CRS in neonates

Neonates with CRS can present with transient thrombocytopenia with or without purpura, "blueberry muffin" skin lesions with dermal erythropoiesis, hemolytic anemia, hepatosplenomegaly,

Table 2
Clinical manifestations of congenital rubella.

	Transient	Permanent	Development and late-onset[a]		Transient	Permanent	Development and late-onset[a]
General				*Central nervous system*			
Intrauterine growth restriction				Microcephaly		+	
Delay in postnatal somatic growth	+	+		Meningoencephalitis	+		
Eyes				Large anterior fontanel	+		
Cataracts		+		Psychomotor developmental delay		+	+
Microphthalmia		+		Autism spectrum disorder		+	+
Pigmentary retinopathy		+		Learning disorder		+	+
Cloudy cornea		+		Neurologic defect		+	+
Glaucoma		+	+	Progressive rubella encephalitis		+	+
Hypoplasia of the iris		+		*Endocrine*			
Cloudy cornea	+			Diabetes mellitus		+	+
Keratic precipitates		+	+	Thyroid diseases		+	+
Keratoconus		+	+	Growth hormone deficiency		+	+
Corneal hydrops		+	+	Addison disease		+	+
Lens absorption		+	+	*Urogenital anomalies*			
Ears				Hypospadias	+	+	
Sensorineural hearing impairment		+	+	Cryptorchidism	+	+	
Central hearing impairment		+		Vesicoureteral reflux	+	+	
Cardiovascular				*Others*			
Patent ductus arteriosus			+	Dermal erythropoiesis	+		
Pulmonary arterial stenosis		+		Thrombocytopenia with/without purpura	+		
Aortic stenosis		+		Hepatosplenomegaly	+		
Coarctation of aorta		+		Hepatitis	+		
Atrial/ventricular septal defects		+		Radiolucent bone disease	+		
Pulmonary hypertension		+		Jaundice	+		
Myocarditis	+			Adenopathy	+		
Hypertension		+	+	Interstitial pneumonitis	+		+
				Chronic diarrhea	+		

The clinical features of CRS are grouped into three categories: transient manifestations in newborns and infants; permanent manifestations, which may be present at birth or become apparent during the first year of life; and development and late-onset manifestations, which usually appear and progress during childhood, adolescence, and early adult life [27,58]. These groupings overlap. "+" suggests the group(s) into which the respective manifestation is categorized commonly.

[a] Some occur early.

hepatitis, jaundice, meningoencephalitis, large anterior fontanelle, interstitial pneumonia, myositis, myocarditis, diarrhea, cloudy cornea, radiolucent bone disease, and adenopathy [26,27]. Most infants with CRS have some degree of intrauterine growth restriction and may continue to fail to thrive [6,28].

In the prospective CRS surveillance study in Khanh Hoa (our first study [15]), we found 84% of the 38 infants with CRS presented with purpura or "blueberry muffin" skin lesions. Hepatosplenomegaly and thrombocytopenia with platelet counts less than 150×10^9/liter were detected in 68% and 76% of the subjects, respectively. Seventy-one percent and 72% of the infants with CRS had low birth weight <2500 g in a prospective surveillance in Khanh Hoa [15] and in a retrospective study in Ho Chi Minh city (Toizumi et al., under review), respectively.

3.2. Hearing impairment of congenital rubella syndrome

Sensorineural hearing loss (SNHL) is the single most common finding among children with CRS [6]. Previous reports from the United States and Oman found hearing impairment in 66–90% of children with CRS. This impairment was generally bilateral and sensorineural [29–32]. SNHL may occur following maternal infection up to the 18th to 20th week of pregnancy, while other rubella-related defects of organogenesis (i.e., cataract and heart disease) only occur after infection before the ninth to eleventh gestational week [30,33].

The worldwide burden of SNHL following CRS remains high, and in countries without RCV in the national immunization program, CRS is still the most important cause of congenital SNHL [34,35]. However, the burden of hearing impairment among infants with CRS has been underestimated due to late recognition. Otoacoustic emissions and automated auditory brainstem responses [36] are now available for screening infants at risk or all neonates universally in order to detect hearing defects; however, they are still not commonly used in developing countries where CRS often occurs. Delays in detecting hearing impairment can make CRS diagnosis difficult, hinder introduction of education for language acquisition, and lead to misdiagnosis of intellectual developmental delay or autism spectrum disorder (ASD).

A Swedish study reported that hearing impairment in CRS may progressively worsen after the first year of life [37]. Desmond and colleagues, in a United States study, observed two children with CRS whose auditory acuity was normal but later suddenly developed SNHL [38].

Twenty-one children with CRS were evaluated in 2013 and 16 of them was examined again in 2015 (five did not come to the examination in 2015) using automated auditory brainstem responses at the median ages of 23 and 47 months, respectively, in the CRS follow-up study in Khanh Hoa, Vietnam (our second study [16]). Thirteen (62%) showed hearing impairment; among these, 10 had moderate or greater level of bilateral hearing impairment, which would hamper their language acquisition without any appropriate hearing aids or education.

3.3. Ophthalmological manifestations of congenital rubella syndrome

Rubella virus can infect every part of the developing fetal eye via the capillary network and slow cell division and maturation [39].

Previous studies of CRS arising from the rubella epidemics of 1960s in the United States [30,40] and the United Kingdom [41] have shown that 53–78% of patients with CRS had ocular problems. A "salt and pepper" pigmentary retinopathy (24–60%) is the most common ocular finding, followed by cataracts (17–63%), nystagmus (13–25%), strabismus (13–24%), microphthalmia (9–23%), amblyopia (16%), and glaucoma (5–12%) [30,31,40–42]. A previous study investigated the etiology of childhood cataracts in south India and found that 25% of cataracts in infants aged less than one year were due to CRS and cataract with nuclear morphology had a 75% positive predictive value for CRS [43].

A study investigated patients born in the early 1960s in the United States with CRS and prior ocular pathology, followed up until late adolescence [44]. It reported that nearly 10% of the patients developed additional forms of eye defects as delayed manifestations. Some of them had developed late-onset glaucoma and the diagnosis was made 3–22 years after birth. Keratic precipitates, keratoconus, corneal hydrops, and spontaneous lens absorption were also reported as late-onset ocular defects [45].

Two hundred and forty-three children attending a school for the deaf in Nepal were examined for ocular defects associated with CRS in 2009, of which 18 (7.4%) met the clinical criteria for CRS and all the 18 children presented with pigmentary retinopathy [46]. This indicated that detection of pigmentary retinopathy in children with congenital hearing impairment could be an indicator of CRS first diagnosed in older age.

An ophthalmologist examined a total of 21 children with CRS at the median ages of 23 months in 2013 and 16 of them were examined again at the median age of 47 months in 2015, in the follow-up study in Khanh Hoa (our second study [16]). Among the 21 children, 11 (52%) had abnormal ocular findings; ten (48%) had pigmentary retinopathy and seven had other ocular abnormalities such as cataract (19%), myopia (11%), hyperopia (11%), strabismus (29%), microphthalmia (19%), and nystagmus (10%). Cataract was detected in four children (19%); one was unilateral and three were bilateral (Fig. 1). All children with cataracts also had microphthalmia and strabismus. Prognosis after surgery for bilateral cataracts can be poor if associated with microphthalmia [40].

3.4. Developmental delay of congenital rubella syndrome

3.4.1. Global developmental delay

Chess observed children with CRS born after the rubella epidemic in 1960s in the United States, and found overlapping neurological manifestations such as unspecified, borderline, mild, moderate, severe, or profound intellectual disability (37%), hard signs of physical neurological defects such as spasticity (44%), and soft signs such as clumsy gait (24%) [29]. Ninety-five percent of children with CRS and intellectual disabilities also presented hearing and/or visual defects in the Chess's study [29]. Givens and colleagues also examined patients with CRS after the 1960s epidemic in the United States and found 62% with mild to severe psychomotor impairments, 41% with mild to severe intellectual disabilities, 18% with hyperactivity, 14% with spastic diplegia, 7% with seizure disorder, 2% with spastic quadriplegia, and a small number of hemiparesis cases [30]. Follow-up through 9–12 years of CRS infants without initial neurologic problems revealed that additional sensory, motor, and behavioral problems, including ASD, can appear in later life and develop progressively [6].

In the follow-up study in Khanh Hoa, Vietnam (our second study [16]), a total of 20 children were evaluated for developmental features using developmental screening tests; 17 (median age 24.7 months) in 2013 and 13 (median age 43.5 months) in 2015 including 10 for the second time and 3 for the first time. Nineteen of the 20 children had an "abnormal" score in at least one domain in the Ages and Stages Questionnaire (ASQ) [47] or a "suspect" score in at least one area of the Denver Developmental Screening Test II (Denver II) [48]. The communication domain in the ASQ and the language area of the Denver II were the most frequently impaired in both assessments. The proportion of children with affected problem-solving and personal-social skills increased at the median age of 44 months. High incidence of hearing impairment and ASD (described later) among the study participants could

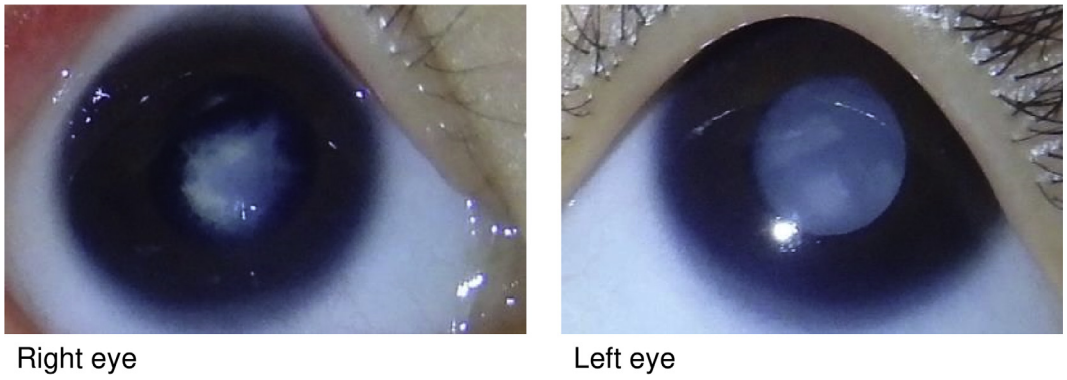

Fig. 1. Cataracts in bilateral eyes of a 21-month-old boy with CRS. A clouding of the lens of the bilateral eyes that was detected by the CRS follow-up study in 2013 is shown [16].

contribute to language and communication disorders [49,50]. Twelve children (71%) failed in two or more ASQ domains in 2013 (n = 17) and could be regarded as having a global developmental delay, which is defined as a significant delay in two or more of the following developmental domains: gross/fine motor, speech/language, cognition, social/personal, and activities of daily living [51]. Twelve participants were examined using the same version of the ASQ at the median age of 25 months. A broad range of total ASQ scores (0–265) was found, indicating that CRS can present with a wide severity range. In this study, children with CRS had multiple areas of developmental difficulties in various levels of severity, with high prevalence of sensory defects and language or communication problems.

3.4.2. Autism spectrum disorder

Chess's study of children with CRS [29] reported a 7.4% prevalence of autism and "partial syndrome of autism" by Kanner's classical criteria [52] which is narrower and more exclusive than current ASD diagnostic criteria. A study estimated that 1228 ASD cases were prevented by RCVs in the United States from 2001 to 2010 [53], using the prevalence (7.4%) of CRS cases presenting with ASD obtained from the Chess's study [29].

In the CRS follow-up study in Khanh Hoa (our second study [16]), 41% of children with CRS at the median age of 25 months failed on the Modified Checklist for Autism in Toddlers (M-CHAT) [54], a tool for screening ASD, in 2013 (n = 17), and 12% met the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [55] for autistic disorder, which is assumed to be a part of ASD according to the DSM-V [56]. Fifteen percent of children tested by the Childhood Autism Rating Scale, second edition (CARS2) [57] at the age of 44 months in 2015 (n = 13) were diagnosed as having severe ASD, and met the DSM-IV criteria for autistic disorder. In this study, a combination of sensory or other impairments made it difficult to diagnose ASD correctly; however, 12–15% of the children with CRS was diagnosed as having ASD.

3.5. Cardiac diseases of congenital rubella syndrome

Cardiac defect is also one of the common findings in CRS. It is detected in 38–70% of patients with CRS [30,31,41,58–60]. Patent ductus arteriosus (PDA) has been reported as the most frequently seen congenital vascular malformation with CRS since Gregg's initial report of CRS in 1941 [3]. The widespread use of cardiac catheterization and echocardiography have improved the ability to diagnose other cardiac vascular malformations in association with CRS, especially pulmonary artery stenosis [61]. A review paper confirmed the association of CRS with branch pulmonary artery stenosis and PDA, summarizing that 78% and 62% of 121 cases with CRS and cardiovascular malformations had branch pulmonary artery stenosis and PDA, respectively, in studies that used cardiac catheterization for evaluation of patients with CRS [61].

In the prospective survey in Khanh Hoa, Vietnam (our first study [15]), we examined 36 children with CRS by echocardiography and detected that 72% of them had cardiovascular malformations, including 67% with PDA (n = 24), 19% with atrial septal defect, 8% with pulmonary stenosis, 3% with ventricular septal defect, and 3% with atrioventricular septal defect. Sixteen cases of PDA (n = 24) were accompanied by pulmonary hypertension (PH) and nine of them died within one year after birth. PH was significantly associated with mortality (hazard ratio 8.33, 95% confidence interval 1.79–38.7) (Fig. 2). Six in 11 children with PDA followed-up regularly by echocardiography underwent transcatheter PDA occlusion therapy and showed a good prognosis without PH.

In Vietnam, an experienced pediatric cardiologist empirically noticed that tubular-type PDA was more frequently seen in PDA associated with CRS than in general PDA without CRS (Do TN, personal communication). Transcatheter closure of tubular-type PDA has difficulty in stabilizing the prosthesis due to lack of a sufficient ampulla; there is the risk of displacement, embolization, or aortic protrusion [62,63]. To clarify the cardiologist's notion and

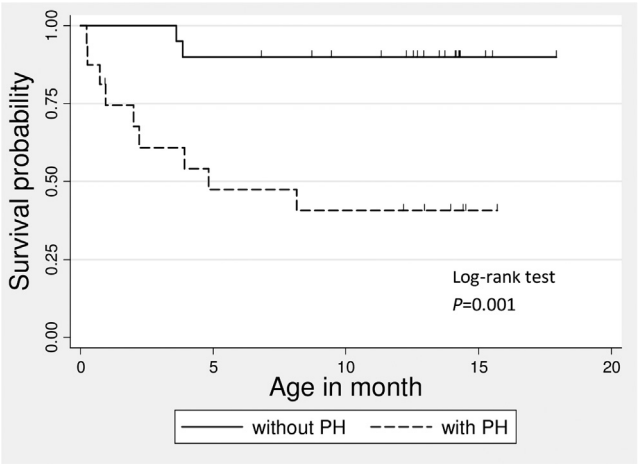

Fig. 2. Kaplan-Meier survival curves of the CRS patients with and without pulmonary hypertension detected on the echocardiographic study in Khanh Hoa, Vietnam, 2011–2012 (reproduced with permission from *Pediatrics*, Vol. 134(2), Pages e519-e526, Copyright© 2014 by the American Academy of Pediatrics) [15]. The Kaplan-Meier curve clearly shows a significantly higher mortality of the CRS patients with pulmonary hypertension compared with those without, with most deaths having occurred before 6 months of age (log-rank test, p = 0.001).

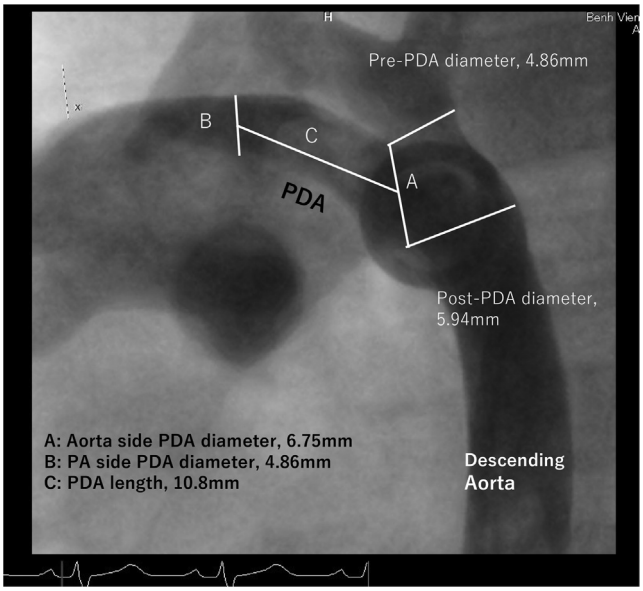

Fig. 3. Tubular type PDA of a 4-month-old boy with CRS. This angiography was taken when he had transcatheter PDA occlusion therapy at Children's Hospital 1 in Ho Chi Minh City, showing a typical tubular type PDA comprising tubular ductus without constriction at the pulmonary insertion (Toizumi et al., under review).

investigate morphological and hemodynamic characteristics of PDA associated with CRS, a retrospective survey of 108 children with CRS and 290 children with PDA but without CRS was conducted in Ho Chi Minh City (Toizumi et al., under review). Echocardiography in 106 children with CRS detected 87% with PDA the most frequently, followed by 65% with tricuspid regurgitation, 50% with atrial septal defect/patent foramen ovale, 44% with pulmonary hypertension, 26% with mitral regurgitation, 23% with pulmonary stenosis, 15% with pulmonary regurgitation, 14% with aortic stenosis, 9% with ventricular septal defect, 7% with aortic regurgitation, 4% with coarctation of aorta and 1% with atrioventricular septal defect. Patients with CRS and PDA (CRS-PDA) (n = 50) had pulmonary stenosis and aortic stenosis more frequently. In addition, they had higher main pulmonary artery pressure (PH) and higher aortic pressure (systemic hypertension) compared to those with PDA without CRS (non-CRS-PDA) (n = 290). The diameter on the pulmonary artery side of PDA was larger and the length of PDA was longer significantly in CRS-PDA than in non-CRS-PDA. Proportion of tubular-type PDA (Fig. 3) was higher in CRS-PDA (16%) than in non-CRS-PDA (3%) (p = 0.020), as the cardiologist noticed. A coil occluder, generally used for small PDA, was more frequently used in those without CRS and a device with double-disk, used to avoid displacing or dropping it in the aorta, was more frequently used in those with CRS, reflecting differences in the morphology and size of PDA between CRS and non-CRS.

Hypertension due to stenosis of renal artery or aorta was previously reported as a late-onset finding in CRS [64]. Obstructive arterial lesions were seen in many vessels in CRS and could cause coronary, cerebral, and peripheral vascular disease in adulthood [65].

Hence, transcatheter closure of PDA in association with CRS needs a more careful choice of device and more detailed follow-up examinations after the intervention.

3.6. Other manifestations of congenital rubella syndrome

We were unable to follow up on long-term prognosis of Vietnamese children with CRS born after the epidemic in 2011. However, it is noted that delayed manifestations can occur in more than 20% of children who have had symptomatic congenital rubella infection [66]. Late-onset diseases of CRS include a variety of endocrine disorders; diabetes mellitus [67,68], thyroid dysfunction [69], growth hormone deficiency [70], and Addison's disease [71]. It has been reported that diabetes mellitus and impaired glucose tolerance occur in approximately 20% of patients with CRS by the age of 35 [67]. Thyroid dysfunction has been reported in 5% of patients with CRS in a previous study [72]. It manifests variedly as hypothyroidism secondary to Hashimoto's thyroiditis, thyrotoxicosis, or idiopathic hypothyroidism [69].

Late-onset interstitial pneumonitis has been detected at the age of 3–12 months and led to death in some cases [6,26,73]. Progressive rubella panencephalitis, a slowly progressive disease of the central nervous system that is due to chronic rubella virus infection of the brain, rarely manifests during the second decade of life among patients with CRS [6]. Urogenital anomalies including hypospadias, cryptorchidism, and vesicoureteral reflux may occur in 20% or children with CRS [74].

4. Conclusions

In CRS, mortality is high and survivors can have a variety of disabilities in different combination and severity, some of which would appear or worsen in later life. Introduction of RCV into the national immunization program and maintenance of high coverage of RCV immunization are critical to prevent rubella and CRS, while early detection and management of patients with CRS are also an imperative clinical and public health issue.

Surveillance and reporting system of rubella and CRS are necessary to recognize suspected cases and call attention to high-risk groups (e.g., women of childbearing age and people around them). If a neonate is suspected of rubella infection, the physicians should complete pediatric, cardiac, auditory, ophthalmologic, and neurologic examinations along with laboratory testing and perform frequent follow-up, especially during the first 6 months. Timely intervention in cardiac defects can be lifesaving. Delays in diagnosis and intervention in hearing and ocular impairments can have critical impacts on the development of language and visual acuity, respectively. Early introduction and continuation of speech, occupational, physical, and behavior therapies, as well as appropriate interventions including hearing aids, cochlear implant, ophthalmological surgeries, eyeglasses or contact lens, or other treatments by a multidisciplinary team approach are required.

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Declarations of interest

The authors declare that they have no conflicts of interest.

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