Original Research Article

Epidemio-clinical aspects of congenital rubella syndrome in Madagascar

Todisoa N. Andriatahina[1]*, Lantonirina Ravaoarisoa[2], Andrianina H. Ranivoson[3], Vonintsoa L. Rahajamanana[3], Zina A. Randriananahirana[4], Jocelyn Andriamahita[5], Jean C. Andrianirinarison[2], Annick L. Robinson[3]

[1]Department of Pediatrics, Regional Health Facility, Moramanga, Madagascar
[2]Ministry of Public Health Madagascar
[3]Department of Pediatrics, Mother Child Teaching's Hospital, Antananarivo, Madagascar
[4]National Institute of Public and Community Health Antananarivo, Madagascar
[5]Department of Pediatrics, Provincial Health Facility, Toliara, Madagascar

*Correspondence:
Dr. Todisoa N. Andriatahina,
E-mail: todiandria@yahoo.fr

ABSTRACT

Background: Congenital rubella syndrome is the first congenital defect preventable by vaccination. The purpose of this study was to provide basic information on the extent and epidemiology of congenital rubella syndrome in Madagascar.

Methods: A retrospective and descriptive study from January 2013 to May 2019 was conducted in 8 hospitals in 2 provinces of Madagascar, Antananarivo and Toliara. The study included children who attended the services selected during the study period and who had the following conditions: children aged of 0 to 59 months, regardless of vaccination status, meeting the World Health Organization clinical criteria for congenital rubella syndrome with or without biological confirmation.

Results: Of the 152,304 cases of children of all ages who visited or were hospitalized during the study period, 112 clinically confirmed cases of congenital rubella syndrome were identified. The age group 0 to 11 months involved 60 children (53.6%). Congenital heart disease was found in 83.0% of cases, mental backwardness in 43.7% and microcephaly in 26.8%. Twenty-three among (20.5%) them died. The death was due to cardiac diseases in 16 children.

Conclusions: Findings confirm that the diagnosis of congenital rubella syndrome is underestimated in current pediatric practice in Madagascar. The introduction of the rubella vaccine in the Expanded Program on Immunization and the implementation of an effective and sustainable surveillance system for congenital rubella syndrome in the country is a proved effective tool for the prevention of this disease.

Keywords: Epidemiological monitoring, Rubella syndrome congenital, Rubella vaccine, World Health Organization

INTRODUCTION

Rubella is a highly contagious benign viral disease of infancy, with no consequences in most cases. This is a preventable disease by vaccination. A maternal infection during the first quarter of pregnancy can cause a fetal malformation syndrome named congenital rubella syndrome (CRS).[1,2]

On December 2016, 152 out of 194 countries worldwide (78%) had introduced rubella vaccine into their national immunization schedule. The Region of the Americas has succeeded in eliminating rubella and CRS. Rubella and CRS elimination targets have been set for the European Region and the Western Pacific Region. The South-East Asia Region has set a target for rubella and CRS control. No regional target or target for rubella control has been established by the African Region and the Eastern Mediterranean Region.[3,4] In Madagascar, rubella surveillance is carried out through the surveillance of measles. Blood sample from patients suspected of measles and tested negative for active measles (IgM) are then tested for rubella according to the guidelines of the World Health Organization Office for the African Region (WHO Afro). The specific surveillance system of the CRS does not yet exist in the country.[5]

The purpose of this study was to provide basic information on the extent and epidemiology of CRS to support the introduction of the rubella vaccine into the Expanded Program on Immunization (EPI) and the establishment of an effective and sustainable system for the monitoring of the CRS in Madagascar.

METHODS

A retrospective and descriptive study from January 1st, 2013 to May 31st, 2019 dealing with the identification of CRS cases was conducted in two provinces of Madagascar, Antananarivo and Toliara. Seven sites were chosen in Antananarivo where five University Hospital Centers (UHC) were involved: Mother- Child Tsaralalana UHC, Joseph Raseta Befelatanana UHC, Mother-Child Ambohimiandra UHC, Andohatapenaka UHC and Joseph Ravoahangy Andrianavalona UHC.

Other hospitals were selected in Antananarivo, a military hospital (Soavinandriana Hospital Center or CENHOSOA) and a private hospital (SALFA Ambohibao Hospital). One site was chosen in Toliara, the Mitsinjo Betanimena UHC.

The study was conducted in 5 pediatric departments, 3 ear, neck and throat departments and 2 ophthalmic departments. The study population was constituted by cases seen, treated and / or hospitalized in the selected services and having medical records. The WHO definitions have been used for CRS cases classification (Table 1).[6]

Table 1: Word Health Organization definitions for CRS cases classification.

Cases classification	Criteria
Suspected CRS case	Any infant less than one year of age in whom a health worker suspects CRS. 1) A health worker should suspect CRS when the infant aged 0-11 months presents with • heart disease, and/or • suspicion of deafness, and/or one or more of the following eye signs: white pupil (cataract); diminished vision; pendular movement of the eyes (nystagmus); squint; smaller eyeball (microphthalmia); larger eyeball (congenital glaucoma) or pigmentary retinopathy. 2) A health worker should suspect CRS when an infant's mother has a history of suspected or confirmed rubella during pregnancy, even when the infant shows no signs of CRS.
Clinically confirmed CRS case	An infant in whom a qualified physician detects at least: • two of the complications listed in group (a) below • or one in group (a) and one in group (b): a) Cataract(s) and/or congenital glaucoma; congenital heart disease; loss of hearing; pigmentary retinopathy. b) Purpura; splenomegaly; microcephaly; mental retardation; meningo-encephalitis; radiolucent bone disease; jaundice with onset within 24 hours of birth.
Laboratory-confirmed CRS case	an infant who is a suspected case (with 1 condition from cataract(s), congenital glaucoma, congenital heart disease, hearing impairment, pigmentary retinopathy) and meets the laboratory criteria for CRS laboratory confirmation.
Congenital Rubella Infection	An infant who does not have group (a) clinical signs of CRS but who meets the laboratory criteria for CRS is classified as having congenital rubella infection (CRI).

The study included children who attended the services selected during the study period and who had the following conditions: children aged of 0 to 59 months, regardless of vaccination status, meeting the WHO clinical criteria for CRS with or without biological confirmation. Children whose medical records were lost were excluded from the study. The variables studied were the patient's socio-demographic variables (age, gender); variables related to the mother's antecedents (age, vaccination status); variables related to the course of pregnancy and childbirth (pre-natal consultations, term of pregnancy, place of delivery, adaptation to ectopic life);

variables related to hospitalization (reason for consultation or hospitalization, patient outcome, diagnosis of discharge or death); variables to classify cases (clinical signs, paraclinical signs).

Data entry and analysis was done with Epi Info 7. Author used descriptive statistics to calculate frequencies and percentages.

The approval of the Ethics Committee for Biomedical Research at the Ministry of Public Health of Madagascar was obtained.

RESULTS

In total, among the 152,304 cases of children of all ages who came for consultation or were hospitalized during the study period, 753 cases of suspected congenital rubella syndrome were reported, representing a hospital frequency of 0.5%. More than half of the suspected cases were recruited from two hospitals, 297 children from the Tsaralalana Mother-Child Hospital (39.5%) and 110 children from CENHOSOA (14.6%) (Table 2).

Table 2: General characteristic of the population study.

Criteria	Suspected cases		
	Clinically confirmed n=112	Not confirmed n=641	Total n=753
Gender			
Male	55(49,1%)	308(48,1%)	363(48,2%)
Female	57 (50,9%)	333(51,9%)	390(51,8%)
Age (months)			
0-11	60 (53,6%)	332 (51,8%)	392 (52,1%)
12-23	26 (23,2%)	96 (15,0%)	122 (16,2%)
24-35	11(9,8%)	73 (11,4%)	84 (11,2%)
36-47	7 (6,3%)	62 (9,7%)	69(9,1%)
48-59	8 (7,1%)	78 (12,1%)	86 (11,4%)
Site of the study			
Antananarivo			
MET UHC	44 (40,2%)	253 (39,3%)	297 (39,5%)
JRB UHC	16 (14,3%)	43 (6,7%)	59 (7,4%)
UHC JRA	0 (0,0%)	86 (13,4%)	86(11,4%)
UHC MEA	21 (18,8%)	55 (8,6%)	76(10,1%)
UHC Andohatapenaka	0 (0,0%)	24 (3,7%)	24 (3,2%)
CENHOSOA	20 (17,9%)	90(14,0%)	110 (14,6%)
CH SALFA	3 (2,7%)	76 (11,9%)	79(10,5%)
Toliara UHC	8 (6,3%)	14 (2,2%)	22(2,9%)

Taking into account WHO definitions, of the 753 suspected CRS cases, 112 children (14.9%) met the clinically-confirmed CRS case definition. No laboratory confirmed cases or congenital rubella infection cases were recorded.

Description of suspected CRS cases

The age group of children aged of 0 to 11 months accounted for 52.1% of the 753 suspected cases. The median age was 10 months with a minimum of 13 days and a maximum of 59 months.

There were 209 hospitalized children (27.8%), the rest of children were seen as an outpatient. A female predominance was observed with a sex ratio of 0.9.

The vaccination against rubella recorded in medical data was carried out only in a mother. The serology of rubella

was performed in 52 mothers including a single positive case of IgM serology.

Classification symptoms to meet the WHO definition are not routinely found in medical records or patient registers depending on the service where the patient was seen. Most of the children were seen as an outpatient, so the consultation sheets were less detailed than the hospital records.

The most frequent symptoms among the group (a) symptoms found in CRS were respectively, congenital heart disease in 432 children (57.4%), followed by hearing loss in 112 children (14.9%). The most common group (b) symptoms were mental backwardness in 70 children (9.3%), microcephaly in 43 children (5.7%) and meningo-encephalitis in 15 children (2%). No symptoms of radiolucent bone disease were recorded (Table 3).

Description of clinically confirmed CRS cases

History of the mother, pregnancy and childbirth

Among the 112 clinically confirmed cases, the median age of mothers was 27 years, with a minimum of 15 years and a maximum of 51 years. No mother of foreign nationality has been registered. The notion of a history of rubella suspicion was mentioned in one mother. The notion of exposure to a rubella epidemic has not been reported in any of the mothers.

Ante-natal consultations were performed at least 4 times in 47 children (42.0%); the delivery took place in a health facility for 60 children (53.6%); prematurity was found in 9 children (8%); low birth weight in 26 children (23.3%); ectopic adaptation was good in 46 children (41.0%).

Characteristics of the passage of the child to the hospital

The age group 0 to 11 months involved 60 children, or 53.6% (Table 2).

Cardiac symptomatology was the first reason for consultation or hospitalization, found in 67 children (59.8%). Other reasons mentioned were ophthalmological (8.0%), neurological (7.1%), infectious (7.1%), ENT (3.6%) and respiratory (2.7%) symptoms.

Regarding the outcome of the children, 23 deaths were recorded, a death rate of 20.5% among the 112 clinically confirmed cases. The age group of the most affected children who died was 0 to 11 months. The diagnosis of death was related to cardiac pathology in 16 children.

Classification according to WHO criteria according to clinical and paraclinical manifestations

Congenital heart disease was the symptom of group (a) found in 93 children (83,0%). Among the symptoms of group (b), mental retardation was found in 49 children (43.7%) of confirmed cases (43.7%), microcephaly in 30 children (26.8%) (Table 3).

Table 3: Clinical presentation of all suspected cases.

Criteria	Suspected cases		
	Clinically confirmed	**Not confirmed**	**Total of cases**
Total	112 (14.8%)	641 (85,2%)	753
Groupe (a)			
Cataract and/or congenital glaucoma	7 (6,3%)	52 (8,1%)	59(7,8%)
Congenital heart disease	93(83,0%)	339(52,9%)	432(57,4%)
Loss of hearing	4 (3,6%)	108(16,8%)	112(14,8%)
Pigmentary retinopathy	2 (1,8%)	1 (0,16%)	3 (0,4%)
Groupe (b)			
Purpura	4 (3,6%)	1(0,16%)	5 (0,7%)
Splenomegaly	12(10,7%)	1(0,16%)	13 (1,7%)
Mental backwardness	49(43,7%)	21 (3,3%)	70(9,3%)
Microcephaly	30(26,8%)	10(1,6%)	43 (5,7%)
Meningo-encephalitis	13(11,6%)	2(0,3%)	15 (2,0%)
Radiolucent bone disease	-	-	0 (0,0%)
Jaundice with onset within 24 hours of birth	11 (9,8%)	3(0,5%)	14 (1,9%)

DISCUSSION

An overview of the CRS in Madagascar is shown in this study. Indeed, even if this disease is not commonly mentioned in daily pediatric practice in the country, the WHO definitions have made it possible to identify 753 suspected CRS cases including 112 clinically confirmed cases. As a retrospective study, the limits of the work are the missing data in the files. The number of files reviewed still gives information on the hospital frequency of suspected cases of CRS (753/152,304). The WHO classification criteria have also been used by other countries such as Morocco to quantify the extent of CRS

in their country to support the introduction of rubella vaccine. From their study, Morocco was able to estimate that the annual incidence of CRS in their country was 8.1 to 12.7 cases per 100,000 live births.[7]

The lack of systematic request for specific IgM screening in suspected cases may also limit the study, as it was impossible to identify cases confirmed in the laboratory. The postnatal diagnosis of congenital rubella infection is based on the detection of specific IgM by immunocapture technique. If the mother is rubella positive, the postnatal diagnosis of rubella should be done even if the child is asymptomatic, because a child infected in utero will

continue to excrete the virus in saliva and urine for several months (or even for years) and will be a potential source of contamination for the environment.[1,6]

The ideal age to diagnose a CRS is before 12 months.[1,6-8] This definition was not respected in this study so as not to miss children with hearing loss often seen late in ENT consultation, as the country does not yet perform routine screening for hearing loss at birth. Thus, hearing loss was found in 14.9% of the 753 suspected cases, but only 4 children met the definition of clinically confirmed cases.

The median age of mothers was 27 in this study. The young age of pregnant women has been reported as a factor related to a low level of titers of anti-rubella IgG antibodies.[9] Other maternal factors are reported to be influencing maternal rubella infection, such as women living in urban areas and women attending school.[10,11] It was impossible for us to verify the immune status because this practice is not yet common during pregnancy follow-up.

Maternal screening for rubella titers in early pregnancy is considered as the standard of care in high-income countries. Any disease resembling rubella in early pregnancy should be evaluated to confirm the diagnosis. Laboratory diagnosis is based of a proven seroconversion with IgG and IgM assays.[1,8] Mothers in this series followed at least 4 antenatal visits in 42.0% of clinically confirmed cases, but the rubella prescription rate remains neglected. The quality of pre-natal consultations should be improved to define the serological status of the mother in order to provide for possible subsequent vaccination to her in case of absence of immunity.

Several clinical symptoms are related to CRS. Few or no obvious clinical manifestations occur at birth in benign forms of the disease. The incidence of congenital rubella infection is high during the first and last weeks of gestation, with much higher birth defects occurring if infection occurs early in pregnancy.[2] In India, in 85 children diagnosed with CRS, 12 children had tear drainage abnormalities. These 12 children all had cardiac malformation including four childern with sensorineural hearing loss and two children with microcephaly associated with micrognathia.[12] The heart symptoms were the most frequent in this study. This finding must arise the clinician's awareness in routinely to asking rubella serology in children under 12 months of age with heart disease. Similarly, other manifestations such as mental backwardness, hearing loss and microcephaly should also be explored.

In India, a systematic review to assess the prevalence of CRS showed that among suspected infants of having an intrauterine infection, biological confirmation was proved for 1 to 15% of those affected by SRC. This syndrome accounts for 10 to 15% of pediatric cataract cases. Children with congenital malformations had biological confirmation of CRS in 10 to 50% of cases.[13,14]

The death rate of the clinically confirmed cases was not trivial. Countries that have integrated the introduction of rubella vaccination into their immunization program have experienced a clear increase in population-specific IgG seropositivity and a decrease or even disappearance of CRS cases. The few cases reported later were all imported cases.[11,15-17]

The obvious factor associated with the occurrence of CRS is the lack of pre-pregnancy rubella immunity in the mother that reflects a low immunization coverage against rubella.[18,19] In Madagascar, the rubella vaccine is not free of charge because it is not yet part of EPI vaccines. The main goal of rubella vaccination programs is to prevent negative outcomes of pregnancy. In 2011, WHO updated its guidance on the vaccine strategy. It favored the introduction of rubella vaccine into national immunization schedules and advocated the organization of an initial vaccination campaign targeting children aged 9 months to 14 years.[3] To ensure the elimination of rubella and congenital rubella, a high immunization coverage with two doses of vaccine during childhood should be supported.[3,13]

CONCLUSION

Rubella is the leading cause of congenital malformation that can be prevented by vaccination. Study confirms that the diagnosis of CRS is underestimated in current pediatric practice in Madagascar. WHO clinical and laboratory classification criteria allow clinicians to diagnose this pathology. The database resulting from this work will provide support for the introduction of rubella vaccination in the national routine immunization program and the establishment of specific CRS epidemiological surveillance.

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