

The aetiology of maculopapular rash diseases in Niterói, State of Rio de Janeiro, Brazil: implications for measles surveillance

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(Accepted 19 May 2001)

SUMMARY

A study investigating the causes of rash diseases using systematic laboratory testing was conducted in Niterói, Rio de Janeiro, between January 1994 to April 1998. Sera from 327 patients were tested for evidence of anti-rubella virus, measles virus, human parvovirus B19 and dengue fever virus specific immunoglobulin IgM and anti-human herpes virus type 6 (HHV-6) IgG antibodies. A laboratory confirmed diagnosis was achieved in 71·3% of the cases investigated: dengue fever (33·0%), rubella (20·2%), parvovirus B19 (9·2%), measles (6·7%) and HHV-6 (2·1%). No diagnosis was established for 94 cases (28·7%). An outbreak of measles was detected during 1997, with a peak in September and October. All of the diseases studied here presented with clinical features similar to measles and classical symptoms were found in all measles confirmed cases. The large overlap of combinations of signs and symptoms seen in this study highlights the difficulties of diagnosing a rash illness on clinical grounds alone.

INTRODUCTION

Despite the introduction of the Brazilian National Immunisation Programme in 1973, measles was still a serious public health problem in the early 1990s, being one of the leading causes of morbidity and mortality among young children. The difficulty in achieving high coverage rates in routine vaccination led some State Health Departments to introduce periodic measles campaigns similar to the National Vaccination Days for poliomyelitis. Nevertheless, this

strategy was not implemented consistently across the whole country and measles outbreaks continued to occur [1].

Consequently, the Brazilian Health Ministry ran a national mass vaccination campaign for measles in 1992, which resulted in a dramatic reduction in measles incidence rates across the country. Measles vaccine was given to approximately 48 million children aged from 9 months to 14 years, achieving more than 95% coverage for the target population [1].

As the overall measles vaccine coverage increased, the epidemiology of the disease changed, leading to a lengthening of the inter-epidemic periods and an effective diminishing of the epidemic peaks. Since 1990 a shift in the age distribution of measles incidence

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Table 1. *Testing methods and algorithm*

Disease	Selection criterion for testing	Methods of test	Number of cases tested
Rubella	None	IgM EIA*	327
Measles	None	IgM EIA [10]	327
Dengue fever	None	IgM EIA [11, 12]	327
Parvovirus B19	Serum negative to rubella, measles and dengue fever	IgM EIA [13]	131
HHV-6	Case less than 5 years old and serum test negative to rubella, measles, dengue fever and parvovirus B19	Indirect immunofluorescence test for HHV-6 IgG [14]	27

* Rubenostika IgM, Organon.

towards older age groups has been seen [2–4]. This shift occurred in a heterogeneous manner across the country and was more marked in states that had achieved better results in the control of the disease [4].

It is recognized that when measles is well controlled, diagnosis based on clinical grounds alone is inaccurate and can be confused with other infectious exanthematous illnesses, such as rubella, erythema infectiosum, dengue, roseola infantum and scarlet fever. Moreover, recent studies have indicated that measles virus may also circulate in vaccinated people, causing mild symptoms or even asymptomatic infections [5, 6]. Thus, for effective control and eventual eradication of measles, a sensitive surveillance system and the ability to unequivocally diagnose measles cases are essential [6]. The role of the laboratory is fundamental to confirm or discard notified cases. Blood specimens should always be obtained in the investigation of a suspected measles case.

The present study was undertaken to define the aetiology of rash diseases with or without fever in Niterói, a population with high measles vaccine coverage and to analyse the clinical case definition of measles for surveillance purposes.

The study population comprised patients attending the two largest primary health care units and a general hospital from the public network with a catchment area of approximately 50% of the population of the municipality of Niterói. The population of that municipality was 450 364 inhabitants in 1996 [7], being one of the five largest administrative districts in Rio de Janeiro, Brazil. Periodic measles vaccination was introduced in 1985 and a mass campaign in 1992 which was associated with a decline in incidence of measles from 6.15 per 100 000 in 1992 to 0.22 per 100 000 in 1994 [8, 9] when study enrolment commenced.

METHODS

Study design

From January 1994 to April 1998 all patients seen at the selected study sites with an acute maculopapular rash, with or without a history of fever, were asked to participate. A standard clinical examination was performed, their vaccination history recorded and a blood sample to confirm the diagnosis collected. The study population was divided in age groups and patients ≥ 15 years of age were considered adults.

A questionnaire was designed for the study and each case was interviewed regarding measured or reported fever, cough, conjunctivitis, coryza, arthropathy, lymphadenopathy and other symptoms, complications and exposure to other cases of exanthematic disease.

Serum samples

A clotted blood sample for serology collected in a sterile glass tube was obtained from each patient (young children: 3.0 ml; other patients: 5.0 ml) at the time of consultation. A second sample was also obtained between 7 and 10 days later from 75 patients that had rash onset within 4 days of the first blood sample. The sera were stored at -20°C until tested. Informed consent was obtained for all participants and from the parents or guardians of patients younger than 18 years of age. The study was approved by the hospital's Institutional Review Board.

Laboratory tests

All serum samples were tested for the presence of anti-rubella virus IgM antibodies by using a commercial enzyme immunoassay (EIA) (Rubenostika IgM, Or-

ganon), for anti-measles virus IgM by using an antibody capture EIA developed at the Centers for Disease Control (Atlanta, USA) [10], and for anti-dengue virus IgM by using an in-house EIA [11, 12]. Those specimens negative for rubella, measles and dengue virus antibodies were also tested for anti-human parvovirus B19 IgM using an antibody capture EIA (MACEIA) [13]. An indirect immunofluorescence test for human herpesvirus type 6 (HHV-6) IgG [14] was also used to detect low avidity antibody in children under 5 years of age without an alternative diagnosis (Table 1).

Data (statistical) analysis

Data were analysed using Epi Info Version 6 [15]. Proportions were compared using the chi-squared test. Differences between individual groups were considered significant at the 0.05 level.

RESULTS

From January 1994 to April 1998 a total of 327 patients with an exanthematous rash presenting with an illness characterized by variable combinations of rash, cough, conjunctivitis, coryza and fever were studied. More than half of the patients were female (191 cases, 58.4%) and this predominance was most evident in adults (60 women, 23 men). A laboratory confirmed diagnosis was achieved in 233 (71.3%) cases investigated: dengue fever (108 cases, 33.0%), rubella (66 cases, 20.2%), human parvovirus B19 (30 cases, 9.2%), measles (22 cases, 6.7%) and HHV-6 (7 cases, 2.1%). No diagnosis was established in 94 cases (28.7%); the proportion was higher in children (71.3%) compared to adults (39.7%) (Table 2). The vast majority of cases were seen as outpatients and only seven cases (all of them with measles complications) were admitted to a hospital (interstitial pneumonia, 3 cases; diarrhoea, 3 cases; haemorrhagic conjunctivitis, 1 case).

The age distribution of the patients with rashes is shown in Table 2. Most cases of measles (86.4%) and dengue fever (67.6%) occurred in adults. Only three cases of measles occurred in children (6, 9, and 12 months), two of them with a history of measles vaccination (1 dose). Of the 19 adults with confirmed measles infection, only one had an immunization card confirming one dose of vaccine before his first birthday. The majority of human parvovirus B19 (73.3%) and more than half of the rubella (54.5%) cases were diagnosed in children.

Table 2. Age distribution of rash disease cases

Age group (years)	Exanthemous diseases													
	Dengue		Rubella		B19		Measles		HHV-6		Unknown		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
< 1	—	—	2	3.0	—	—	2	9.1	4	57.1	9	9.6	17	5.2
1-4	7	6.5	16	24.2	5	16.7	1	4.5	3	42.9	20	21.3	52	15.9
5-9	11	10.2	10	15.2	13	43.4	—	—	—	—	16	17.0	50	15.3
10-14	17	15.7	8	12.1	4	13.3	—	—	—	—	12	12.8	41	12.5
15-19	6	5.6	12	18.2	1	3.3	2	9.1	—	—	7	7.4	28	8.6
20-29	20	18.5	10	15.2	2	6.7	15	68.2	—	—	12	12.8	59	18.0
30-39	20	18.5	5	7.6	4	13.3	2	9.1	—	—	9	9.6	40	12.2
40-49	18	16.7	3	4.5	1	3.3	—	—	—	—	5	5.3	27	8.3
50-59	8	7.4	—	—	—	—	—	—	—	—	2	2.1	10	3.1
≥ 60	1	0.9	—	—	—	—	—	—	—	—	2	2.1	3	0.9
Total	108		66		30		22		7		94		327	

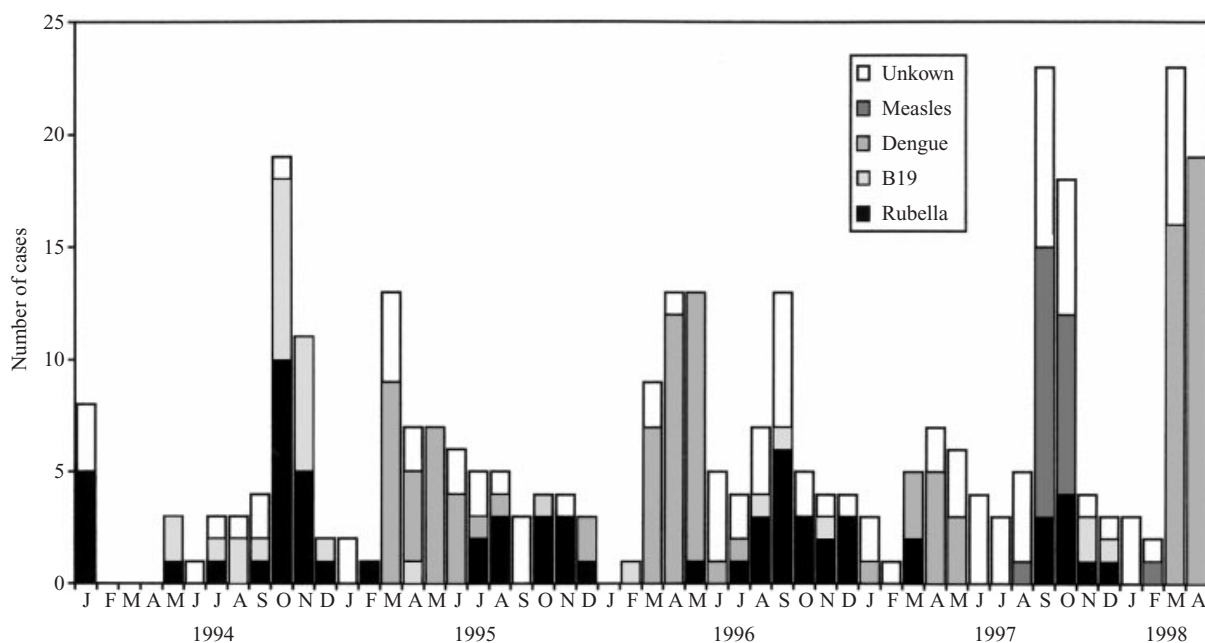


Fig. 1. Time distribution of rash disease cases during the study period (January 1994–April 1998).

Twenty-seven serum samples from children < 5 years of age known not to contain IgM specific for measles virus, rubella virus, dengue fever virus, or human parvovirus B19 were tested for HHV-6 IgG. Of the 27 children, 26 (96.3%) were HHV-6 IgG positive, and of these 7 (26.9%) had low avidity antibody. Four (30.8%) out of 13 children aged under 1 year had low avidity antibody to HHV-6.

Figure 1 shows the temporal distribution of cases over the study period. No measles cases were confirmed in the first 3 years of the study even in cases that fulfilled the criteria of a clinically suspected case by the Brazilian Health Ministry [16], i.e. presence of a generalized maculopapular rash of ≥ 3 days-duration, fever, and at least, one of the following: cough, coryza or conjunctivitis. However, an outbreak of measles was detected during the second part of 1997, with a peak in September and October. Higher rates for rubella were observed during the second half of all 4 years studied. A similar pattern was seen for human parvovirus B19 cases in the first year of the study. For 4 years high rates of dengue infection were seen between March and June. The seven patients with HHV-6 infection were sporadic cases apparently not associated with an outbreak. Cases with unknown aetiology were seen throughout the study.

Categories in Table 3 are defined by different combinations of fever, cough, conjunctivitis, coryza, lymphadenopathy, and arthropathy with rash. Frequency of fever was substantially lower in human

parvovirus B19 infections, whereas lower proportion of cough, coryza and conjunctivitis was found in dengue cases. However, categories overlap widely making difficult the diagnosis of rash diseases on clinical grounds only. A large proportion of cases fulfilled the case definition constructed for measles surveillance.

The distribution of lymphadenopathy was evaluated in all cases (Table 3). Posterior auricular and occipital lymphadenopathy were seen more frequently in rubella cases (59.1%) than in measles (36.4%), dengue fever (36.1%), or human parvovirus B19 (20.0%) [χ^2 (5 D.F.) = 16.16, $P < 0.01$]. Lymphadenopathy was common in the few cases of HHV-6 infection seen.

Arthropathy (arthralgia and/or arthritis) occurred more frequently in adults (50.3%) than in children (11.9%) [χ^2 (1 D.F.) = 55.91, $P < 0.01$], and among the adults joint complaints prevailed in women (57.5%) compared to men (37.7) [χ^2 (1 D.F.) = 6.10, $P < 0.02$]. Arthropathy was most frequently seen in human parvovirus B19 (85.7%) and rubella (72.2%) cases and was common in dengue fever (63.8%) and measles (44.4%) cases. In general joint involvement was symmetrical, affecting preferentially the small joints of the hands, feet, knees, shoulders and wrists. Less frequently, ankles, elbows and cervical spine were affected.

Of the 94 patients without a conclusive diagnosis 45 (47.9%) were investigated less than 5 days after the

Table 3. Distribution of the most common signs and symptoms observed in 327 cases of rash disease according to serological diagnosis

Disease	Measles		Rubella		Dengue		B19*		HHV-6†		Unknown	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Signs and symptoms												
Fever	22	100	46	69.7	86	79.6	14	46.7	7	100	45	47.9
Cough	22	100	25	37.9	20	18.5	9	30.0	4	57.1	31	33.0
Conjunctivitis	22	100	25	37.9	19	17.6	8	26.8	3	42.8	14	14.9
Coryza	22	100	30	45.5	15	13.9	7	23.3	4	57.1	23	24.5
Lymphadenopathy	8	36.4	39	59.1	39	36.1	6	20.0	4	57.1	40	42.6
Arthropathy	7	31.8	21	31.8	50	46.3	9	30.0	—	—	16	17.0
Total	22		66		108		30		7		94	

* Human parvovirus B19.

† Humanherpes virus 6.

onset of the rash and of these 40 (88.9%) within 3 days of onset. Twenty-nine (30.9%) of these cases were children aged under 5 years of age.

DISCUSSION

The results of this study highlight the difficulty in diagnosing infectious exanthematous diseases on clinical grounds alone. Moreover, serological surveillance of rash diseases proved to be relevant to uncover the distinct patterns of the different causal infections that make up a substantial proportion of health care demands across a wide age range of patients. These patterns cannot be established without confirmation by laboratory data because of the overlapping combination of signs and symptoms seen in the diseases studied.

The testing algorithm for parvovirus B19 and HHV-6 selected out sera which were previously tested positive for measles virus, rubella virus and dengue fever virus. In case of concomitant infectious with parvovirus B19 and HHV-6 their frequency might have been underestimated. However, clinical and epidemiological data suggest that the probability of such occurrence would be low.

Our data were obtained from two health care units (outpatients) and a reference hospital known to represent a fair approximation of the current endemic situation in the city [17]. Nevertheless, individuals who seek and get medical care for exanthematic diseases represent only a fraction of all those infected. In this regard, the proportion of each disease in this group reflects the perceived seriousness of disease by the sick person or their parents. With this context and the limitations of the study, our results are likely to reflect the seasonal distribution of exanthematic diseases in Niterói during the study period.

Our findings support the decreased incidence of measles reported for the municipality. No suspected measles cases were laboratory confirmed in the first 3 years of the study, even in those cases which fulfilled the criteria for a clinically suspected case set by the Brazilian Health Ministry [16]. However, as reported for some states of the country [3], an outbreak of measles was detected in Niterói during the second part of 1997. Of the 45 confirmed cases reported from the whole municipality, 21 (46.7%) were seen at the study sites, showing good sensitivity of the surveillance to detect measles cases. All of the study cases presented with typical symptoms. Therefore, it seems that the occurrence of ‘mild modified measles’, described by

some authors in patients who have previously been vaccinated [5, 6], is still sporadic in our community or does not lead to them presenting for clinical attention.

The low number of measles cases observed during the study period is not particularly surprising, since there is a high level of immunity to measles in the population of Niterói, as shown by the seroepidemiological survey carried out in 1992 [18] and the high rates of vaccination coverage achieved during the mass vaccination campaigns [19]. Most of the study cases (77.3%) occurred in young adults and a similar pattern was observed in the municipality [9]. It should be pointed out that this shift to older age groups had already been reported in other states in Brazil and was more marked in those states which had achieved better results in the control of the disease [4].

Rubella infections usually have a peak in late winter and spring [20, 21], and in this study the same distribution was found for the period examined. In 1994 the seasonal distribution of human parvovirus B19 was similar to that of rubella, as reported by others [21–23]. Cohen [23] suggested that human parvovirus B19 epidemics may occur at intervals of 2 years. In the following years only scattered cases of human parvovirus B19 were seen which is consistent with the pattern of infection seen elsewhere. Although some small studies [24–26] have been published in recent years, the epidemiology of human parvovirus B19 is still not well documented in Brazil.

After the reappearance of dengue virus in the State of Rio de Janeiro, outbreaks and large epidemics of dengue fever have been described in several Brazilian States, and also in Niterói, mainly during the rainy season [27, 28]. Our results are very similar to those reported throughout the state, and reflect the high incidence of the disease in the last 12 years. Although no dengue fever cases were observed in 1994, during the following years high rates were seen in the first half of the year between March and June, mainly in 1995, 1996 and 1998. The consistent pattern of cases and the low incidence of other exanthematic diseases help to make physicians consider strongly a diagnosis of dengue fever in the differential diagnosis of a rash illness during these periods.

Other common causes of exanthematic diseases such as streptococcal infection, enteroviruses and allergic reaction to medicines for which specific tests were not used, and false negative laboratory results may explain part of the large proportion of cases without diagnosis. The former could be related to the higher proportion of virus antibody negative indi-

viduals in younger age groups. The later result probably from the timing of specimen collection, since test sensitivity is known to be lower in the early period of the disease, when antibody levels are not high enough to be detected [12, 29, 30].

As described by other authors [23, 31, 32], arthropathy was a frequent complaint in adult women with human parvovirus B19, rubella, and dengue fever. Joint involvement has not been reported in measles patients, however, in our study 44.4% of the cases developed arthralgia. This finding may be due to the shift in the age distribution of measles cases to older age groups, and this may increase the difficulty for clinically diagnosing measles. It may also be a result of co-infection with human parvovirus B19 as patients with measles virus IgM were not tested for human parvovirus B19 IgM.

The typical post-auricular and sub-occipital lymphadenopathy described in rubella patients [33] was seen in 59.1% of our rubella cases. Although this result was significant when compared with the other rash diseases studied, we did not find that lymphadenopathy was a pathognomonic marker for rubella. Except for human parvovirus B19, the proportion of patients with lymphadenopathy associated with the other illnesses was not much lower than that seen in the rubella cases.

A study by Tait et al. [34] showed that exanthem subitum is a frequent cause of rash disease in children under 2 years of age and many cases are clinically misdiagnosed as measles and rubella. Seven of our patients presented with low avidity antibody to HHV-6 suggesting recent infection had clinical symptoms – fever, rash, cough, conjunctivitis and coryza could be confused with measles and rubella. Although in this study the proportion of children under 1 year (30.7%) who had low avidity antibody to HHV-6 had been lower than that found by Tait et al. (50%), this result confirms the role of HHV-6 as a cause of rashes in young children and reinforces the role of laboratory diagnosis in the effectiveness of measles and rubella surveillance programmes.

In conclusion, our study showed the frequent occurrence of several acute infectious diseases that fit the working case definition of measles and are clinically indistinguishable from it. It strengthens the notion that to achieve the goal of measles eradication, surveillance of exanthematic diseases must rely heavily on laboratory diagnosis. Moreover, rubella and dengue, which are the other diseases from this group also targeted by intervention programmes, benefit

from serological surveillance, as well. The large proportion of inconclusive cases after laboratory tests suggests that there is room for improvement in the use of laboratory resources.

The case definition for measles surveillance cannot be made more specific without conceding on sensitivity. It represents a screening set of criteria meant to be sensitive enough to capture most cases that will be confirmed by specific tests. As it is, the measles case definition may be missing cases with attenuated measles in partly immunized individuals. Even for typical measles, the positive predictive value of the current definition has certainly dropped as a result of the reduction in the incidence of measles. Again, this supports the critical role of laboratory diagnosis. However, combinations of signs and symptoms in syndromes suggestive of rash diseases play an important role in disease surveillance to trigger investigation and to confirm cases by epidemiological linkage to cases confirmed by laboratory tests.

ACKNOWLEDGEMENTS

We gratefully acknowledge the general practitioners from the Department of Infectious Diseases/Hospital Universitário Antonio Pedro and from the Centros de Saúde Santa Rosa and São Lourenço, Niterói, Rio de Janeiro, Brazil, who supplied clinical specimens. We also acknowledge Dr Jussara P. Nascimento from Fundação Oswaldo Cruz, Rio de Janeiro, Brazil, for advice, and Conselho Nacional de Pesquisa e Desenvolvimento (CNPq-grant No. 52-0406/94-0 and 52-0689/96-8) for providing financial support for the research and Fundação de Ampares à Pesquisa do Rio de Janeiro (FAPERJ-Proc. No. E-26/170.575199).

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