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Modified Clinical Manifestations of Measles in Young Infants: 10 Years' Experience in a Tertiary Referral Centre of Hong Kong

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Abstract

Background: Measles still causes significant morbidity and mortality. The diagnosis of measles relies on early recognition of clinical manifestations. We identified a group of young infants who presented with a modified clinical picture after contracting measles, but there is scarce literature describing this observation. ***Method:*** We conducted a retrospective study of all infants <1 year old with measles confirmed by serological or virological methods in Princess Margaret Hospital, a territory-wide tertiary referral centre for infectious diseases in Hong Kong, over a period of 10 years from 1999 to 2008. The study population (n=165) was divided into 2 groups: 29 infants were aged <7 months and 136 infants were 7-12 months of age. Their clinical manifestations were compared and analysed, which included the timing of skin rash in relation to onset of fever, duration of fever, presence or absence of characteristic clinical features of measles such as coryza, cough, conjunctivitis, Koplik's spots, staining of convalescent rash, and other associated features and complications. ***Results:*** The mean duration of fever in infants aged <7 months and 7-12 months were 4.6 and 6.8 days, respectively (p<0.001, 95% CI 1.24-3.04). Shorter duration of fever was noted in the younger age group with a positive correlation observed for age and duration of fever (r=0.307, p<0.001). The onset of skin rash was 2.3 and 3.7 days after the onset of fever for the 2 age groups, respectively (p=0.001, 95% CI 0.58-2.12). Earlier onset of skin rash was noted in the younger age group with a positive correlation observed for age and timing of skin rash from the onset of fever (r=0.255, p=0.001). Conjunctivitis (p=0.001) and staining of skin rash during convalescence (p=0.026) were significantly less common in the younger infant group. There were no significant differences between the 2 groups regarding presence of coryza (p=0.07), cough (p=0.28), Koplik's spots (p=0.18), diarrhoea (p=0.72), pneumonia (p=0.74) and the use of antibiotics (p=0.74). ***Conclusion:*** Our study revealed a modified clinical picture of non-specific and milder form of measles in young infants. The presence of modified features may be due to partial protection provided by maternally derived measles antibody (anti-measles IgG). We should maintain a high index of suspicion for measles presenting in this group of patients because of the possibility of atypical presentation. The use of rapid diagnostic test (e.g. anti-measles IgM) in such situation facilitates early diagnosis, proper treatment and institution of appropriate infection control measures. Early airborne isolation of hospitalised infants should be considered in all suspected cases to interrupt transmission and prevent potential nosocomial outbreaks.

Key words Clinical features; Clinical manifestations; Measles; Modified

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Introduction

Measles is the leading killer among vaccine preventable diseases in childhood and is one of the most contagious infectious diseases of mankind. Each year, it affects 30-40 million people worldwide and causes half a million deaths.[1] The case fatality rate in developing countries reaches 30%, particularly among young infants.[2] Even in many developed countries, epidemics are frequently resurgent.[3-6]

The clinical diagnosis of measles almost invariably depends on recognition of the typical pattern of presentation.[7] The clinical spectrum can be classified into typical, atypical or modified measles syndrome. The majority of cases are typical measles that follows a classical pattern of clinical manifestations due to natural infection in immunocompetent hosts. Atypical measles has been described in several case series in 1960s for individuals who received inactivated measles vaccine and were subsequently infected with wild-type measles. They developed a more prolonged and severe disease, presumably due to hypersensitivity reaction.[8] Recent discussions have focused on vaccine-modified measles syndrome, a condition which is usually mild, benign and associated with a very low complication rate, which may be due to pre-existing yet incompletely protective anti-measles antibody resulting from previous vaccination.[9, 10]

We identified a group of young infants without prior measles vaccination who presented with modified measles which ran a more benign clinical course. These infants were presumably still partially protected by passively acquired maternal antibody at the time of presentation.[11] We postulate that the presence of partially protective maternal anti-measles antibody (anti-measles IgG) in neonates and young infants to be associated with the modified clinical features of natural infection. Literature review in this area yielded only one single report substantiating our hypothesis. During a measles outbreak in Shenzhen, amongst 29 infants aged 3 months to 7 months who contracted measles, 25 of them developed a milder form of illness.[12] However, this report was only written in Chinese with an English abstract. Since there is scarce information in the literature addressing this issue, we decided to conduct a study to investigate whether measles in young infants has a different clinical presentation.

Method

We conducted a retrospective study of all patients less than 1 year of age who were hospitalised at Princess Margaret Hospital of Hong Kong over a 10-year period from January 1999 to December 2008 with the discharge diagnosis of measles. There were no major outbreaks of measles in our locality during the study period. Our hospital is the only designated tertiary referral centre for isolation and treatment of paediatric infectious diseases in Hong Kong. As maternally derived measles antibodies persist in infants for up to 6-9 months after birth and Szenborn et al reported in 2003 that more than two-thirds of infants do not have sufficient levels of such antibodies for disease protection by 7 months, we divided our patients into two groups for comparison: young infants <7 months of age and older infants aged 7-12 months.[13-17] We did not include patients aged above 12 months because most of them had already received measles vaccine according to the universal childhood immunisation program in our locality. Infants who had received measles vaccination before reaching their first birthdays were excluded. Preterm infants born before 37 weeks of gestation were also excluded due to probable deficiency of maternally derived measles antibodies.[18,19]

Infants with measles confirmed by positive anti-measles IgM antibody, four-fold or more rise in anti-measles IgG antibody titre, or virus isolation from cell culture were included. Hospital records of all laboratory confirmed measles cases were reviewed for vaccination status; clinical manifestations including onset of skin rash in relation to fever, duration of fever, presence of cough, coryza, conjunctivitis, Koplik's spots, staining of convalescent rash and other associated clinical features such as diarrhoea, complications during hospitalisation (e.g. pneumonia), and the use of antibiotics. Statistical analysis was performed using unpaired student t-test and Pearson correlation for parametric values and Chi square test (Fisher's exact test for values <5) for non-parametric values. SPSS version 17.0 was used for statistical analysis.

Results

During the study period, 185 hospitalised infants less than 12 months of age with the discharge diagnosis of measles were identified. Thirteen patients were excluded from the study because laboratory confirmation of the diagnosis was not available. Seven other patients were excluded: 2 had already received MMR vaccine at 9 months of age in Mainland China, 2 had incomplete documentation of clinical features, and 3 were born prematurely at 32-36 weeks of gestation. The decision algorithm for the inclusion of study population is shown in Figure 1.

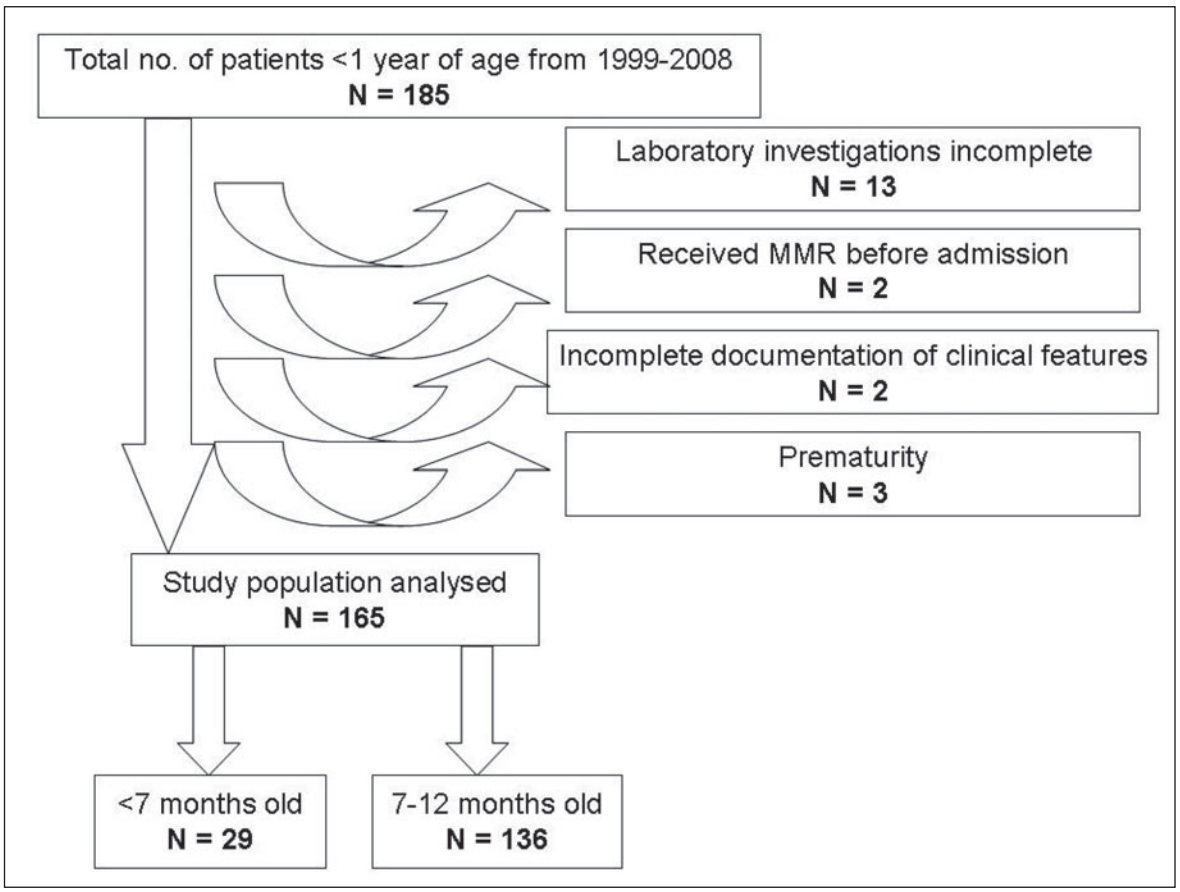

Figure 1 Algorithm for inclusion of study population.

Of the 165 infants analyzed, 29 patients were <7 months old and 136 patients were aged 7-12 months. The mean age of patients at presentation was 5.2 months for the younger age group and 9.8 months for the older group. The youngest patient was a 2-month-old infant. Except 6 Indian and 2 Pakistani infants, most patients were Chinese. Interestingly, infants in the older age group were more likely to be taken care of in mainland China at the time of presentation (p=0.001) (Table 1).

Concerning the method of laboratory diagnosis in the younger age group, 28 infants were positive for anti-measles IgM and one was confirmed by viral culture of throat swab. In the older age group, 129 infants were positive for anti-measles IgM, 4 had a four-fold or more rise in anti-measles IgG titres, and 2 were confirmed by viral culture of throat swab (Table 1).

The mean duration of fever in the younger age group was 4.6 days, which is significantly shorter as compared to 6.8 days for the older infants (p<0.001, 95% CI 1.24-3.04). The age of patient correlated with the duration of fever

Table 1 Demographic data for the 2 groups of study population

	<7 months old (n=29)	**7-12 months old (n=136)**
Age (months)	5.2	9.8
Mean	6.0	10
Median	1.2	1.6
SD	2-6	7-12
Range		
Ethnicity (no.)		
Chinese	27	130
Pakistani	0	2
Indian	2	4
Lives in China (no.)	3 (10%)	58 (43%)*
Method of diagnosis (no.)		
Anti-measles IgM	28	129
Anti-measles IgG (↑ ≥4-fold)	0	4
Viral culture	1	2

* p=0.001

(r=0.307, p<0.001). An earlier onset of skin rash was observed in the younger infants at a mean of 2.3 days from onset of fever compared to 3.7 days for the older infants (p=0.001, 95% CI 0.58-2.12). The age of patient again correlated with the timing of skin rash from the onset of fever (r=0.255, p=0.001) (Table 2).

There were significantly less patients in the younger age group developing conjunctivitis (p=0.001) and staining of the convalescent rash (p=0.026). Less coryzal symptoms were also observed in younger infants although it is not statistically significant (p=0.07). There were no significant differences between the two age groups with respect to the presence of cough (p=0.28), Koplik's spots (p=0.18), diarrhoea (p=0.72), pneumonia (p=0.74), and the use of antibiotics (p=0.74) (Table 2).

Discussion

This is the first study of such scale to specifically examine the clinical features of measles in non-immunised infants less than one year of age. It revealed several modified manifestations of natural measles in young infants. Shorter duration of fever and earlier onset of skin rash were noted during the course of their illness. The exact mechanism for the earlier onset of skin rash in younger infants is not clear, but the presence of incomplete immunity derived from partially protective maternally derived measles antibodies (anti-measles IgG) might be a modifying factor. Conjunctivitis and staining of convalescent rash were also significantly less common when compared with older infants.

Universal measles immunisation programme was introduced in Hong Kong since 1967. The coverage rate was excellent with marked increase from 85% in 1980s to 99% in 1996.[20] Considering that the vaccine efficacy was estimated to be 95%, majority of the mothers of our study population was probably immune or likely to be at least partially immune to measles infection with natural decline of antibody levels with age.

Maternally derived measles antibody is known to persist in infants for up to 6-9 months.[13-17] The antibody

Table 2 Summary of clinical parameters analysed for the study population

Clinical parameters	Age <7 months (n=29)	Age 7-12 months (n=136)	95% CI	p-value
Duration of fever (days)				
Mean	**4.6**	**6.8**	**1.24-3.04**	**<0.001**
Median	4	7		
SD	2.3	2.1		
Minimum	2	0		
Maximum	9	14		
Onset of rash (days from onset of fever)				
Mean	**2.3**	**3.7**	**0.58-2.12**	**0.001**
Median	2	4		
SD	2.6	1.7		
Minimum	- 4	- 2		
Maximum	9	13		
Cough	27 (93.1%)	132 (97%)		0.28*
Coryza	28 (97%)	134 (99%)		0.07
Conjunctivitis	8 (28%)	88 (65%)		**0.001**
Koplik's spots	18 (62%)	106 (78%)		0.18
Staining of convalescent rash	20 (69%)	117 (86%)		**0.026**
Diarrhoea	1 (3%)	1 (1%)		0.72*
Pneumonia as complication	2 (7%)	14 (10%)		0.74*
Antibiotic usage	9 (31%)	38 (28%)		0.74*

* Fisher's exact test

- no. of days of skin rash before onset of fever

level and hence the protective immunity against measles declines with age. Since partial immunity has been known to modify the clinical features of natural measles in immunocompetent patients with prior measles vaccination and immunocompromised patients who received post-exposure immunoprophylaxis with anti-measles immunoglobulin, we believe that similar mechanism contributes to the modified and milder clinical manifestations of measles in non-vaccinated young infants whose mothers are most likely immune or partially immune to measles due to prior vaccination or natural infection during their childhood.

The association of more older infants being taken care of in Mainland China may be due to the fact that more infants went back to China for care after they were weaned from breastfeeding and had completed the primary series of childhood immunisation (first 6 months after birth) in Hong Kong, by which time they were also more suitable for long distance travel.

There is a statutory requirement for all doctors in Hong Kong to report suspected or confirmed cases of measles to the Centre for Health Protection, Department of Health for further epidemiological investigation. Our hospital is the only tertiary referral centre for communicable diseases in Hong Kong. Most patients who are suspected to have measles requiring hospitalisation are transferred to our centre for airborne isolation and further management. Hence, our patient population should be quite representative of patients with measles requiring hospital admission in our locality.

We only included patients with laboratory confirmed measles because clinical diagnosis of measles may not be accurate. Although the sensitivity of well-accepted clinical case definition for measles is reasonably high (76-88%), it is less sensitive in vaccine-modified disease or following post-exposure immunoprophylaxis. Moreover, the specificity and the positive predictive value are poor due to the low incidence of measles in non-outbreak situations.[7]

Since our study was retrospective, there may be ascertainment bias and selection bias in data collection. Those prominent clinical features such as fever, cough, coryza, conjunctivitis and staining of rash etc. could be reliably retrieved, but subtle signs (e.g. Koplik's spots) might be missed or not documented. Ideally, the clinical features should be routinely solicited and prospectively documented on a standardised chart by one experienced paediatrician or a small group of well-trained investigators to improve the data quality. Some data concerning the duration of fever, skin rash and staining were not fully documented as the patients were already discharged before the resolution of characteristic clinical features. The pre-morbid levels of anti-measles IgG in our patients and their mothers were not available to document prior immunity.

Our study has the drawback of possibly missing patients who presented with very mild clinical features whom might be treated in an outpatient setting or the diagnosis of which could have been missed by primary care providers. However, we did show that measles in hospitalised young infants tend to have milder clinical features and the presentation and clinical course may not be typical. The actual difference may be even more obvious if younger patients who escaped clinical detection were able to be included. We should maintain a high index of suspicion for measles in young infants presenting with fever and skin rash, and the appearance of skin rash being not on or around the expected fourth day of fever.

Reporting to local health authority immediately for any suspected case of measles is imperative to facilitate appropriate public health measures. Early use of rapid test (e.g. anti-measles IgM) to confirm the diagnosis of measles should be considered particularly in hospitalised young infants to facilitate proper management, including the institution of prompt appropriate infection control measures to interrupt transmission and prevent potential nosocomial outbreaks. As anti-measles IgM may be falsely negative especially in the first 5 days from the onset of symptoms, the test should be repeated if there is clinical suspicion.[21] Infection control measures must not be delayed pending laboratory confirmation.

Further prospective study with measurement of transplacentally acquired antibody levels against measles in the study population might be considered to confirm our impression of modified measles manifestations in young infants with presumed maternally derived partial immunity against measles. However, to investigate the relationship between modified clinical features of measles in young infants and maternally derived anti-measles antibodies will require measurement of the level of protective anti-measles IgG levels in pregnant women before delivery to confirm partial immunity, and correlation with the anti-measles IgG levels subsequently measured in their infants after delivery at defined time points to document pre-existing partial immunity, before they were exposed to measles infection and immunised with measles vaccine. The feasibility of conducting such a cohort study is questionable given the relatively low incidence of measles during inter-epidemic periods and the logistical difficulties likely to be encountered.

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