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Novel facial characteristics found in congenital rubella syndrome: a prospective study of 115 cases in Bangladesh.

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SUMMARY

What is already known:

- Clinical diagnosis of congenital rubella syndrome is possible from a characteristic triad: cataract, deafness, and congenital heart disease.
- There are also some minor criteria, such as microcephaly, hepatosplenomegaly, thrombocytopenia, developmental delay, and failure to thrive.

What this study adds:

- Our study reports some novel facial characteristics (triangular face, wide forehead, prominent nose and hair whorl on the anterior hairline) that will assist in the early recognition and diagnostic confirmation of CRS in developing countries where pregnant women and neonates are not screened for rubella infection and CRS.

ABSTRACT

Objective: To establish novel facial characteristics unique to congenital rubella syndrome (CRS) as prediagnostic criteria to supplement the disease diagnosis in cases with or without a history of maternal rubella infection.
Design: A prospective analysis of 115 cases of CRS (2018–2020) diagnosed based on the presence of any of the triad features.
Setting: One tertiary care referral cardiac hospital in Dhaka, Bangladesh.
Participants: In total, 115 participants (53.04% males) participated in this study. Participants underwent echocardiography if they presented with cardiac symptoms along with deafness, cataract, or microcephaly.
Main outcome measures: Age, sex, and socioeconomic status of the participants; history of maternal vaccination and infection; facial characteristics unique to CRS (triangular face, prominent nose, wide forehead, and a whorl on either side of the anterior hairline) named 'rubella facies'; and frequency of systemic involvements in CRS.
Results: The mean age of the patients was 4.42±2.8 years (53.04% male). The income of 50.43% of the participating families was <1500 USD. Further, 32 mothers (27.83%) were infected with rubella during the first trimester of pregnancy, 15 (13.04%) during the second trimester, and three (2.6%) during the third trimester. The remainder (65.21%) recalled no history of infection during pregnancy. Rubella facies comprised a triangular-shaped face in 95 (82.60%) cases, a broad forehead in 88 (76.52%) cases, and a prominent nose in 75 (65.21%) cases. A rubella whorl was present on the right or left side of the anterior hairline in 80% and 18.26% of cases, respectively. Immunoglobulin G and M antibodies were present in 91.30% and 8.69% of children, respectively. Cataract, deafness, microcephaly, and congenital heart disease were detected in 53.04%, 75.65%, 68.69%, and 99.13% of cases, respectively.
Conclusions: 'Rubella facies', a set of facial characteristics that can support early diagnosis and treatment of CRS may supplement the existing CRS triad.

Keywords: rubella facies, novel, congenital rubella syndrome

INTRODUCTION

Rubella virus belongs to the *Togaviridae* family and is a teratogenic agent that can cross the placenta and cause foetal infection at a risk rate dependent on gestational age.[1] If acquired in the first trimester, such an infection can lead to congenital rubella syndrome (CRS), which is characterised by a triad consisting of congenital deafness, cataract, and congenital heart disease (CHD).[2] Sir Norman Gregg, an Australian ophthalmologist, first identified the relationship between gestational rubella infection and cataract in 1941 during a rubella outbreak in Australia.[3] This discovery was followed by the identification of other complications associated with rubella infection, including microcephaly, low birth weight, hepatosplenomegaly, bone lesions, dental defects, hypospadias, cryptorchidism, and inguinal hernia; additionally, interstitial pneumonitis, thyroid dysfunction, cerebral calcification, diabetes mellitus, and micrognathia may also be present.[4] CRS is associated with high mortality rates and significant morbidity.[5] It can be prevented by an anti-rubella vaccine, which has been available since 1969.[6] However, CRS remains common in countries where access to the anti-rubella vaccine is restricted; moreover, its incidence is often underreported or underestimated. Due to insufficient vaccination coverage among women of reproductive age in countries such as Bangladesh, Nigeria, Vietnam, and Ethiopia, the incidences of rubella and CRS in these countries remain high.[7,8] In Bangladesh, the anti-rubella vaccination was launched in January 2014 and included in the expanded program for immunisation (EPI).[9] However, girls and women who are currently of reproductive age (15-49 years) were not included in the program.[10] Moreover, serological status with respect to rubella antibodies is rarely assessed during pregnancy, and serial screening is not advised. Additionally, screening for hearing defects in neonates is not routinely performed in developing countries, further delaying the diagnosis of CRS.

Rubella virus infection in children and adults usually causes a mild, self-limiting, rash-like illness with minor complications. However, if a rubella infection is contracted during pregnancy, particularly during the first trimester, it may lead to significant complications. One such complication is CRS, which is challenging to diagnose due to variability in signs and symptoms at presentation. Variable factors include the time lapsed between maternal infection and the birth of an infant, an unclear history of maternal infection, restricted access to hearing tests at birth, and varied availability of echocardiography-based screening among babies from mothers with a suspected history of gestational rubella.[7,11,12] Moreover, more than half of the women infected with rubella do not present with classic symptoms such as fever and rash.

Since the discovery of the rubella vaccine, the incidence of CRS has seen significant reduction in developed countries, resulting in very few studies being conducted in this field of medicine in recent times. However, due to the aforementioned reasons, CRS is still a pressing public health issue in the developing world, and it is essential to establish an easier and faster diagnostic method. Several congenital syndromes are associated with facial characteristics that allow early diagnosis and management, including Down's, Noonan's, and Turner's syndromes, among others.[13] This study examined the facial characteristics of CRS patients and identified and reported unique features for the first time. It aimed to characterise the facial morphology of CRS patients from a visual impression and to establish these novel facial characteristics as a prediagnostic tool that may aid in earlier diagnosis and subsequent management of CRS.

METHODS

Subjects

Patients were referred from ophthalmologists, otorhinolaryngologists, and paediatricians for cardiac evaluation of suspected or clinically confirmed CRS. These patients showed one or more components of the rubella characteristic triad. All of the patients had undergone echocardiography as part of their cardiac evaluation. During these examinations, the echocardiographer noticed that these patients possessed similar facial characteristics. Therefore, after collecting written informed consent from the parents of these patients, he took their photographs with a Samsung Galaxy S8 (Samsung Electronics, South Korea) camera and kept these photos with the patients' clinical records for further analysis. This study was conducted as per the Helsinki declaration and was approved by the ethical committee of Labaid Cardiac Hospital, Dhaka (Protocol number: 200716/01).
The inclusion criteria for this study were clinically diagnosed and suspected cases of CRS (71.3% were diagnosed) aged between 3 months and 14 years. Patients with other syndromes that are also associated with particular facial characteristics such as Noonan's and Turner's syndromes were excluded from the study. It was not possible for the patients to take part in the design or planning of the study since most of them were under 18, and do not have the mental capacity to take part in such activities.

Design

A prospective analysis was conducted in the Paediatric Cardiology Department of a tertiary cardiac hospital in Dhaka, Bangladesh (January 2018 to January 2020).

Data collection

Demographic characteristics, such as age, sex, socioeconomic status, presence of rubella triad, maternal vaccination status, and history of rubella infection during pregnancy were documented, reviewed, and analysed. Rubella antibody (IgG and IgM) statuses of the patients were collected from their clinical charts.
Photographs were taken (with guardians' written consent) when the patients visited the hospital for echocardiography follow-up.
Photographs were collected for this study beginning in 2018. The facial characteristics were visually examined in person during the patients' visits and later analysed from photographs. The patterns of patients' heart diseases were recorded from their echocardiography reports, and treatments for CHD were administered accordingly.

Case definition of CRS

a. *Clinically confirmed case*: A patient with two major components of triad or one major and another minor criterion, such as microcephaly, hepatomegaly, developmental delay, failure to thrive, and thrombocytopenia.
b. *Probable case:* A patient with heart disease and suspected hearing impairment, or at least one eye sign.

Major and minor criteria of CRS:

Deafness: As confirmed by the distraction test.
Eye findings (cataract and other findings): As confirmed by a detailed eye examination by an ophthalmologist.

Microcephaly: As confirmed by measurement of occipitofrontal circumference. If the circumference was less than the 3rd percentile for the patient's age and sex, then the diagnosis was confirmed as microcephaly.
Congenital heart disease: As identified by clinical examination and echocardiography.

Definition of rubella facies
A triangular face, a prominent nose, a wide or broad forehead, and the presence of a whorl on the right or left side of the anterior hairline were components of 'rubella facies.' The whorl on the hairline was named 'rubella whorl.' All of these characteristics were checked by visual examination. These findings were further analysed from photographs of the patients.
Triangular face: The forehead was considered as the base and the chin as the apex of the triangle.
Prominent nose: A nose is defined as prominent if there is an increased distance between the subnasale and pronasale.[14] The nasal bridge was sharp and formed a straight line with the tip of the nose.
Wide forehead: The frontal hairline was retreated, forming a wide space above the eyebrow.
Whorl in the anterior hairline: The circular distribution of hair on the scalp that revolves around an axis as determined by the follicle growing direction.

Statistical analysis
Continuous data were expressed as means ± standard deviations; categorical data were expressed as frequencies and percentages. Since this was a single-variant study, no comparative tests were needed.

Patient and public involvement
Patients were recruited at the beginning of the study from referrals to the cardiac centre from various specialists, after the author realised the similarities in facial characteristics of CRS patients referred to the author. Written consent was taken from all the patients to take part in the study and the reason for taking their photographs thoroughly explained. Photographs were taken to establish novel facial characteristics in CRS patients.

As this study was conducted in a cardiac centre, the patients will be followed up for their cardiac symptoms. Since the study is not the result of treatment outcome, only observation of new facial characteristics, so no active participation other than consent to use photograph for analysis and publications were needed. If this article gets published, participants will be informed.

RESULTS

From January 2018 to January 2020, 115 confirmed and suspected cases of CRS were reported to the paediatric cardiology department of the Labaid Cardiac Hospital for cardiac evaluation and management. Due to the lack of a routine screening program in pregnant women and newborns, the mean age of detection in the study population was high, ranging from 3 months to 14 years (4.42±2.8 years). Poor socioeconomic status of approximately half of the study population (50.43%) was a reason for delayed reporting to the treatment facility. It took time for the parents themselves to identify CRS criteria and to seek treatment. None of the mothers were immunised with the rubella vaccine. Some mothers were able to give a history of fever and rash in the first trimester (27.83%), which is the most critical time for teratogenicity of the rubella virus. The majority of mothers (65.21%) had either no history or an unknown history of such an illness (Table 1).

Table 1. Demographic characteristics of the children and mothers included in the study

Sl/ No	Variables		Mean ± SD/ No (%)
1	Patient age (years)		4.42 ± 2.80
2	Case definition	Suspected case	33 (28)
		Confirmed case	82 (71.30)
2	**Sex**		
	Male		61 (53.04)
	Female		54 (46.96)
3	**Socioeconomic Status**		
	a. Income <1500 USD/year		58 (50.43)
	b. Income 1500–4500 USD/year		49 (42.60)
	c. Income >4500 USD/year		9 (7.82)
4	**Maternal vaccination status**		0
5	**Maternal infection status**		
	1st Trimester		32 (27.83)
	2nd Trimester		15 (13.04)
	3rd Trimester		3 (2.60)
	Unknown/no history		75 (65.21)

SD: standard deviation

Serological tests identified acute infection in children by presence of Immunoglobulin M in 10 (8.69%) cases. All of them were less than one year of age and were capable of infecting pregnant women, spreading the virus (Figure 1).

Among systemic manifestations of CRS and established major components of triad, 99.13% of cases reported congenital heart disease. All of the cases were suspected of having CRS or were diagnosed with it during referral (Table 1). Otolaryngologists referred 87 cases and ophthalmologists referred 61 cases. Microcephaly cases (68.69%) were referred from paediatricians (Figure 2).

Rubella facies is composed of four components. Patients presented with different variations of these components. Triangular face was found in 95 cases (82.60%), broad forehead in 88 (76.52%) cases, prominent nose in 75 (65.21%) and whorl on the right side or left side of the anterior hairline in 92 and 21 cases, respectively. In the later part of the study period, many cases were suspected following face observation upon first sight. Triangular face with a whorl on the hairline was the most frequent combination (Table 2).

Table 2. Frequency of facial characteristics (rubella facies) observed among patients with congenital rubella syndrome (N=115)

Sl/ No	Rubella facies	No (%)
1	Triangular face	95 (82.60)
2	Broad forehead	88 (76.52)
3	Whorl in hairline on right side of forehead (rubella whorl)	92 (80)
4	Whorl in hairline on left side of forehead (rubella whorl)	21(18.26)
5	Prominent nose	75 (65.21)

The patterns of congenital heart diseases and treatments offered to the study population were analysed. Patent ductus arteriosus (PDA) was the most common isolated and combined lesion

with other valvular diseases (76.52%). PDA device closure (40.86%) was the most common curative treatment offered from the paediatric cardiology department (Table 3).

Table 3. Types of congenital heart disease and treatment offered (N=115)

CHD	No	Percentage (%)	Treatment offered	No	Percentage (%)
PDA (isolated and with other lesions)	88	76.52	PDA transcatheter closure	47	40.86
			PDA ligation	1	0.86
Valvular stenosis, AS, PS (isolated and in combination with other CHDs)	44	38.26	Balloon valvoplasty	25	21.74
RPA, LPA stenosis (isolated and combined)	17	14.78	Balloon Angioplasty	5	44.35
VSD (isolated or with PS)	3	2.60	Medical management/ Follow up	3	2.60
ASD (isolated or with PS)	10	8.69	Medical management/ Follow up	10	8.69
COA (isolated and combined)	6	5.21	Coarctoplasty	2	1.73
Cor triatriatum	1	0.86	Surgical management	1	0.86
Normal	2	1.73	Discharged	2	1.73

PDA: patent ductus arteriosus, AS: aortic stenosis, PS: pulmonary stenosis, CHD: congenital heart disease, RPA: right pulmonary artery, LPA: left pulmonary artery, VSD: ventricular septal defect, ASD: atrial septal defect, COA: coarctation of aorta

Figure 3-7 show CRS patients with triangular face and wide forehead.
Figure 8 illustrates photographs of patients diagnosed with CRS having a wide forehead. CRS patients also have a prominent nose (Figure 9-10) and a hair whorl on the anterior hairline, either on the right or left side (Figure 11-14).

DISCUSSION

Principal findings

In this prospective study involving 115 children, four components of facial characteristics emerged, which were named 'rubella facies.' These 4 components were a triangular face, a wide forehead, a prominent nose, and a whorl on the right or left side of the anterior hairline. Not all patients demonstrated all four components of 'rubella facies,' but most patients showed a combination of these components (Table 2). There were no age-related differences in the facial characteristics themselves (i.e., the characteristics were not different between older and younger patients); however, the features were more prominent in older participants. This study also found that there was a wide variation in the age of the participants (3 months to 14 years). Therefore, even though this is a congenital disease, the wide age range of the

study population indicates the lack of screening among pregnant women and the delayed diagnosis of CRS patients.
As this study was conducted in a paediatric cardiology clinic, the pattern of heart disease in CRS was also analysed. PDA was found to be the most common cardiac condition associated with CRS.

Comparison with other studies

In an epidemiological study conducted in the USA, 60% of the infants and children were diagnosed with CRS at birth or before 1 month of age; 16% were not diagnosed until 3–16 months of age. These patients also presented with PDA, hepatomegaly, and thrombocytopenic purpura.[15] In another study, the mean age of patients with confirmed cases was 3 months.[8] In our study, the mean age of the participants was 4.42±2.80 years, which indicated delayed identification of these cases compared to those in the aforementioned studies.
A global survey of CRS systemic involvements showed that among the study population, 45% had congenital heart disease, 60% had hearing impairment, and 25% had cataract.[16] Another study in India showed that 78.8% of CRS patients had CHD, 59.9% had eye involvement, and 38.6% had hearing impairment.[5] Many other studies also documented cardiac involvement as the major systemic involvement.[5, 8, 17–20] In this study, the frequency of heart disease was 99.2%; the most common defect was PDA (76.52%), followed by pulmonary valve and artery stenosis (38.26%).
Facial dysmorphism is the hallmark of many genetic and congenital disorders. The most frequently encountered chromosomal abnormality with distinct facial characteristics is Down's syndrome.[21] Turner's syndrome is another disease that can be identified using facial appearances of patients and is characterised by a triangular face (flattened cranial base, posteriorly inclined mandible); its incidence is 1 in 2500 female live births.[22, 23] Children with fragile X syndrome have long, narrow faces, prominent ears, joint hypermobility, and flat feet, which become more obvious with increasing age and may help with this syndrome's diagnosis.[24] Another disease that can be diagnosed from the appearance of patients is Noonan's syndrome. It is a genetic disorder, characterised by mildly unusual facial features, such as tall forehead, hypertelorism, down slanting palpebral fissures, short and broad nose, deep philtrum, widely spaced eyes, thick hooded eyelids, and excessive nuchal skin with low posterior hairline, among others.[25,26]
'Rubella facies' is a novel set of characteristics established in this study. However, the components of 'rubella facies' are found in different combinations in many other syndromes. "Triangular face" has been defined as a hypoplastic face with prominent zygomatic arches, orbital hypertelorism, sunken cheeks, downturned mouth, and occasionally brownish facial discolouration, which is characteristic of Mulibrey nanism.[27] Triangular face is also a characteristic feature of Russel-Silver syndrome, Noonan's syndrome, Prader-Willi syndrome, and Angelman syndrome, among others.[28]
Wide or broad forehead is associated with some rare disorders such as facial dysmorphism-immunodeficiency-livedo-short stature syndrome (FILS syndrome). This feature is also associated with poor language, strabismus, grimacing face, long fingers, and intellectual disability.[29] The presence of a wide forehead in CRS may be due to CHD, as this is one of the components of the CRS triad.
Prominent nose is found in patients with Traboulsi syndrome, heart diseases, and autism spectrum disorder, among other diseases. [30–32] CRS has never been associated with a prominent nose. The presence of this facial feature in CRS patients may be due to its relationship with CHD and mental retardation.

Another component of 'rubella facies' was a hair whorl on the anterior hairline, also known as a hair crown or cowlick. Abnormal hair whorls are also present in many other diseases, such as microcephaly, Apert's syndrome, and Crouzon's syndrome, among others.[33]

Strengths and limitations of this study

This prospective study involved 115 cases that were already confirmed to have or suspected of having CRS. Hence, patients were included in the study with a diagnosis of CRS, so the facial features that were being examined on the patients were definite of being associated with CRS. Further, follow-ups of the cases were performed on multiple occasions during the study period. A large portion of the study population having a diagnosis, or a suspected case of CRS helped physicians to correlate this condition with the visual impression of the facial features upon first sight. Additionally, photographs of the patients were taken with a Samsung Galaxy S8 (Samsung Electronics, South Korea) mobile phone for future visual reference, and hence, it was possible to examine the faces as often as necessary. Facial features of CRS, named 'rubella facies,' can be used as a landmark for detection of CRS in the developing world, where the universal availability of the rubella vaccine, especially for girls and women of reproductive age, remains low.[7,8] Most women infected during pregnancy were overlooked or missed because they showed only mild symptoms. Additionally, serological screening is not a part of antenatal check-ups in these countries (e.g., Bangladesh, Nigeria, India, Vietnam, Ethiopia).[34] Acute symptoms, such as thrombocytopenic purpura, hepatomegaly, and PDA with heart failure are not always seen in neonates;[15] neonatal hearing assessment by otoacoustic emission (OAE) and auditory brainstem response (AVR) are not performed in developing countries routinely, and therefore, diagnosis is often missed.[35] As a result, some infants and children become permanently blind or deaf by the time the diagnosis is made. Many others die from heart failure due to PDA. 'Rubella facies' will be a valuable diagnostic clue indicating that clinicians and parents in such undeveloped or developing countries should provide to a patient whatever medical care is available. These facial features were analysed in 115 cases repeatedly. Though triangular face, whorl in the anterior hairline, prominent nose, and wide forehead are components of some other syndromes, CRS was confirmed in the study cases by serological test and presence of combinations of triad. This is another strength that showcases 'rubella facies' as a component of CRS. CRS is associated with characteristic congenital heart lesions like PDA, pulmonary valve stenosis (PS), etc., which also indicate CRS. Therefore, the existence of 'rubella facies' implies that clinicians and parents should consider the presence of triad and PDA (present in 76.52% of cases), and vice versa.

Limitations of this study exist primarily in the design. First, photographs were taken by non-professional photographers; in most cases, the echocardiographer or cardiologist took the photo using a mobile phone with a 2-dimensional (2D) camera. Second, 3-dimensional (3D) digital anthropometric analysis was not performed. This restricted an advanced, detailed analysis of face such as measuring the accurate circumference of forehead, exact distance between prenasale and subnasale etc. 3D photographic methods have been used for facial analysis or anthropometric measurement of various races to compare them with other races and genders.[36,37] Therefore, exact measurements of faces, noses, and foreheads were not taken, and comparison with normative data was not possible. Normative data for Bangladeshi Asian populations were also not available. Third, this was a preliminary study on the findings of rubella facies by visual impression alone; no comparison was done with facial features of unaffected children (i.e., a patient's wide forehead was not measured or compared with the forehead of a normal child). This study was conducted on CRS patients who were sent for cardiac evaluation. Therefore, many cases with milder symptoms in the community were not included. Hence, the epidemiology in this study does not represent the true status.

Implication of study and future research

Identification of 'rubella facies' will help clinicians and parents to suspect CRS earlier in children, even at a primary healthcare level or at home. Initial suspicion will lead to subsequent investigation and management, thus preventing permanent visual and hearing disabilities in hundreds of children. Early identification and treatment of CHD will prevent mortality due to heart failure in CRS cases.

Future research is necessary to compare patients with rubella facies with control patients and to compare the influence of triad on components of facies. In this study, no age-related influence on the facial characteristics was observed. Further studies are necessary to observe the variation of rubella facies with age (i.e., to compare affected neonates, infants, adolescents, and adults). Correlation of 'rubella facies' with mental retardation and microcephaly may also be studied.

CONCLUSION

In conclusion, 'rubella facies' has the potential to become a landmark prediagnostic criterion of CRS, especially in developing countries, where rubella remains a major public health concern with underrepresentation and high morbidity and mortality rates. Pregnant women are not screened for rubella antibodies during antenatal check-ups, and vaccine coverage of girls and women of reproductive age is insufficient, resulting in high rates of CRS. Using facial features to identify suspected cases of CRS may help achieve earlier diagnoses and treatment. Developing countries should consider the following: achieving complete anti-rubella vaccination coverage for adolescent girls and women of childbearing age is paramount; rubella antibody screening of all pregnant women is recommended; screening of all infants for hearing impairment is encouraged; and sustainable birth defect surveillance (e.g., screening of all children with congenital heart disease, cataract, microcephaly, congenital deafness, unexplained hepatosplenomegaly, or thrombocytopenia) for rubella and correlating them with 'rubella facies' (which is evident at first sight) is crucial. Dysmorphologists should conduct more research on these findings.

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TRANSPARENCY DECLARATION: The author of this paper affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

DISSEMINATION DECLARATION: The author of this paper would like to disseminate the results and new findings of this study.

EXCLUSIVE LICENCE STATEMENT:

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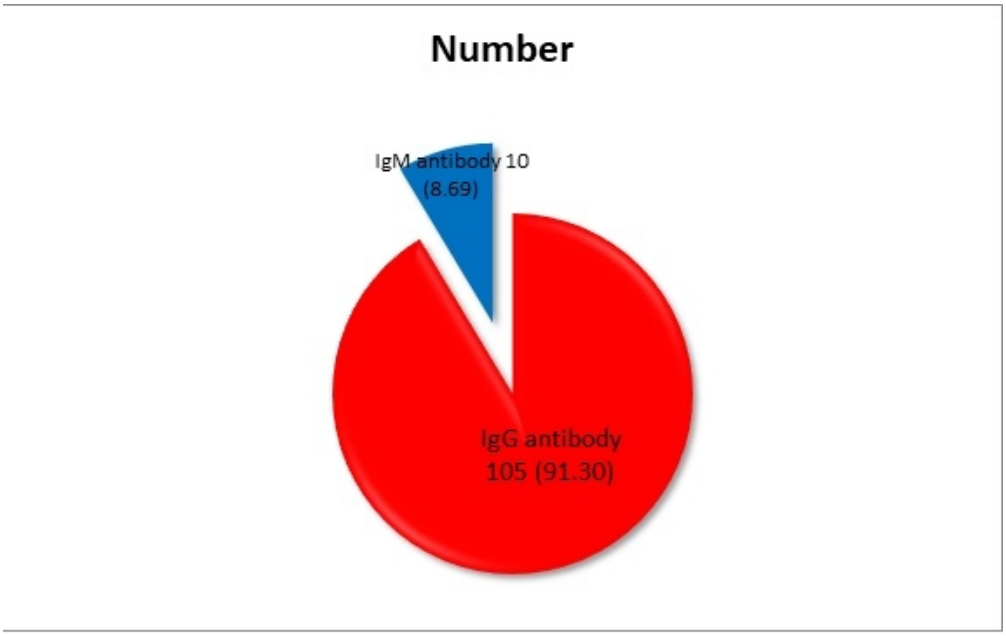
Figure Legends

Figure 1. Frequency of rubella antibodies in patients with congenital rubella syndrome (N=115)
Figure 2. Distribution of clinical characteristics among patients with congenital rubella syndrome (N=115)
Figure 3-7. Triangular face and wide forehead observed in patients with CRS.
Figure 8. Wide forehead observed in a patient with CRS.
Figure 9-10. Prominent nose observed in CRS patients
Figure 11-14. Photographs of patients with CRS exhibiting hair whorl on their anterior hairline, either on left or right side.



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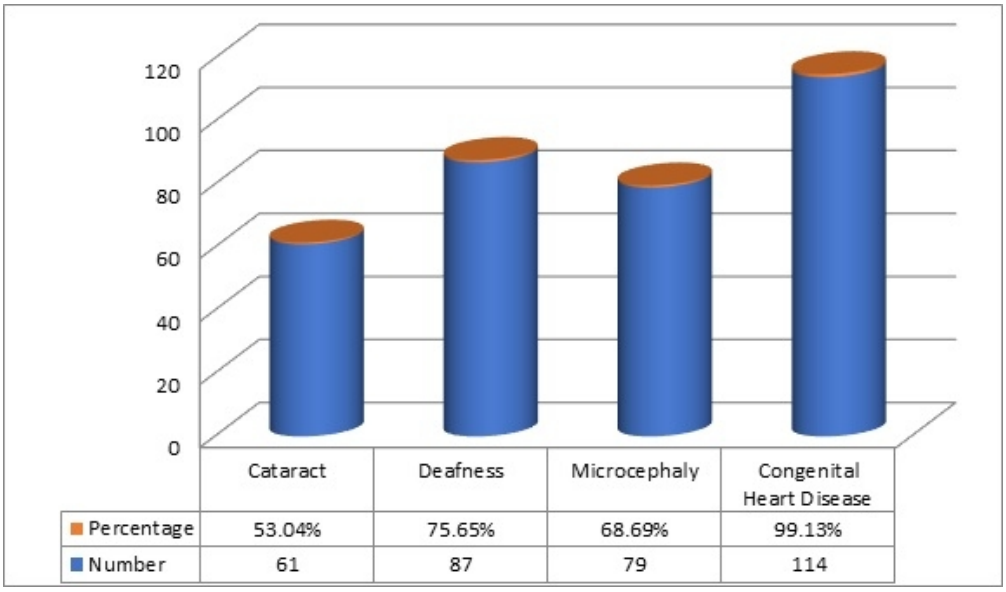

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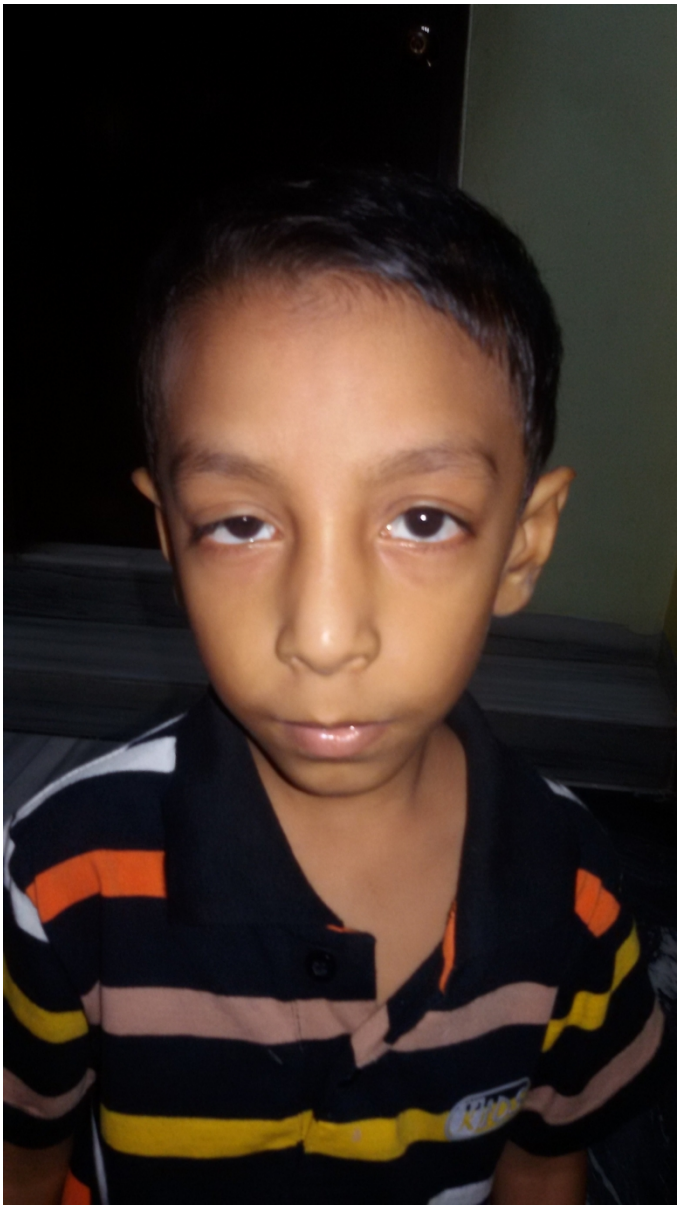

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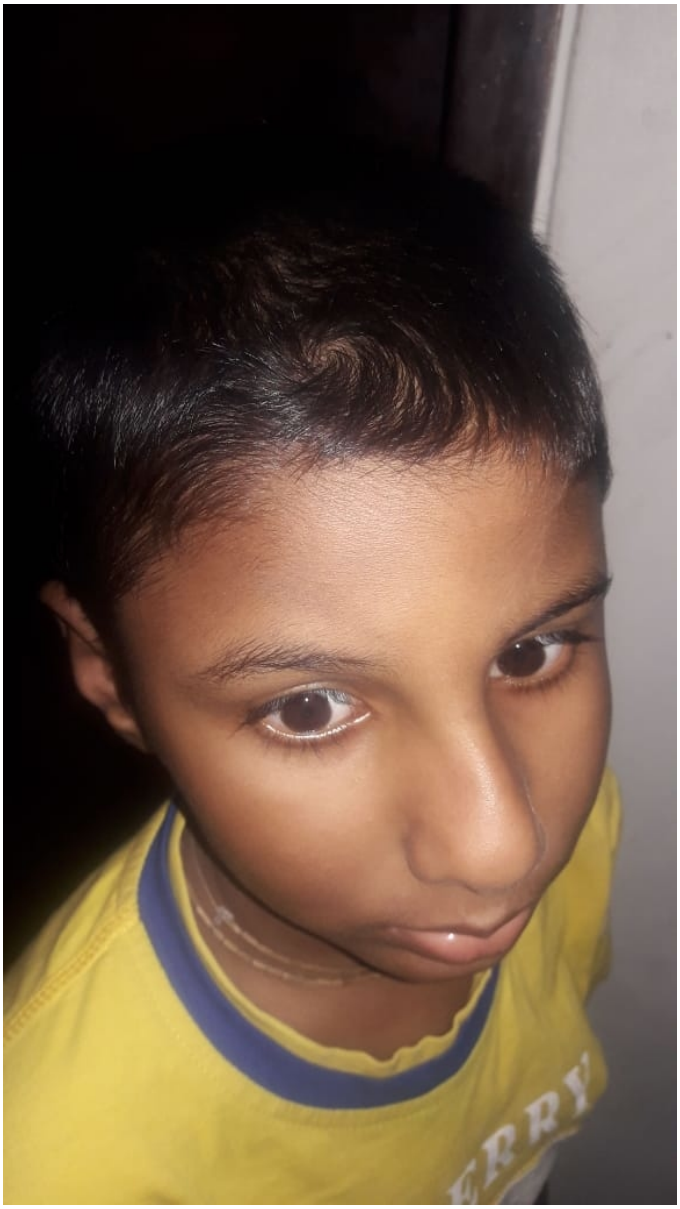

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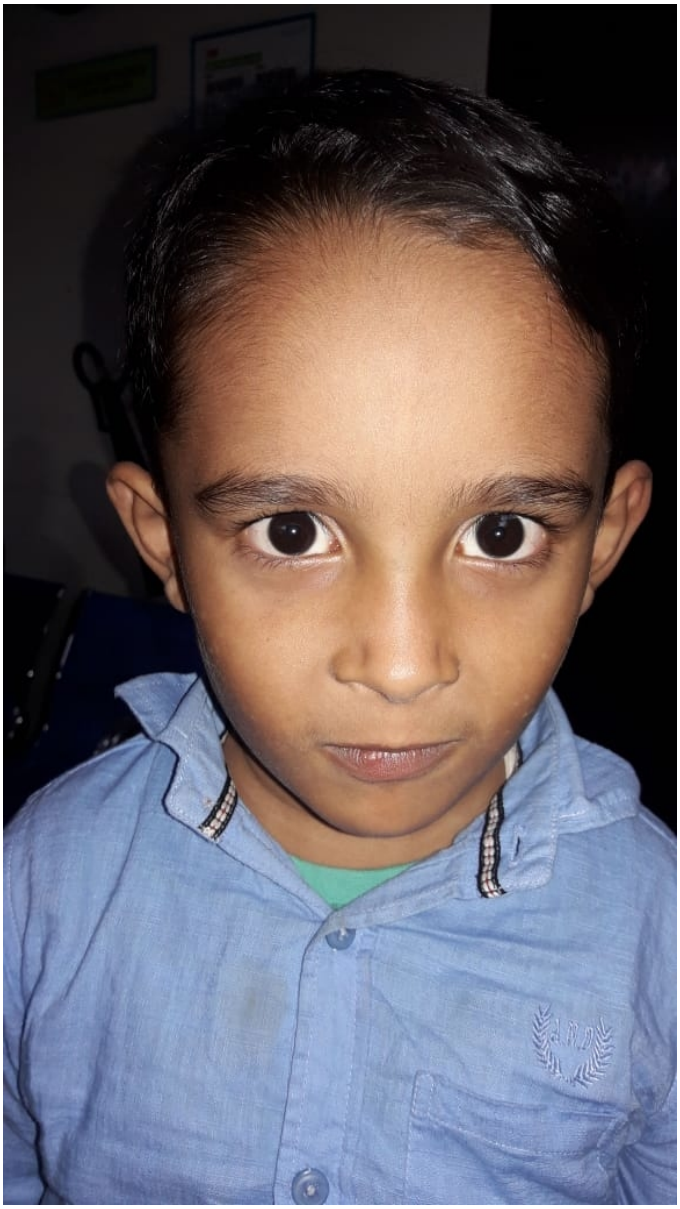

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[14/08/2020]

Fiona Godlee
Editor-in-Chief
British Medical Journal

Dear Editor,

I wish to submit an original article for publication in the *British Medical Journal,* titled 'Novel facial characteristics found in congenital rubella syndrome: a prospective study of 115 cases in Bangladesh.'

Congenital rubella syndrome (CRS) is common in the developing world, where access to vaccinations for women of childbearing age is limited. An infection with rubella virus during pregnancy increases the risk of CRS, which, in turn, increases the risk of adverse outcomes among newborns. In developing countries, CRS is underrecognised and tends to be underreported. In this article, I have identified novel facial characteristics associated with CRS which can help clinicians recognise suspected cases and help ensure early diagnosis and treatment. This study examined facial characteristics of children referred for echocardiography and described distinct features observed among children with confirmed CRS. I believe that this study makes a significant contribution to the literature because it provides preliminary evidence that a triangular-shaped face, wide/broad forehead, and presence of rubella whorls in the anterior hairline might help distinguish children at risk of CRS, in particular, where maternal history of rubella infection is unclear.

Further, we believe that this paper will be of interest to the readership of your journal because it presents evidence that is potentially relevant to an international audience of clinicians with broad spectrum specialties.

Please consider, as potential referees, _____.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board. We have read and understood your journal's policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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BMJ Paediatrics Open

Novel facial characteristics in congenital rubella syndrome: a study of 115 cases in a cardiac hospital of Bangladesh

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Novel facial characteristics in congenital rubella syndrome: a study of 115 cases in a cardiac hospital of Bangladesh

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SUMMARY

What is already known:

- Clinical diagnosis of congenital rubella syndrome (CRS) is possible from a characteristic triad: cataract, deafness, and congenital heart disease.
- There are also some minor criteria such as microcephaly, splenomegaly, thrombocytopaenia, developmental delay, and failure to thrive.

What this study adds:

- This study reports novel facial characteristics (triangular face, wide forehead, prominent nose, and hair whorl on the anterior hairline) as supplementary findings in early recognition and diagnostic confirmation of CRS in low- and middle-low-income countries where pregnant women and neonates are not screened routinely for rubella infection and CRS.

ABSTRACT

Objective: To establish novel facial characteristics unique to congenital rubella syndrome (CRS) as prediagnostic criteria to supplement disease diagnosis in patients with or without a history of maternal rubella infection.

Design: A randomised cross-sectional analysis of 115 CRS cases (2018–2020) identified based on the presence of any of the triad features.

Setting: Outpatient department of a tertiary care referral cardiac hospital in Dhaka, Bangladesh.

Participants: In total, 115 participants (53.04% male) were enrolled. Participants underwent echocardiography if they presented with suspected cardiac symptoms along with deafness, cataract, or microcephaly.

Main outcome measures: Age, sex, and socioeconomic status of the participants; history of maternal vaccination and infection; facial characteristics unique to CRS (triangular face, prominent nose, wide forehead, and a whorl on either side of the anterior hairline) named 'rubella facies'; and frequency of systemic involvements in CRS.

Results: The mean patient age was 4.42±2.8 years. The income of 50.43% of the participating families was < 1500 USD. Further, 32 mothers (27.83%) were infected with rubella during the first trimester of pregnancy, 15 (13.04%) during the second trimester, and 3 (2.6%) during the third trimester. The remainder (65.21%) recalled no history of infection during pregnancy. Rubella facies presented as a triangular-shaped face in 95 (82.60%) cases, a broad forehead in 88 (76.52%), and a prominent nose in 75 (65.21%). A rubella whorl was present on the right or left side of the anterior hairline in 80% and 18.26% of cases, respectively. Immunoglobulin G and M antibodies were present in 91.30% and 8.69% of children, respectively. Cataract, deafness, microcephaly, and congenital heart disease were detected in 53.04%, 75.65%, 68.69%, and 99.13% of cases, respectively.

Conclusions: 'Rubella facies', a set of unique facial characteristics can support early CRS diagnosis and treatment and may supplement the existing CRS triad.

Keywords: rubella facies, novel, congenital rubella syndrome

INTRODUCTION

Rubella virus belongs to the *Togaviridae* family and is a teratogenic agent that can cross the placenta and cause foetal infection at a risk rate dependent on gestational age.[1] If acquired in the first trimester, such an infection can lead to congenital rubella syndrome (CRS), which is characterised by a triad consisting of congenital deafness, cataract, and congenital heart disease (CHD).[2] Sir Norman Gregg, an Australian ophthalmologist, first identified the relationship between gestational rubella infection and cataract in 1941 during a rubella outbreak in Australia.[3] This discovery was followed by the identification of other complications associated with rubella infection, including microcephaly, low birth weight, hepatosplenomegaly, bone lesions, dental defects, hypospadias, cryptorchidism, and inguinal hernia; additionally, interstitial pneumonitis, thyroid dysfunction, cerebral calcification, diabetes mellitus, and micrognathia may also be present.[4] CRS is associated with high mortality rates and significant morbidity.[5] It can be prevented by an anti-rubella vaccine, which has been available since 1969.[6] However, CRS remains common in countries where access to the anti-rubella vaccine is restricted; moreover, its incidence is often under reported or underestimated. Owing to insufficient vaccination coverage among women of reproductive age in countries such as Bangladesh, Nigeria, Vietnam, and Ethiopia, the incidence of rubella and CRS in these countries remains high.[7,8] In Bangladesh, the anti-rubella vaccination was launched in January 2014 and included in the expanded program for immunisation for children.[9] Girls and women who are currently of reproductive age (15-49 years) and at risk were not included in the programme.[10] The serological status with respect to rubella antibodies is rarely assessed during pregnancy, and serial screening is not advised in these countries. Additionally, screening for hearing defects in neonates is not routinely performed, further delaying the diagnosis of CRS.

Rubella virus infection in children and adults usually causes a mild, self-limiting, rash-like illness with minor complications. However, if a rubella infection is contracted during pregnancy, particularly during the first trimester, it may lead to significant complications. One such complication is CRS, which is challenging to diagnose owing to variability in signs and symptoms at presentation. Variable factors include the time elapsed between maternal infection and the birth of an infant, an unclear history of maternal infection, restricted access to hearing tests at birth, and varied availability of echocardiography-based screening among babies of mothers with a suspected history of gestational rubella.[7,11,12] Moreover, most women infected with rubella do not present with classic symptoms such as fever and rash. Since the discovery of the rubella vaccine, the incidence of CRS has been significantly reduced in high-income countries, resulting in very few studies being conducted in this field of medicine in recent times. However, owing to the aforementioned reasons, CRS is still a pressing public health issue in the low- and lower-middle-income countries, and it is essential to establish an easier and faster diagnostic method. Several congenital syndromes are associated with facial characteristics such as those observed in Down's, Noonan's, and Turner's syndromes, among others, and could allow early diagnosis and management. [13] This study examined the facial characteristics of CRS patients and identified and reported unique features for the first time. It aimed to characterise the facial morphology of CRS patients from a visual impression and to establish these novel facial characteristics as a prediagnostic tool that may aid in earlier diagnosis and subsequent management of CRS.

METHODS

Subjects

Patients were referred from ophthalmologists, otorhinolaryngologists, and paediatricians for cardiac evaluation of suspected or clinically confirmed CRS. These patients showed one or more components of the rubella characteristic triad. All the patients had undergone clinical examination and echocardiography as part of their cardiac evaluation. During these examinations, the echocardiographer and cardiologist noticed that all these patients possessed similar facial characteristics. Therefore, after obtaining written informed consent from the parents of these patients, their photographs with Samsung Galaxy S8 (Samsung Electronics, South Korea) camera were taken and stored with the patients' clinical records for further analysis. This study was conducted as per the Declaration of Helsinki and was approved by the Ethics committee of Labaid Cardiac Hospital, Dhaka (Protocol number: 200716/01).
Clinically diagnosed and probable cases of CRS aged between 3 months and 14 years were included in the study. Nineteen patients with other syndromes who were also associated with particular facial characteristics such as those in Noonan's and Turner's syndromes were excluded from the study. It was not possible for these patients to participate in the design or planning of the study since all were under 18 years and did not have the mental capacity to participate in such activities.

Design

A randomised cross-sectional analysis was conducted in the outpatient department of a Paediatric Cardiology unit in a tertiary cardiac hospital in Dhaka, Bangladesh (January 2018 to January 2020).

Data collection

Demographic characteristics, such as age, sex, socioeconomic status, presence of one or more components of the rubella triad, maternal vaccination status, and history of rubella infection during pregnancy were documented, reviewed, and analysed. The rubella antibody (IgG and IgM) status of the patients was obtained from medical records. Paired maternal antibody was not recommended for them.
Photographs were taken when the patients visited the hospital for echocardiography. Photographs were collected for this study since January 2018. The facial characteristics were visually examined in person during the patients' visits and later analysed using the photographs. The patterns of patients' heart diseases were recorded from their echocardiography reports.

Case definition of CRS

a. *Clinically compatible case*: A patient with two major components of the triad or one major and another minor component, such as microcephaly, splenomegaly, developmental delay, failure to thrive, thrombocytopaenia, and meningoencephalitis.
b. *Probable case:* A patient with heart disease and suspected hearing impairment, or at least one eye defect (cataract, glaucoma, pigmentary retinopathy, microphthalmos, optic atrophy, strabismus, nystagmus).
c. *Laboratory confirmed case*: Infant having at least one major component and meeting one of the following laboratory criteria: i) Detection of rubella IgM antibody or ii) sustained level of rubella IgG antibodies, as determined at age 6-12 months in the absence of rubella vaccination.

Major criteria of CRS:

Deafness: As confirmed by the distraction test in the paediatric cardiology outpatient clinic and otoacoustic emission (OAE) and auditory brainstem response (ABR) in the otolaryngology department.
Eye findings (cataract and other findings): As confirmed by a detailed eye examination, including examination of the lens, ocular pressure (tonometry), examination of the retina and refraction test, under general anaesthesia by an ophthalmologist.
Congenital heart disease: As identified on clinical examination and confirmed on echocardiography.

Minor criteria of CRS:

Microcephaly: As confirmed by measurement of the occipitocircumference. If the circumference is > 2 standard deviation (2SDs) smaller than the mean for the patient's age and sex.
Others: Splenomegaly, developmental delay, failure to thrive, thrombocytopaenia, and meningoencephalitis, jaundice.

Definition of rubella facies
A triangular face, a prominent nose, a wide or broad forehead, and the presence of a whorl on the right or left side of the anterior hairline were components of 'rubella facies'. The whorl on the hairline was named 'rubella whorl'. All these characteristics were checked on visual examination. These findings were further analysed using photographs of the patients.
Triangular face: The forehead was considered as the base and the chin as the apex of the triangle.
Prominent nose: An increased distance between the subnasale and pronasale. [14] The nasal bridge was sharp and formed a straight line with the tip of the nose.
Wide forehead: The frontal hairline was retreated, resulting a wide space above the eyebrow.
Whorl in the anterior hairline: The circular distribution of the hair on the scalp that revolves around an axis as determined by the direction of the growing follicle.
Facial characteristics overlapping with those of other diseases were excluded by thorough analysis.

Statistical analysis
Continuous data are expressed as means ± standard deviations; categorical data are expressed as frequencies and percentages. Since this was a single-variant study, no comparative tests were needed.

Patient and public involvement
Patients were recruited from pediatric cardiology outpatient department Written informed consent for participation in the study was obtained from all the parents of the patients, and the reason for taking their photographs was thoroughly explained. Photographs were taken to establish novel facial characteristics of CRS patients.

As this study was conducted in a cardiac centre, the patients were followed up for their cardiac symptoms. This study did not intend to evaluate treatment outcome, rather it aimed to investigate only observation of new facial characteristics; hence, there was no active participation other than requiring consent to use patients' photograph for analysis and publication. When the paper gets published, participants will be informed.

RESULTS

From January 2018 to January 2020, 115 confirmed and suspected cases of CRS were reported to the Paediatric Cardiology Department of Labaid Cardiac Hospital for cardiac evaluation and management. Owing to the lack of a routine screening programme for pregnant women and newborns, the mean age of detection in the study population was high, ranging from 3 months to 14 years (mean 4.42±2.8 years, median 2 years). A poor socioeconomic status of most patients (50.4%) resulted in delayed reporting to the treatment facility. It took time for the parents themselves to identify any abnormality and to seek treatment. Clinically compatible laboratory confirmed cases were 71.3%. None of the mothers were immunised with the rubella vaccine. Some mothers were able to report a history of fever and rash in the first trimester (27.8%), the most critical time for teratogenicity due to rubella. Most mothers (65.2%) had either no history or an unknown history of such an illness (Table 1).

Table 1. Demographic characteristics of the children and mothers included in the study

Sl/ No	Variables		Mean ± SD/ No (%)
1	Patient age (Range 3 months-14 years, Median 2 years)		4.4 ± 2.8 years.
2	Case definition	probable case	33 (28.7)
		clinically compatible and laboratory confirmed case	82 (71.3)
2	**Sex**		
	Male		61 (53.0)
	Female		54 (46.9)
3	**Socioeconomic Status**		
	a. Income <1500 USD/year		58 (50.4)
	b. Income 1500–4500 USD/year		49 (42.6)
	c. Income >4500 USD/year		9 (7.8)
4	**Maternal vaccination status**		0
5	**Maternal infection status**		
	1st Trimester		32 (27.8)
	2nd Trimester		15 (13.0)
	3rd Trimester		3 (2.6)
	Unknown/no history		75 (65.2)

SD: standard deviation

Serological tests identified acute infection in children owing to the presence of Immunoglobulin M in 10 (8.6%) cases. All were aged < 1 year and were capable of infecting pregnant women, thereby transmitting the infection (Figure 1).
Among systemic manifestations of CRS and established major components of the triad, 98.2% of cases reported CHD. All patients were suspected of having CRS or were diagnosed with it during referral (Table 1). Otolaryngologists referred 87 (75.6%) cases and ophthalmologists referred 61(53.1) cases. Microcephaly cases (68.6%) were referred from paediatricians (Figure 2).

Rubella facies is composed of four different components. Triangular face was found in 95 cases (82.6%), broad forehead in 88 (76.5%), prominent nose in 75 (65.2%), and whorl on the right or left side of the anterior hairline in 92(80) and 21(18.2%) cases, respectively. In the later part of the study period, many cases were suspected following face observation upon

first sight. A triangular face with a whorl on the hairline was the most frequent combination (Table 2, Figure 3,4,5).

Table 2. Frequency of facial characteristics (rubella facies) observed among patients with congenital rubella syndrome (N=115)

Sl/ No	Rubella facies	No (%)
1	Triangular face	95 (82.6)
2	Broad forehead	88 (76.5)
3	Whorl in hairline on right side of forehead (rubella whorl)	92 (80)
4	Whorl in hairline on left side of forehead (rubella whorl)	21(18.2)
5	Prominent nose	75 (65.2)

The patterns of CHD in the study population were analysed. Patent ductus arteriosus (PDA) was the most common isolated and combined lesion (76.5%) with other valvular diseases (Table 3).

Table 3. Types of congenital heart diseases (N=115) in CRS cases revealed from echocardiography.

Echocardiography Findings	No.	Percentage (%)	
PDA (isolated and with other lesions)	88	76.5	Total CHD
Valvular stenosis, AS, PS (isolated and in combination with other CHDs)	44	38.2	98.2
RPA, LPA stenosis (isolated and combined)	17	14.7	
VSD (isolated or with PS)	3	2.6	
ASD (isolated or with PS)	10	8.6	
COA (isolated and combined)	6	5.2	
Cor triatriatum	1	0.8	
Normal Heart	2	1.7	

PDA: patent ductus arteriosus, AS: aortic stenosis, PS: pulmonary stenosis, CHD: congenital heart disease, RPA: right pulmonary artery, LPA: left pulmonary artery, VSD: ventricular septal defect, ASD: atrial septal defect, COA: coarctation of the aorta

DISCUSSION

Principal findings

In this cross-sectional study that included 115 children, four components of facial characteristics emerged, named 'rubella facies'. The 4 components were triangular face (Figure 3), wide forehead (Figure 4), prominent nose (Figure 4) and whorl on the right or left side of the anterior hairline (Figure 5). Not all patients demonstrated all four components of 'rubella facies', but most patients showed a combination of these components (Table 2). Cardiac involvement was 98.2% as patients were referred from other departments for cardiac evaluation after suspicion.

There were no age-related differences in the facial characteristics themselves (i.e., the characteristics were not different between older and younger patients); however, the features were more prominent in older participants.

This study also found that there was a wide variation in the age of the participants (3 months to 14 years, median 2 years). Therefore, even though this is a congenital disease, the wide age range of the study population indicates the lack of screening for pregnant women and infants using laboratory tests (Rubella IgG and IgM antibody and RT-PCR for virus detection), thus delaying the diagnosis of CRS patients.

As this study was conducted in a paediatric cardiology clinic, the pattern of heart disease in CRS was also analysed. PDA was found to be the most common cardiac condition associated with CRS.

Comparison with other studies

In an epidemiological study conducted in the USA, 60% of the infants and children were diagnosed with CRS at birth or before 1 month of age and 16% were not diagnosed until 3–16 months of age. These patients also presented with PDA, hepatomegaly, and thrombocytopaenic purpura.[15] In another study, the mean age of patients at diagnosis of CRS was 3 months.[8] In our study, the mean age of the participants was 4.42±2.8 years, which indicated a more delayed identification of these cases than those in the aforementioned studies.

A global survey of CRS systemic involvements showed that among the study population, 45% had CHD, 60% had hearing impairment, and 25% had cataract.[16] Another study in India showed that 78.8% of CRS patients had CHD, 59.9% had eye involvement, and 38.6% had hearing impairment.[5] Many other studies also documented cardiac involvement as the major systemic involvement.[5, 8, 17–20] In this study, the frequency of heart disease was 98.2%; the most common defect was PDA (76.5%), followed by pulmonary valve and artery stenosis (38.2%).

Facial dysmorphism is the hallmark of many genetic and congenital disorders. The most frequently encountered chromosomal abnormality with distinct facial characteristics is Down's syndrome.[21] Turner's syndrome is another disease that can be identified by a triangular face [22, 23] Children with fragile X syndrome have long, narrow faces, prominent ears, joint hypermobility, and flat feet, which become more obvious with increasing age and may help with this syndrome's diagnosis.[24] Noonan's syndrome is a genetic disorder, characterised by mildly unusual facial features, such as long forehead, hypertelorism, down slanting palpebral fissures, short and broad nose, deep philtrum, widely spaced eyes, thick hooded eyelids, and excessive nuchal skin with low posterior hairline.[25,26]

'Rubella facies' is a novel set of characteristics established in this study, which can serve as a hallmark such as those in the aforementioned syndromes. However, the components of 'rubella facies' are found in different combinations in many other syndromes. "Triangular face" has been defined as a hypoplastic face with prominent zygomatic arches, orbital

hyperterlorism, sunken cheeks, downturned mouth, a characteristic of Mulibrey nanism.[27] Triangular face is also a characteristic feature of the Russel–Silver syndrome, Noonan's syndrome, the Prader–Willi syndrome, and the Angelman syndrome, among others.[28] A wide or broad forehead is associated with some rare disorders such as facial dysmorphism-immunodeficiency-livedo-short stature syndrome.[29] A prominent nose is found in patients with Traboulsi syndrome, heart diseases, and autism spectrum disorder, among other diseases.[30–32] Another component of 'rubella facies' was the hair whorl on the anterior hairline, also known as a hair crown or cowlick. Abnormal hair whorls are also present in many other diseases, such as microcephaly, Apert's syndrome, and Crouzon's syndrome, among others.[33] Components of rubella facies were found unique after excluding other possibilities mentioned.

Strengths and limitations of this study

This study included 115 cases that were already confirmed to have or suspected of having CRS. Hence, the facial features examined were indicative of CRS. A large portion of the study population with a diagnosis or having a suspected case of CRS helped physicians correlate this condition with the visual impression of the facial features upon first sight. Additionally, photographs of the patients were taken with the Samsung Galaxy S8 (Samsung Electronics, South Korea) mobile phone for future visual reference; hence, it was possible to examine these faces, when necessary.

Facial features of CRS, named 'rubella facies', can be used as a landmark for the detection of CRS in the low and low middle income countries where the universal availability of the rubella vaccine, especially for girls and women of reproductive age, remains low.[7,8] Most women infected during pregnancy were overlooked or missed because they showed only mild symptoms. Additionally, serological screening is not a part of antenatal check-ups in these countries (e.g., Bangladesh, Nigeria, India, Vietnam, Ethiopia).[34] Acute symptoms, such as thrombocytopaenic purpura, hepatomegaly, and PDA with heart failure are not always seen in neonates;[15] neonatal hearing assessment using OAE and ABR is not performed in low and low middle income countries routinely, and therefore, diagnosis is often missed.[35] Therefore, some infants and children are permanently blind or deaf at the time of diagnosis. Many others die from heart failure due to PDA. 'Rubella facies' will be a valuable diagnostic clue informing clinicians and parents in these countries to the available seek medical care.

These facial features were examined in 115 cases repeatedly from photographs. Although triangular face, whorl in the anterior hairline, prominent nose, and wide forehead are components of some other syndromes, CRS was confirmed in the study cases using serological test and presence of triad components. This is another strength that showcases 'rubella facies' as a component of CRS. CRS is associated with characteristic congenital heart lesions like PDA, pulmonary valve stenosis (PS), etc., also indicating its presence. Therefore, the existence of 'rubella facies' implies that clinicians and parents should consider the presence of triad and PDA (present in 76.5% of cases), and vice versa.

Limitations of this study exist primarily in the design. First, photographs were taken by non-professional photographers; in most cases, the echocardiographer or cardiologist photographed the patient using a mobile phone with a 2-dimensional (2D) camera. Second, 3-dimensional (3D) digital anthropometric analysis was not performed. This restricted an advanced, detailed analysis of the face, such as measuring the accurate circumference of the forehead or the exact distance between prenasale and subnasale. 3D photographic methods have been used for facial analysis or anthropometric measurement of various races to compare them with other races and genders.[36,37] Therefore, exact measurements of faces, noses, and foreheads were not taken; hence, comparison with normative data was not

possible. Normative data for Bangladeshi Asian populations were also not available. Third, this was a preliminary study on the findings of rubella facies by visual impression alone; no comparison was done with facial features of unaffected children (i.e., a patient's wide forehead was not measured or compared with the forehead of a normal child). This study was conducted on CRS patients who were referred for cardiac evaluation. Therefore, many cases with milder symptoms in the community were not included. Hence, the epidemiology in this study does not represent the true status.

Implication of study and future research

Identification of 'rubella facies' will help clinicians and parents suspect CRS earlier in children both at a primary healthcare level or at home. Initial suspicion will lead to subsequent investigation and management, thus preventing permanent visual and hearing disabilities in several children. Early identification and treatment of CHD will prevent mortality due to heart failure in CRS cases.

Future research by dysmorphologist is necessary to compare patients with rubella facies with control group and to compare the influence of the triad on components of facies. In this study, no age-related influence on the facial characteristics was observed. Further studies are necessary to observe the variation of rubella facies with age (i.e., to compare affected neonates, infants, adolescents, and adults). Correlation of 'rubella facies' with mental retardation and microcephaly may also be studied.

CONCLUSION

'Rubella facies' has the potential to serve as a landmark prediagnostic criterion of CRS, especially in low and lower middle income countries, where rubella remains a major public health concern with high morbidity and mortality rates. Using facial features to identify suspected cases of CRS with minimal or unrevealed criteria may help achieve earlier diagnoses and treatment. Low- and lower-middle-income countries should consider the following: achieving complete anti-rubella vaccination coverage for uncovered adolescent girls and women of childbearing age along with universal immunisation programme containing MMR vaccine is paramount; rubella antibody screening for all pregnant women is recommended; screening of all infants for hearing impairment is encouraged; and sustainable birth defect surveillance (e.g., screening of all children with congenital heart disease, cataract, microcephaly, congenital deafness, unexplained hepatosplenomegaly, or thrombocytopaenia) for rubella and correlating them with 'rubella facies' (which is evident at first sight) is crucial

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TRANSPARENCY DECLARATION: The author of this paper affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

DISSEMINATION DECLARATION: The author of this paper would like to disseminate the results and new findings of this study.

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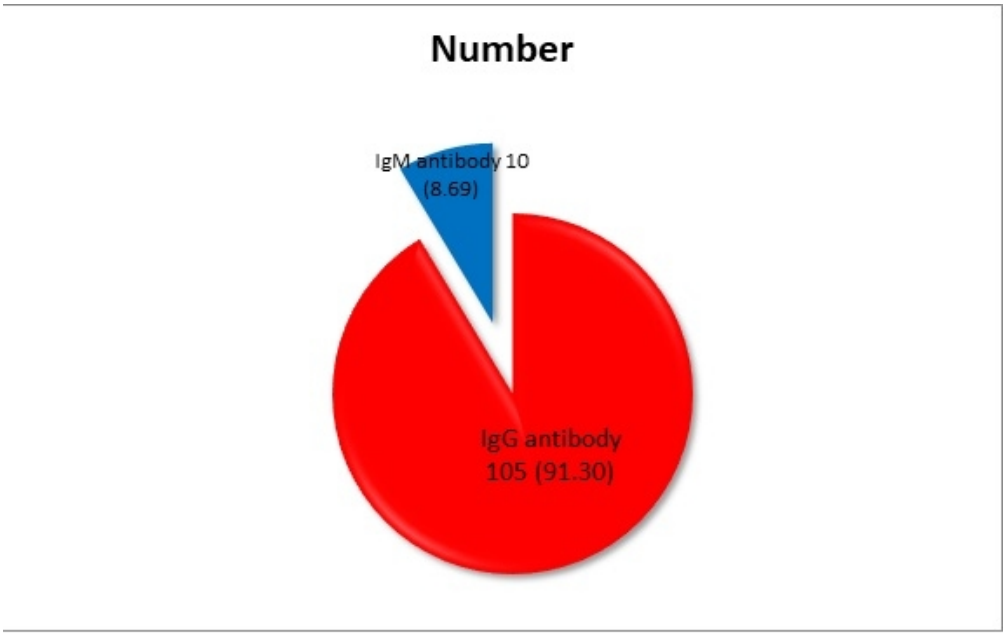
Figure Legends

Figure 1. Frequency of rubella antibodies in patients with congenital rubella syndrome (N=115)
Figure 2. Distribution of systemic involvements among patients with congenital rubella syndrome (N=115)
Figure 3. Triangular face in patients with congenital rubella syndrome.
Figure 4. Prominent nose and Wide forehead observed in patients with congenital rubella syndrome.
Figure 5.. Photographs of patients with congenital rubella syndrome exhibiting hair whorl on their anterior hairline, either on left or right side.



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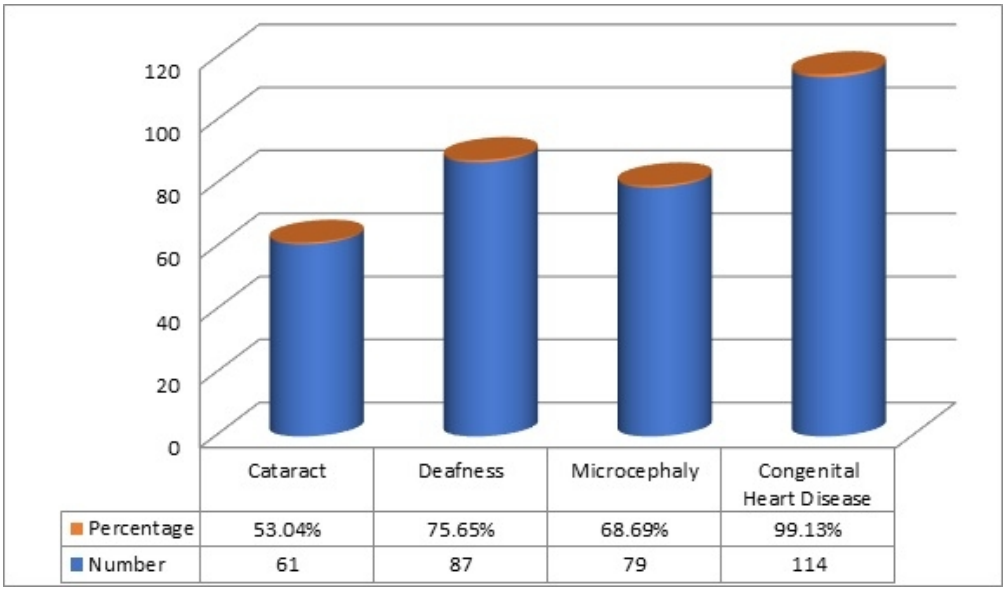

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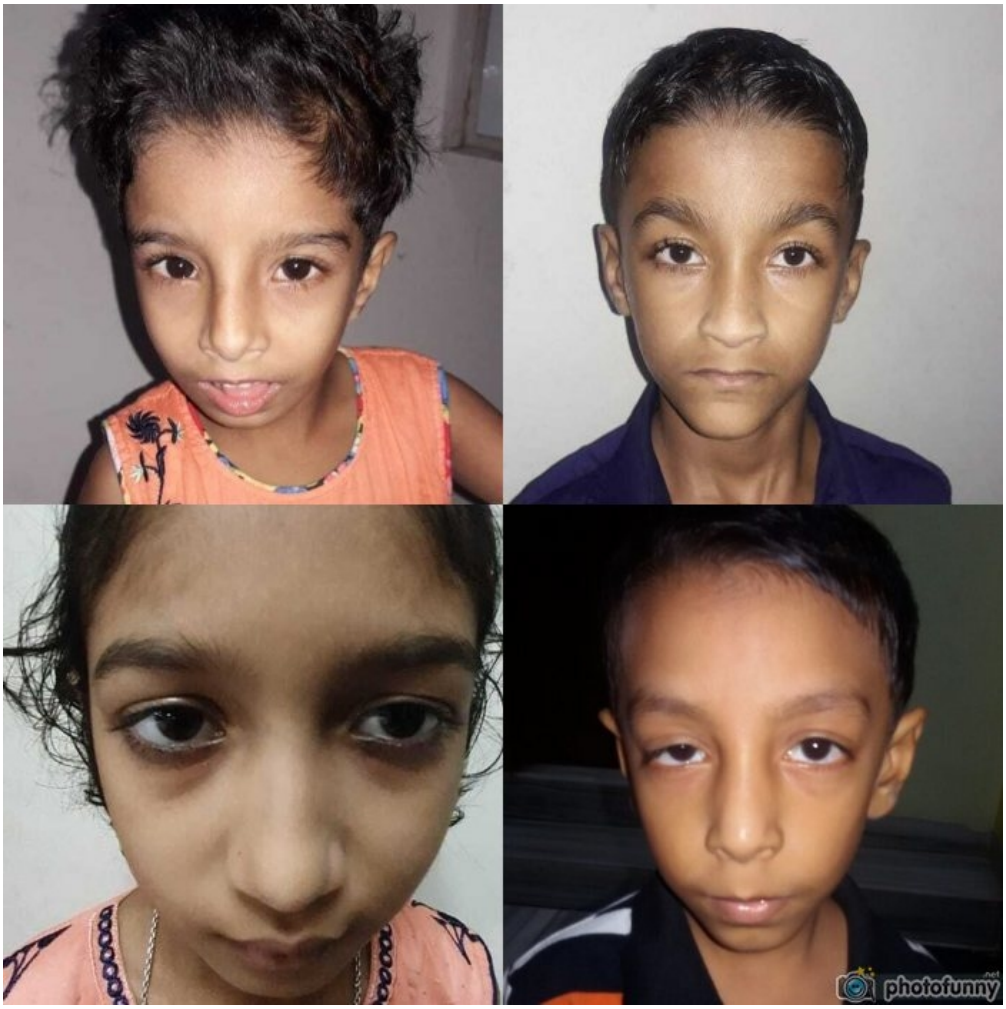

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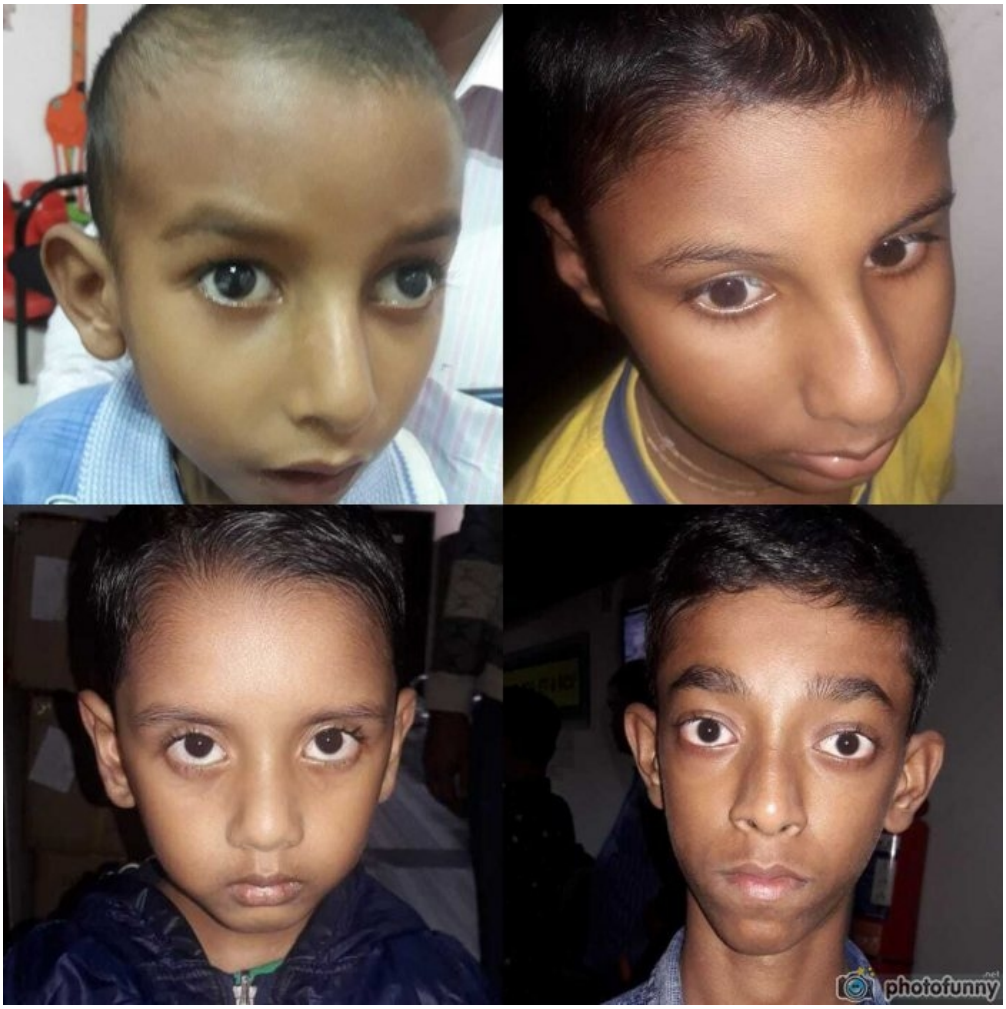

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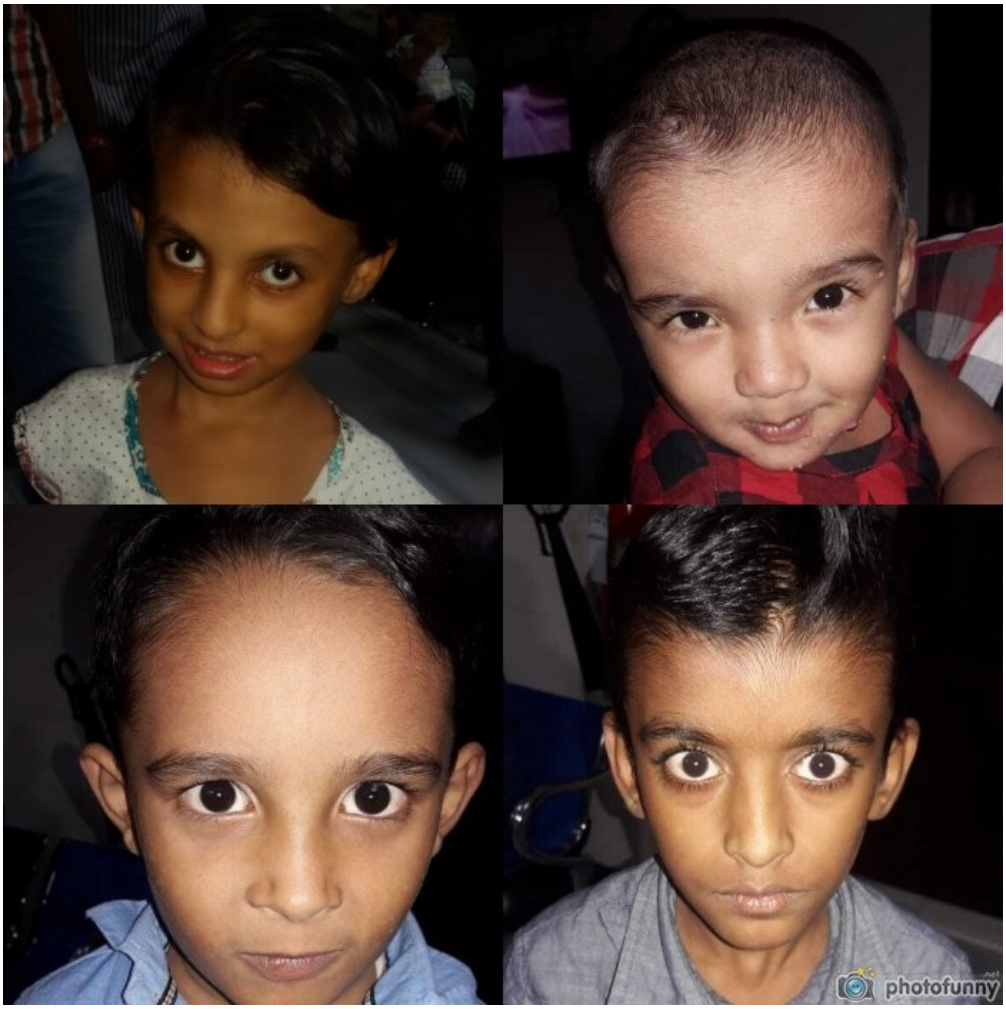

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Novel facial characteristics in congenital rubella syndrome: a study of 115 cases in a cardiac hospital of Bangladesh

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SUMMARY

What is already known:

- Clinical diagnosis of congenital rubella syndrome (CRS) is possible from a characteristic triad: cataract, deafness, and congenital heart disease.
- There are also some minor criteria such as microcephaly, splenomegaly, thrombocytopenia, developmental delay, and failure to thrive.
- In low- and middle-low-income countries, pregnant women and neonates are not screened routinely for rubella

What this study adds:

- This study reports novel facial characteristics (triangular face, wide forehead, prominent nose, and hair whorl on the anterior hairline) as supplementary findings in early recognition and diagnostic confirmation
- None of the mothers had received a rubella vaccine.
- The median age of diagnosis was 2 years

ABSTRACT

Objective: To establish novel facial characteristics unique to congenital rubella syndrome (CRS) as pre-diagnostic criteria to supplement disease diagnosis in patients with or without a history of maternal rubella infection.

Design: An analysis of 115 CRS case series (2018–2020) based on the presence of any of the triad features.

Setting: Outpatient department of a tertiary care referral cardiac hospital in Dhaka, Bangladesh.

Participants: In total, 115 participants (53.1% male) were enrolled. Participants underwent echocardiography if they presented with suspected cardiac symptoms along with deafness, cataract, or microcephaly.

Main outcome measures: Age, sex, and socioeconomic status of the participants; history of maternal vaccination and infection; facial characteristics unique to CRS (triangular face, prominent nose, wide forehead, and a whorl on either side of the anterior hairline) named 'rubella facies'; and frequency of systemic involvements in CRS.

Results: The median patient age was 2 years. The income of 50.4% of the participating families was < 1500 USD. Further, 32 mothers (27.8%) were infected with rubella during the first trimester of pregnancy, 15 (13.0%) during the second trimester, and 3 (2.6%) during the third trimester. The remainder (65.2%) recalled no history of infection during pregnancy. Rubella facies presented as a triangular-shaped face in 95 (82.6%) cases, a broad forehead in 88 (76.5%), and a prominent nose in 75 (65.2%). A rubella whorl was present on the right or left side of the anterior hairline in 80% and 18.2% of cases, respectively. Immunoglobulin G and M antibodies were present in 91.3% and 8.6% of children, respectively. Cataract, deafness, microcephaly, and congenital heart disease were detected in 53.0%, 75.6%, 68.6%, and 99.1% of cases, respectively.

Conclusions: 'Rubella facies', a set of unique facial characteristics can support early CRS diagnosis and treatment and may supplement the existing CRS triad.

Keywords: rubella facies, novel, congenital rubella syndrome

INTRODUCTION

Rubella virus belongs to the *Togaviridae* family and is a teratogenic agent that can cross the placenta and cause foetal infection at a risk rate dependent on gestational age.[1] If acquired in the first trimester, such an infection can lead to congenital rubella syndrome (CRS), which is characterised by a triad consisting of congenital deafness, cataract, and congenital heart disease (CHD).[2] Sir Norman Gregg, an Australian ophthalmologist, first identified the relationship between gestational rubella infection and cataract in 1941 during a rubella outbreak in Australia.[3] This discovery was followed by the identification of other complications associated with rubella infection, including microcephaly, low birth weight, hepatosplenomegaly, bone lesions, dental defects, hypospadias, cryptorchidism, and inguinal hernia; additionally, interstitial pneumonitis, thyroid dysfunction, cerebral calcification, diabetes mellitus, and micrognathia may also be present.[4] CRS is associated with high mortality rates and significant morbidity.[5] It can be prevented by an anti-rubella vaccine, which has been available since 1969.[6]

However, CRS remains common in countries where access to the anti-rubella vaccine is restricted; moreover, its incidence is often under reported or underestimated. Owing to insufficient vaccination coverage among women of reproductive age in countries such as Bangladesh, Nigeria, Vietnam, and Ethiopia, the incidence of rubella and CRS in these countries remains high.[7,8] In Bangladesh, the anti-rubella vaccination was launched in January 2014 and included in the expanded program for immunisation for children.[9] Girls and women who are currently of reproductive age (15-49 years) and at risk were not included in the programme.[10] The serological status with respect to rubella antibodies is rarely assessed during pregnancy, and serial screening is not advised in these countries. Additionally, screening for hearing defects in neonates is not routinely performed, further delaying the diagnosis of CRS.

Rubella virus infection in children and adults usually causes a mild, self-limiting, rash-like illness with minor complications. However, if a rubella infection is contracted during pregnancy, particularly during the first trimester, it may lead to significant complications. One such complication is CRS, which is challenging to diagnose owing to variability in signs and symptoms at presentation. Variable factors include the time elapsed between maternal infection and the birth of an infant, an unclear history of maternal infection, restricted access to hearing tests at birth, and varied availability of echocardiography-based screening among babies of mothers with a suspected history of gestational rubella.[7,11,12] Moreover, most women infected with rubella do not present with classic symptoms such as fever and rash. Since the discovery of the rubella vaccine, the incidence of CRS has been significantly reduced in high-income countries, resulting in very few studies being conducted in this field of medicine in recent times. However, owing to the aforementioned reasons, CRS is still a pressing public health issue in the low- and lower-middle-income countries, and it is essential to establish an easier and faster diagnostic method.

Several congenital syndromes are associated with facial characteristics such as those observed in Down's, Noonan's, and Turner's syndromes, among others, and could allow early diagnosis and management. [13] Forrest et al had identified Elfin like facies in congenital rubella syndrome (ADC 1970) [14] .This study examined the facial characteristics of CRS patients and identified and reported unique features of rubella facies which came from observation of a treating cardiologist that they all possessed similar facial characteristics. It aimed to characterise the facial morphology of CRS patients from a visual

impression and to establish these novel facial characteristics as a prediagnostic tool that may aid in earlier diagnosis and subsequent management of CRS.

METHODS

Subjects

Patients were referred from ophthalmologists, otorhinolaryngologists, and paediatricians for cardiac evaluation of suspected or clinically confirmed CRS. These patients showed one or more components of the rubella characteristic triad. All the patients had undergone clinical examination and echocardiography as part of their cardiac evaluation. Therefore, after obtaining written informed consent from the parents of these patients, their photographs with Samsung Galaxy S8 (Samsung Electronics, South Korea) camera were taken and stored with the patients' clinical records for further analysis. This study was conducted as per the Declaration of Helsinki and was approved by the Ethics committee of Labaid Cardiac Hospital, Dhaka (Protocol number: 200716/01).

All children referred with suspected CRS aged between 3 months and 14 years were included in the study. Nineteen patients with other syndromes who were also associated with particular facial characteristics such as those in Noonan's and Turner's syndromes were excluded from the study. It was not possible for these patients to participate in the design or planning of the study since all were under 18 years and did not have the mental capacity to participate in such activities.

Setting

The study was conducted in the outpatient department of a Paediatric Cardiology unit in a tertiary cardiac hospital in Dhaka, Bangladesh (January 2018 to January 2020).

Data collection

Demographic characteristics, such as age, sex, socioeconomic status, presence of one or more components of the rubella triad, maternal vaccination status, and history of rubella infection during pregnancy were documented, reviewed, and analysed. The rubella antibody (IgG and IgM) status of the patients was obtained from medical records. Paired maternal antibody was not recommended for them.

Photographs were taken when the patients visited the hospital for echocardiography. Photographs were collected for this study since January 2018. The facial characteristics were visually examined in person during the patients' visits and later analysed using the photographs. The patterns of patients' heart diseases were recorded from their echocardiography reports.

Case definition of CRS

a. *Clinically compatible case*: A patient with two major components of the triad or one major and another minor component, such as microcephaly, splenomegaly, developmental delay, failure to thrive, thrombocytopenia, and meningoencephalitis.

b. *Probable case:* A patient with heart disease and suspected hearing impairment, or at least one eye defect (cataract, glaucoma, pigmentary retinopathy, microphthalmos, optic atrophy, strabismus, nystagmus).

c. *Laboratory confirmed case*: Infant having at least one major component and meeting one of the following laboratory criteria: i) Detection of rubella IgM antibody or ii) sustained level

of rubella IgG antibodies, as determined at age 6-12 months in the absence of rubella vaccination.

Major criteria of CRS:

Deafness: As confirmed by the distraction test in the paediatric cardiology outpatient clinic and otoacoustic emission (OAE) and auditory brainstem response (ABR) in the otolaryngology department.

Eye findings (cataract and other findings): As confirmed by a detailed eye examination, including examination of the lens, ocular pressure (tonometry), examination of the retina and refraction test, under general anaesthesia by an ophthalmologist.

Congenital heart disease: As identified on clinical examination and confirmed on echocardiography.

Minor criteria of CRS:

Microcephaly: As confirmed by measurement of the occipitofrontal (OFC) circumference. If the circumference is > 2 standard deviation (2SDs) smaller than the mean for the patient's age and sex.

Others: Splenomegaly, developmental delay, failure to thrive, thrombocytopenia, meningoencephalitis, and jaundice.

Definition of rubella facies

A triangular face, a prominent nose, a wide or broad forehead, and the presence of a whorl on the right or left side of the anterior hairline were components of 'rubella facies.' The whorl on the hairline was named 'rubella whorl'. All these characteristics were checked on visual examination. These findings were further analysed using photographs of the patients.

Triangular face: The forehead was considered as the base and the chin as the apex of the triangle.

Prominent nose: An increased distance between the subnasale and pronasale. [15] The nasal bridge was sharp and formed a straight line with the tip of the nose.

Wide forehead: The frontal hairline was retreated, resulting a wide space above the eyebrow.

Whorl in the anterior hairline: The circular distribution of the hair on the scalp that revolves around an axis as determined by the direction of the growing follicle.

Facial characteristics overlapping with those of other diseases were excluded by thorough analysis.

Statistical analysis

Continuous data are expressed as means $\pm$ standard deviations; categorical data are expressed as frequencies and percentages. Since this was a single-variant study, no comparative tests were needed.

Patient and public involvement

Patients were recruited from paediatric cardiology outpatient department Written informed consent for participation in the study was obtained from all the parents of the patients, and the reason for taking their photographs was thoroughly explained. Photographs were taken to establish novel facial characteristics of CRS patients.

As this study was conducted in a cardiac centre, the patients were followed up for their cardiac symptoms. This study did not intend to evaluate treatment outcome, rather it aimed to investigate only observation of new facial characteristics; hence, there was no active

participation other than requiring consent to use patients' photograph for analysis and publication. When the paper gets published, participants will be informed.

RESULTS

From January 2018 to January 2020, 115 confirmed and suspected cases of CRS were reported to the Paediatric Cardiology Department of Labaid Cardiac Hospital for cardiac evaluation and management. Owing to the lack of a routine screening programme for pregnant women and newborns, the median age of detection in the study population was 2 years which was high. A poor socioeconomic status of most patients (50.4%) resulted in delayed reporting to the treatment facility. It took time for the parents themselves to identify any abnormality and to seek treatment. Clinically compatible cases in the series were 62.7%, probable cases were 28.7% and laboratory confirmed cases were 8.6%. None of the mothers were immunised with the rubella vaccine. Some mothers were able to report a history of fever and rash in the first trimester (27.8%), the most critical time for teratogenicity due to rubella. Most mothers (65.2%) had either no history or an unknown history of such an illness (Table 1).

Table 1. Demographic characteristics of the children and mothers included in the study

Sl/ No	Variables		Mean ± SD/ No (%)
1	Patient age (Range 3 months-14 years, Median 2 years)		4.4 ± 2.8 years.
2	Case definition	Clinically compatible case	72 (62.7)
		Probable case	33(28.7)
		Laboratory confirmed case	10 (8.6)
2	**Sex**		
	Male		61 (53.0)
	Female		54 (46.9)
3	**Socioeconomic Status**		
	a. Income <1500 USD/year		58 (50.4)
	b. Income 1500–4500 USD/year		49 (42.6)
	c. Income >4500 USD/year		9 (7.8)
4	**Maternal vaccination status**		0
5	**Maternal infection status**		
	1st Trimester		32 (27.8)
	2nd Trimester		15 (13.0)
	3rd Trimester		3 (2.6)
	Unknown/no history		75 (65.2)

SD: standard deviation

Serological tests identified acute infection in children owing to the presence of Immunoglobulin M in 10 (8.6%) cases. All were aged < 1 year and were capable of infecting pregnant women, thereby transmitting the infection (Figure 1).
Among systemic manifestations of CRS and established major components of the triad, 98.2% of cases reported CHD. All patients were suspected of having CRS or were diagnosed with it during referral (Table 1). Otolaryngologists referred 87 (75.6%) cases and

ophthalmologists referred 61(53.1) cases. Microcephaly cases (68.6%) were referred from paediatricians (Figure 2).

Rubella facies is composed of four different components. Triangular face was found in 95 cases (82.6%), broad forehead in 88 (76.5%), prominent nose in 75 (65.2%), and whorl on the right or left side of the anterior hairline in 92 (80%) and 21(18.2%) cases, respectively. In the later part of the study period, many cases were suspected following face observation upon first sight. A triangular face with a whorl on the hairline was the most frequent combination (Table 2, Figure 3,4,5).

Table 2. Frequency of facial characteristics (rubella facies) observed among patients with congenital rubella syndrome (N=115)

Sl/ No	Rubella facies	No (%)
1	Triangular face	95 (82.6)
2	Broad forehead	88 (76.5)
3	Whorl in hairline on right side of forehead (rubella whorl)	92 (80)
4	Whorl in hairline on left side of forehead (rubella whorl)	21(18.2)
5	Prominent nose	75 (65.2)

The patterns of CHD in the study population were analysed. Patent ductus arteriosus (PDA) was the most common isolated and combined lesion (76.5%) with other valvular diseases (Table 3).

Table 3. Types of congenital heart diseases (N=115) in CRS cases revealed from echocardiography.

Echocardiography Findings	No.	Percentage (%)	
PDA (isolated and with other lesions)	88	76.5	Total CHD
Valvular stenosis, AS, PS (isolated and in combination with other CHDs)	44	38.2	98.2
RPA, LPA stenosis (isolated and combined)	17	14.7	
VSD (isolated or with PS)	3	2.6	
ASD (isolated or with PS)	10	8.6	
COA (isolated and combined)	6	5.2	
Cor triatriatum	1	0.8	
Normal Heart	2	1.7	

PDA: patent ductus arteriosus, AS: aortic stenosis, PS: pulmonary stenosis, CHD: congenital heart disease, RPA: right pulmonary artery, LPA: left pulmonary artery, VSD: ventricular septal defect, ASD: atrial septal defect, COA: coarctation of the aorta

DISCUSSION

In this study, four components of facial characteristics emerged, named 'rubella facies.' The 4 components were triangular face (Figure 3), wide forehead (Figure 4), prominent nose (Figure 4) and whorl on the right or left side of the anterior hairline (Figure 5). Not all patients demonstrated all four components of 'rubella facies', but most patients showed a combination of these components (Table 2). Cardiac involvement was 98.2% as patients were referred from other departments for cardiac evaluation after suspicion.

There were no age-related differences in the facial characteristics themselves (i.e., the characteristics were not different between older and younger patients); however, the features were more prominent in older participants.

This study also found that there was a wide variation in the age of the participants (3 months to 14 years, median 2 years). Therefore, even though this is a congenital disease, the wide age range of the study population indicates the lack of screening for pregnant women and infants using laboratory tests (Rubella IgG and IgM antibody and RT-PCR for virus detection), thus delaying the diagnosis of CRS patients.

As this study was conducted in a paediatric cardiology clinic, the pattern of heart disease in CRS was also analysed. PDA was found to be the most common cardiac condition associated with CRS.

In an epidemiological study conducted in the USA, 60% of the infants and children were diagnosed with CRS at birth or before 1 month of age and 16% were not diagnosed until 3–16 months of age. These patients also presented with PDA, hepatomegaly, and thrombocytopaenic purpura.[16] In another study, the mean age of patients at diagnosis of CRS was 3 months.[8] In our study, the mean age of the participants was 4.42±2.8 years, and median was 2 years which indicated a more delayed identification of these cases than those in the aforementioned studies.

Facial dysmorphism is the hallmark of many genetic and congenital disorders. The most frequently encountered chromosomal abnormality with distinct facial characteristics is Down's syndrome.[17] Turner's syndrome is another disease that can be identified by a triangular face [18,19] Children with fragile X syndrome have long, narrow faces, prominent ears, joint hypermobility, and flat feet, which become more obvious with increasing age and may help with this syndrome's diagnosis.[20] Noonan's syndrome is a genetic disorder, characterised by mildly unusual facial features, such as long forehead, hypertelorism, down slanting palpebral fissures, short and broad nose, deep philtrum, widely spaced eyes, thick hooded eyelids, and excessive nuchal skin with low posterior hairline.[21,22]

'Rubella facies' is a novel set of characteristics established in this study, which can serve as a hallmark such as those in the aforementioned syndromes. However, the components of 'rubella facies' are found in different combinations in many other syndromes. "Triangular face" has been defined as a hypoplastic face with prominent zygomatic arches, orbital hypertelorism, sunken cheeks, downturned mouth, a characteristic of Mulibrey nanism.[23] Triangular face is also a characteristic feature of the Russel–Silver syndrome, Noonan's syndrome, the Prader–Willi syndrome, and the Angelman syndrome, among others.[24]

A wide or broad forehead is associated with some rare disorders such as facial dysmorphism-immunodeficiency-livedo-short stature syndrome.[25]
A prominent nose is found in patients with Traboulsi syndrome, heart diseases, and autism spectrum disorder, among other diseases.[26-28]
Another component of 'rubella facies' was the hair whorl on the anterior hairline, also known as a hair crown or cowlick. Abnormal hair whorls are also present in many other diseases, such as microcephaly, Apert's syndrome, and Crouzon's syndrome, among others.[29]
Components of rubella facies were found unique after excluding other possibilities mentioned.

Facial features of CRS, named 'rubella facies', can be used as a landmark for the detection of CRS in the low and low middle income countries where the universal availability of the rubella vaccine, especially for girls and women of reproductive age, remains low.[7,8] Most women infected during pregnancy were overlooked or missed because they showed only mild symptoms. Additionally, serological screening is not a part of antenatal check-ups in these countries (e.g., Bangladesh, Nigeria, India, Vietnam, Ethiopia).[30] Acute symptoms, such as thrombocytopaenic purpura, hepatomegaly, and PDA with heart failure are not always seen in neonates;[16] neonatal hearing assessment using OAE and ABR is not performed in low and low middle income countries routinely, and therefore, diagnosis is often missed.[31] Therefore, some infants and children are permanently blind or deaf at the time of diagnosis. Many others die from heart failure due to PDA. 'Rubella facies' will be a valuable diagnostic clue informing clinicians and parents in these countries to seek medical care available there.

Limitations of this study exist primarily in the design. First, photographs were taken by non-professional photographers; in most cases, the echocardiographer or cardiologist photographed the patient using a mobile phone with a 2-dimensional (2D) camera. Second, 3-dimensional (3D) digital anthropometric analysis was not performed. This restricted an advanced, detailed analysis of the face, such as measuring the accurate circumference of the forehead or the exact distance between prenasale and subnasale. 3D photographic methods have been used for facial analysis or anthropometric measurement of various races to compare them with other races and genders.[32,33] Therefore, exact measurements of faces, noses, and foreheads were not taken; hence, comparison with normative data was not possible. Normative data for Bangladeshi Asian populations were also not available. Third, this was a preliminary study on the findings of rubella facies by visual impression alone; no comparison was done with facial features of unaffected children (i.e., a patient's wide forehead was not measured or compared with the forehead of a normal child). This study was conducted on CRS patients who were referred for cardiac evaluation. Therefore, many cases with milder symptoms in the community were not included. Hence, the epidemiology in this study does not represent the true status.

Identification of 'rubella facies' will help clinicians and parents suspect CRS earlier in children both at a primary healthcare level or at home. Initial suspicion will lead to subsequent investigation and management, thus preventing permanent visual and hearing disabilities in several children. Early identification and treatment of CHD will prevent mortality due to heart failure in CRS cases.
Future research by dysmorphologist is necessary to compare patients with rubella facies with control group and to compare the influence of the triad on components of facies. In this study, no age-related influence on the facial characteristics was observed. Further studies are necessary to observe the variation of rubella facies with age (i.e., to compare affected

neonates, infants, adolescents, and adults). Correlation of 'rubella facies' with mental retardation and microcephaly may also be studied.

Recommendations for low and lower middle-income countries:

- Achieving complete anti-rubella vaccination coverage for uncovered adolescent girls and women of childbearing age along with universal immunisation programme containing MMR vaccine is paramount.
- Rubella antibody screening for all pregnant women
- Screening of all infants for hearing impairment is encouraged
- Sustainable birth defect surveillance (e.g., screening of all children with congenital heart disease, cataract, microcephaly, congenital deafness, unexplained hepatosplenomegaly, or thrombocytopenia) for rubella and correlating them with 'rubella facies' (which is evident at first sight) is crucial

CONCLUSION

'Rubella facies' has the potential to serve as a landmark pre-diagnostic criterion of CRS, especially in low and lower middle-income countries, where rubella remains a major public health concern with high morbidity and mortality rates. Using facial features to identify suspected cases of CRS with minimal or unrevealed criteria may help achieve earlier diagnoses and treatment.

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TRANSPARENCY DECLARATION: The author of this paper affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

DISSEMINATION DECLARATION: The author of this paper would like to disseminate the results and new findings of this study.

EXCLUSIVE LICENCE STATEMENT:

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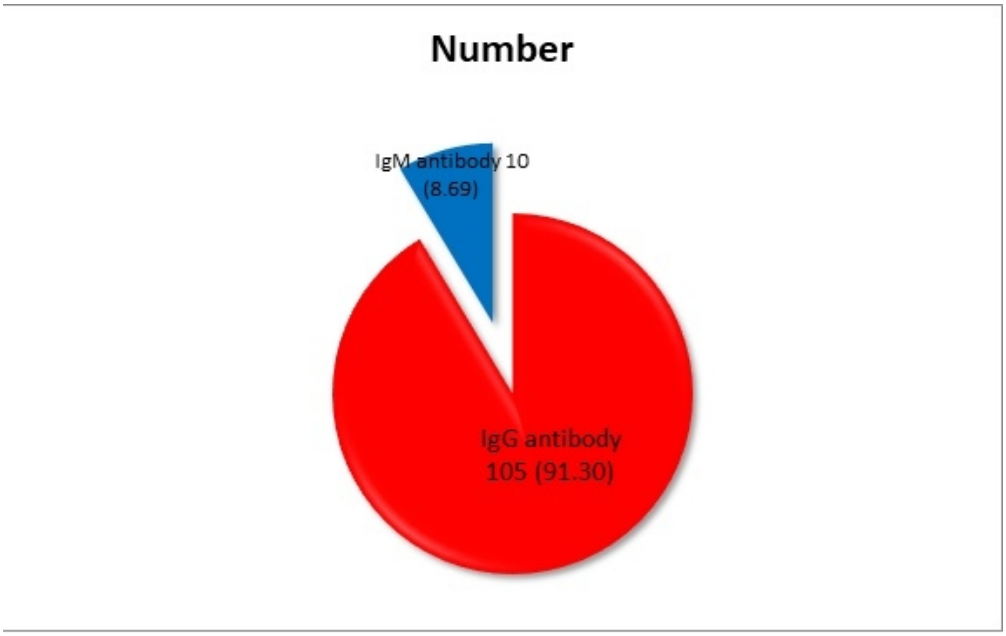
Figure Legends

Figure 1. Frequency of rubella antibodies in patients with congenital rubella syndrome (N=115)
Figure 2. Distribution of systemic involvements among patients with congenital rubella syndrome (N=115)
Figure 3. Triangular face in patients with congenital rubella syndrome.
Figure 4. Prominent nose and wide forehead observed in patients with congenital rubella syndrome.
Figure 5. Photographs of patients with congenital rubella syndrome exhibiting hair whorl on their anterior hairline, either on left or right side.



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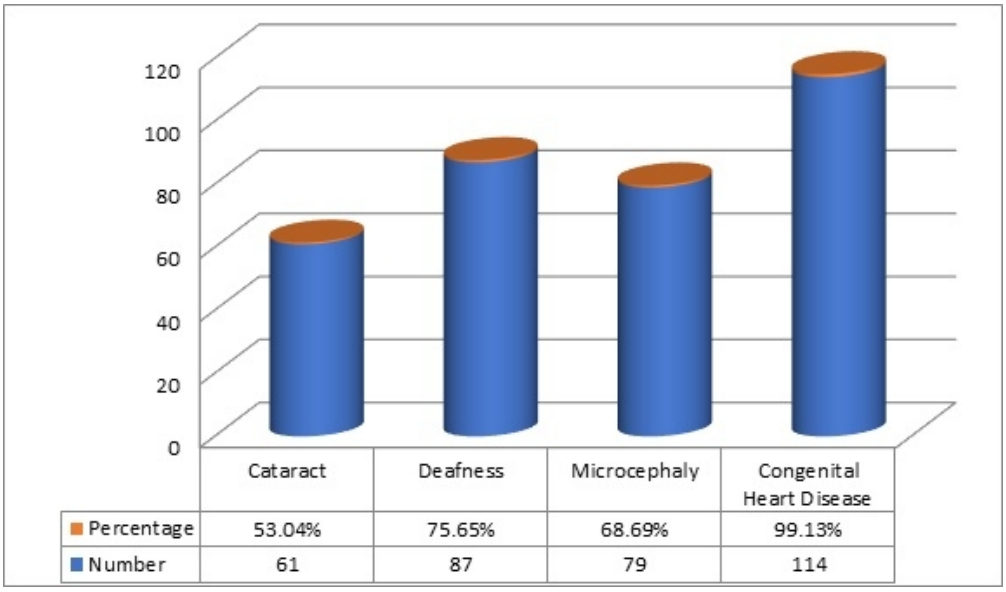

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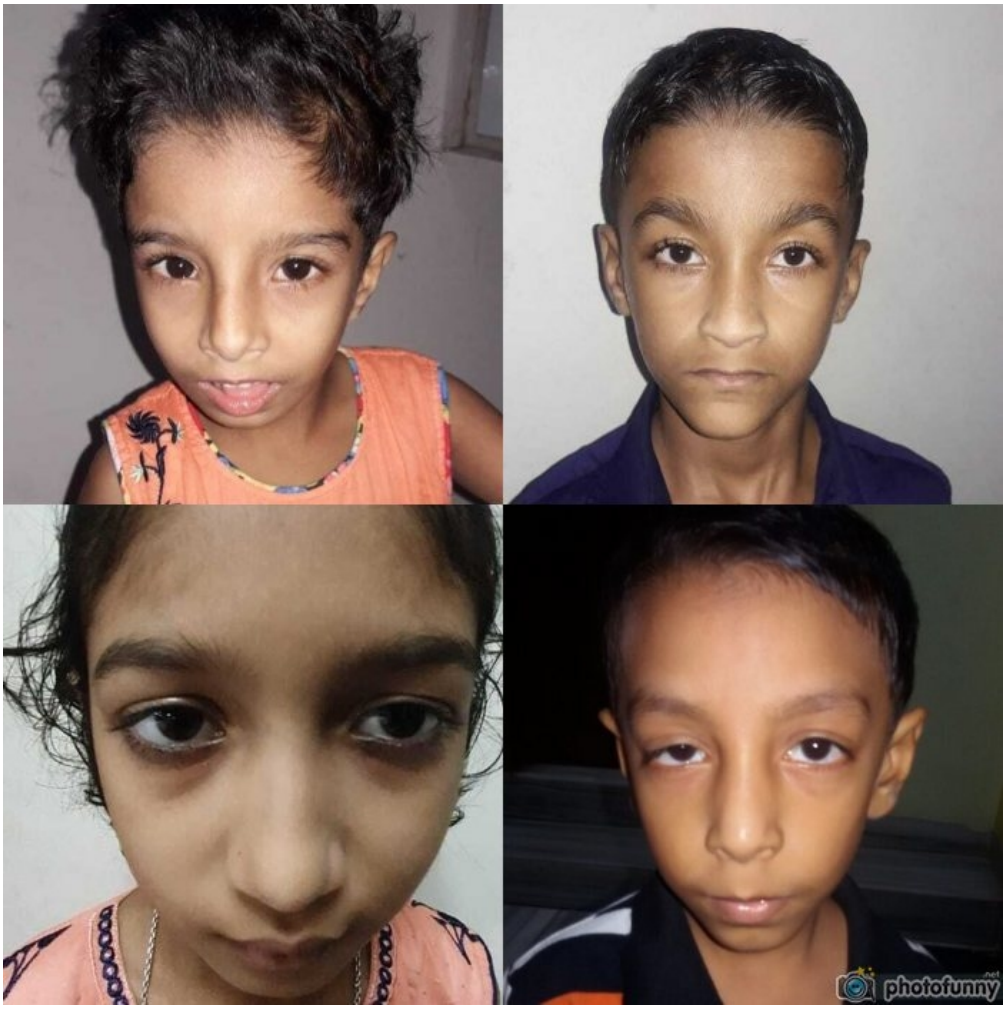

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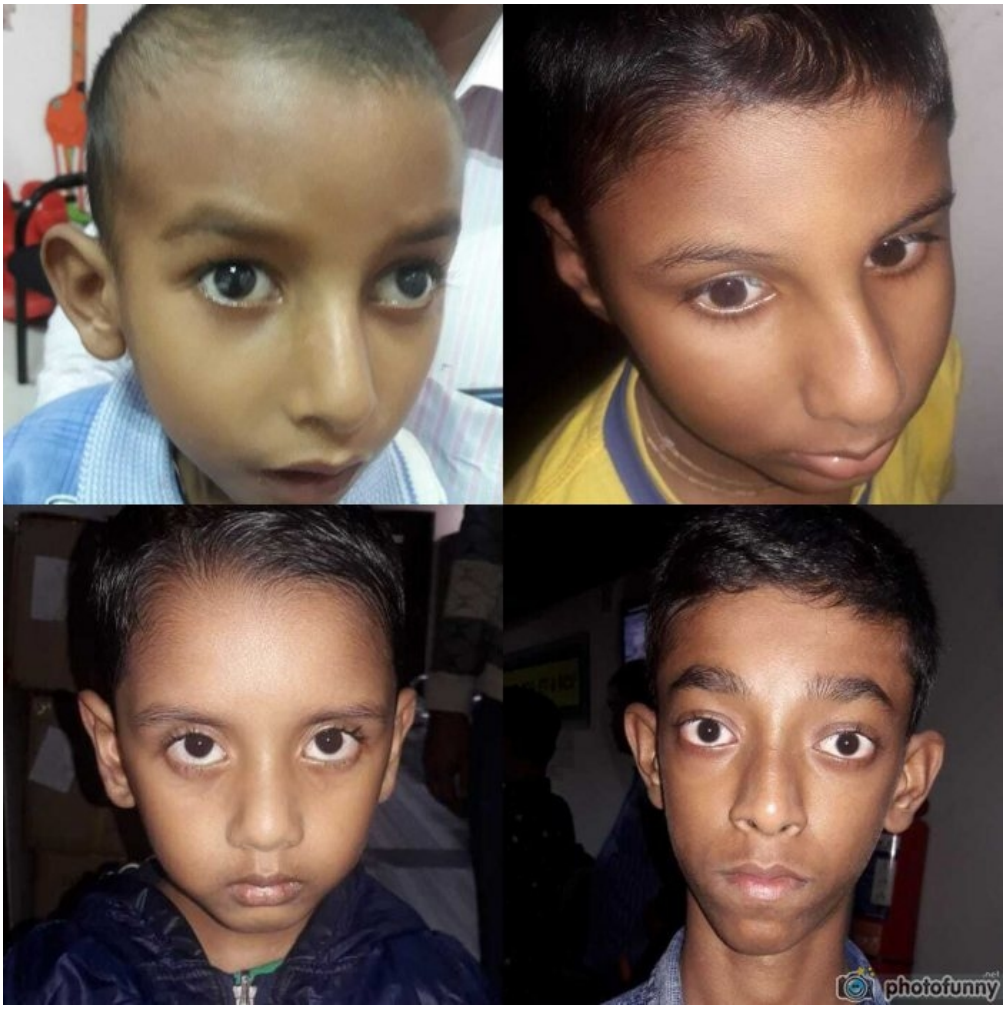

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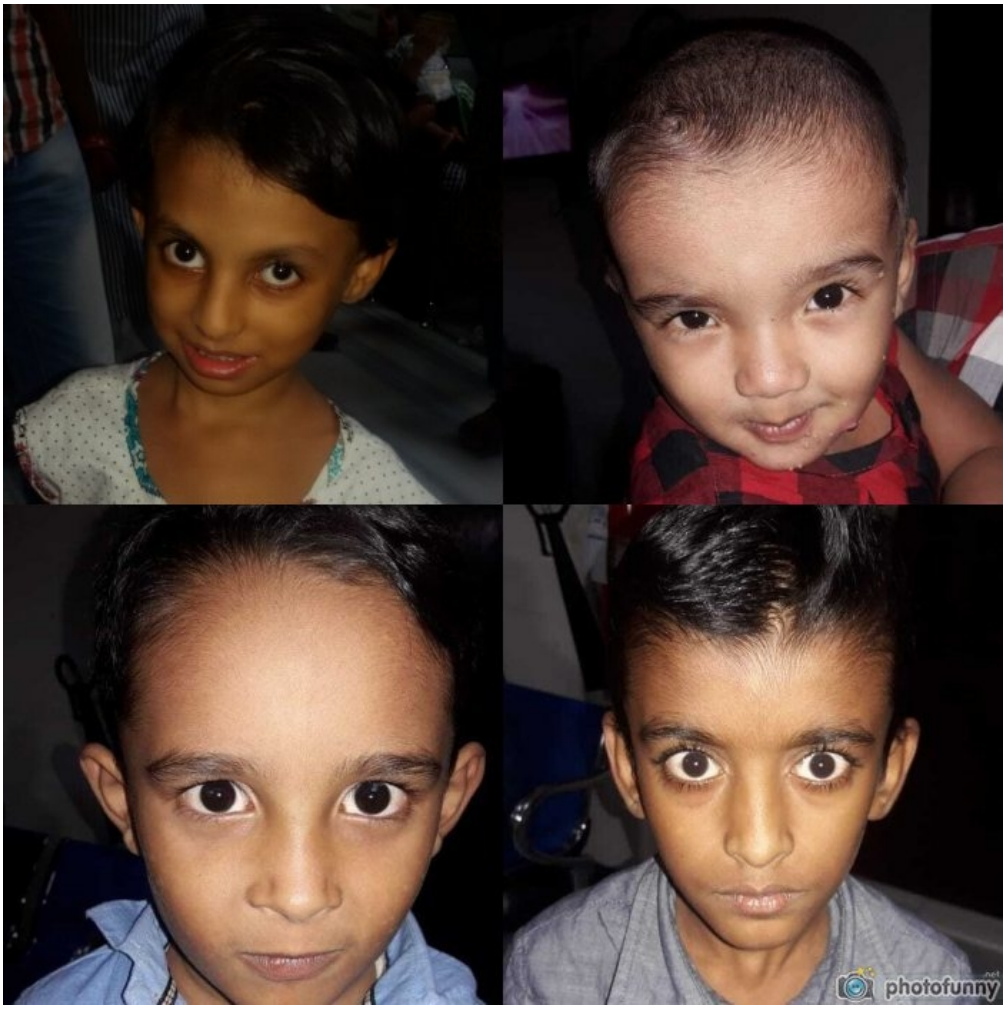

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