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SEROLOGICAL FINDINGS DURING A MEASLES OUTBREAK OCCURRING IN A POPULATION WITH HIGH VACCINE COVERAGE

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SUMMARY

From March 1991 to April 1992, serum samples for IgM detection were collected from 112 clinical measles cases reported to the Health Department of Niterói, State of Rio de Janeiro. The positivity exceeded 90% for specimens collected from the 5th to the 29th day after the onset of the disease. After day 30 a decline in IgM detection was observed, although positivity has been detected up to 90 days after the onset of the symptoms. Forty-four patients (48.9%) with an IgM response had a history of prior measles vaccination. In 5 of the 22 measles-IgM negative cases the infection was due to other agents (rubella: 4 cases, dengue: 1 case).
These results show that sensitivity of the test employed for confirming suspected measles cases is high, even in vaccinated patients.

KEYWORDS: Measles; Diagnosis; IgM.

INTRODUCTION

A remarkable decrease in the number of reported measles cases has been observed in Brazil since the introduction of mass vaccination campaigns in 1985[3,8]. In places where measles is under control the diagnosis of suspected cases is frequently inaccurate when made on clinical grounds alone. In the U.S.A., because of the great reduction in number of measles cases, it is believed that measles-mimicking diseases may account for a substancial proportion of reported cases, mainly in vaccinated people[26].

On the other hand, other agents, mainly viral, responsible for syndromes very similar to measles, can rise questions about the accuracy of measles surveillance based on clinical diagnosis[26]. At this stage, the role of the laboratory is fundamental to confirm or discard notified measles cases.

In our country, despite the improvement of vaccine coverage, this fact was not concomitantly followed by the implementation of network of laboratories capable of confirming the clinical diagnosis of the disease and the development of techniques suitable for use at the primary health care level[27].

The present work was undertaken to investigate serologically the measles cases reported to the Health Department of the Municipality of Niterói, State of Rio de Janeiro, and to verify the usefulness of a specific measles IgM assay in the rapid diagnosis of ongoing and recent measles infections.

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MATERIALS AND METHODS

Study design

From March 1991 to April 1992 an intensive surveillance system was instituted by the Division of Epidemiology of The Niterói Department of Health. Physicians were required to immediately report suspected measles cases based on the criteria established by the Centers for Diseases Control (CDC)[4] for a clinical case definition: an illness characterized by fever $\geq$ 38.3°C, generalized maculopapular rash of $\geq$ 3 days-duration, and at least, one of the following: cough, coryza or conjunctivitis. Each case reported was investigated by epidemiologists or nurses of the Department of Health especially trained to confirm clinical diagnosis and to obtain laboratory specimens of suspected cases. Only people with a well - documented history of prior immunization were assumed to be vaccinated.

Serum samples

After parental consent, a single serum sample was obtained from patients with suspected acute measles infection up to 90 days after the onset of the disease and stored at - 70° C.

Serologic techniques

Serum samples were first tested for the presence of anti-measles antibodies using a IgM capture and a direct IgG immunoassays developed at the CDC, Atlanta, USA[9]. Those specimens classified as negative anti-measles IgM were also tested for anti rubella IgM using a commercial assay (Organon Tecknika, Belgium), and for anti-human parvovirus B19 IgM[5] or anti-dengue IgM[16] using in-house developed assays.

RESULTS

During the study period 290 cases that fulfilled the criteria for clinical measles were reported to the Health Department of Niterói, but only 112 serum samples were obtained from the reported cases.

Measles IgM antibodies were positive in 90 (80.4%) cases, indicating acute infection. In 5 the infection was due to other agents: in 4 cases IgM antibodies were positive to rubella and in 1 case to dengue. The other 17 cases were negative for measles specific IgM and also for IgM antibody against rubella, dengue and human parvovirus B19. Thirteen of these cases had measles IgG antibodies, however, it was not possible to draw a second specimen to test a significant rise in IgG antibody level to confirm an acute infection.

Twelve (70.6%) of the 17 patients with negative measles-specific IgM test had a history of prior vaccination with live attenuated measles vaccine: 8 cases were vaccinated before one year of age, 1 case had received one dose after the first birthday and 3 had received more than one dose of measles vaccine.

The appearance and persistence of measles IgM antibodies are shown in Table 1. A response was seen as early as after the third day of onset of measles reaching more than 90% positivity from the 5th to the 29th day. After 30 days, a decline in IgM detection was observed, although in 16.7% of cases positivity was detected up to 90 days after the onset of symptoms.

Forty-four patients (48.9%) with an IgM antibody response had a well-documented history of prior vaccination. Of these 30 (68.2%) were vaccinated before their first birthday, 7 had received one dose of measles vaccine after first birthday and 7 had received two or more doses.

DISCUSSION

Until 1984 the epidemiology of measles in the Municipality of Niterói, RJ, was characterized by high rates of morbidity and mortality, mainly reported in children under five. Since 1985, following the introduction of national immunization campaigns mainly directed to children 9 to 23 months of age, measles incidence and mortality have declined rapidly. Measles incidence in Niterói began to increase during the 90's, but at this time most cases were observed in teenagers and young adults[8]. On the other hand, during the summer of 1990 and 1991 the incidence of measles and rubella increased simultaneously with the epidemic of dengue type 2, leading to misdiagnosis[7].

However, the relative mildness of the majority of measles cases in areas where vaccine coverage has already reached high levels makes parents and medical practitioners reluctant to take blood for diagnosis[21]. Such fact was observed in this research where from 290 clinical measles cases only 112 (38.6%) agreed to take a single blood specimen for laboratory diagnosis. Of these, the infection was due to rubella in 4 cases and dengue in 1 case. The finding that only in 5 cases (4.5%) other viral agents account for measles-like diseases shows that at least in the Municipality studied this fact is still sporadic; in contrast to these observed by SMITH et al.[26] where 27% of the clinically diagnosed cases were not serologically characteristic of measles.

In the primary acute measles infection, detectable IgG and IgM antibodies generally appear in the serum

within the first days of rash, peak within about 4 weeks and then decline. IgG antibodies are detectable long after infection, while IgM antibodies are rarely detected after 6 weeks[20]. After re-exposure, a characteristic anamnestic response with boosting of IgG antibody is usually observed. Until recently, IgM was not usually detected by using the currently available serologic assays[20,26]. However, in 1991, ERDMAN et al.[6], using capture EIA, detected specific IgM antibodies in cases of clinical measles with a history of prior vaccination, and showed the high sensitivity of this test and its applicability in the diagnosis on of acute measles infections. This fact was confirmed in this study where 44 (48.9%) patients with an IgM antibody response had a well-documented history of prior vaccination: 68.2% (30 cases) of them were vaccinated once before their first birthday and 31.8% (14 cases) had received one or more doses at or after the age of one.

The occurrence of the disease in patients previously vaccinated can be related to vaccine failure due to: neutralization of vaccine virus by maternal or those artificially administered (gamma globin) antibodies[2,13,18,25], and improper storage or handling of the vaccine[11,22,23,25]. In addition, vaccination below the age of one is known to induce a relatively low percentage of seroconversion as well as significantly lower geometric mean antibody titers[1,10,14,18].

In Brazil because of the high incidence of measles at a young age, since 1982 measles vaccine has been recommended for routine use for children 9 months of age or more. As 13-15% of the children remain susceptible with this strategy a few States decided to administer a second dose of the vaccine after 15 months of age. Nevertheless this policy was not adopted by the country as a whole[3]. Moreover, alterations in measles vaccine quality detected by OLIVEIRA et al. in 1986[17], and again in 1990[19] in public health units of the Municipality studied can also have contributed to the results related above.

Measles IgM antibodies were detected from the third day of the disease, reaching more than 90% positivity from the 5th to the 29th day after the onset of measles. Although positivity had declined after 30 days, it could be detected up to 90 days, after the onset of symptoms.

ERDMAN et al.[6] also verified that the optimal time for specimen collection for IgM detection after natural measles virus infection is approximately 2 to 3 weeks after the few days of the onset of rash.

The negative IgM test in 17 cases diagnosed as having clinical measles, but not confirmed by a significant rise in IgG antibody, could be by factors as: a) Blood collection out of the optimal time for IgM detection: in 4 cases the blood was drawn within the first 4 days of the beginning of the disease and in 9 cases after the 30th day; b) Secondary vaccine failure, as history of prior vaccination, was observed in 12 cases (70.6%) of the 17 cases analysed.

It was not possible to confirm those 17 clinical measles cases because a second serum specimen was not available during the course of the disease. To LIEVENS & BRUNELL[12], in cases in which the initial serum sample is negative, a second specimen should be drawn 1 to 3 weeks after the onset of the disease. To these authors measles diagnosis will be unlikely if this second sample is also negative for IgM antibody. In addition, a second serum specimen might also provide the etiologic diagnosis if a significant rise in IgG antibody levels was demonstrated.

TABLE 1

Specific IgM antibodies detected in reported measles cases according to the interval between onset of the disease and sample collection.

Days after onset of the disease	Positive		Total
	Nº	%	Nº
3-4	14	77.8	18
5-15	49	94.2	52
16-29	12	92.3	13
30-90	15	62.5	24
Total	90	84.1	107

Results of this work show that capture IgM EIA was highly efficient for serological confirmation of recent measles infection by testing a single serum sample.

RESUMO

Achados sorológicos durante um surto de sarampo em uma população com alta cobertura vacinal

No período de março/1991 a abril/1992, foram escolhidas 112 amostras sanguíneas para a detecção de anticorpos da classe IgM de casos de sarampo notificados à Divisão de Epidemiologia da Fundação Municipal de Saúde de Niterói, Estado do Rio de Janeiro. A positividade ultrapassou 90% para os espécimens colhidos entre o 5º e o 29º dia após o início da doença. A partir do 30º dia foi observado um declínio na detecção de IgM, embora positividade tenha sido constatada até noventa dias do início dos sintomas. História de vacinação prévia estava presente em 48,9% destes pacientes. Dos 22 casos restantes, em 5 a infecção era devido a outros agentes (rubéola: 4 casos, dengue: 1 caso).

Estes resultados demonstram que a sensibilidade do teste empregado para confirmação de casos suspeitos de sarampo é elevada mesmo em pacientes vacinados.

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