

What are the most useful clinical symptoms or signs for diagnosing measles in children with HIV?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What are the most useful clinical symptoms or signs for diagnosing measles in children with HIV?*

The **WHO Pocketbook of Hospital Care for Children** states:

Diagnose measles if

~ the mother clearly reports that the child has had a typical measles rash

or

~ if the child has: fever, a generalized maculopapular rash, and one of the following - cough, runny nose, or red eyes.

In children with HIV infection, these signs may not be present and the diagnosis of measles may be difficult.

(Pocketbook chapter 6.6.4, page 154).

Introduction:

It has long been realised that measles occurring in immunosuppressed hosts, can present without the characteristic signs and with uncommon manifestations and complications.¹ In HIV-

infected patients, measles is also typically more severe with increased complications and a higher case fatality rate.²

As the incidence of measles falls worldwide,³ the positive predictive value of the clinical case definition has also fallen⁴ leading to many low incidence countries requiring serological confirmation of suspected measles cases.^{5 6} However the limited resources and high caseload of the developing world can mean this is impossible and a reliable case definition is crucial. This is especially true in regions of high HIV prevalence where variable immune response and the questionable efficacy of vaccination in HIV patients means measles elimination has proved difficult.^{7 8 9} It is in these patients that atypical manifestations of measles, especially those without a rash, may go unrecognised, and in the absence of serological testing, a reliable clinical case definition is needed.

Methodology

The following search strategy was used in Medline, Embase, Global Health, CAB, Web of Science, CENTRAL, Indmed, BIOSIS and Pascal and the WHO databases, limited to "English" and "Human":

Measles AND (HIV OR AIDS OR Human Immunodeficiency Virus or Acquired Immunodeficiency Syndrome) AND (rash OR exanthema OR fever OR febrile OR afebrile OR temperature OR koplik spots OR koplick spots OR coryza OR runny nose OR cold OR conjunctivitis OR red eye* OR cough)

All cases had to be serologically, or epidemiologically confirmed (within one incubation period of confirmed contact with a serologically confirmed case)¹⁰ and in children

under 18 years old. Studies immediately after vaccination were excluded. All studies were cross-checked for duplication and cited references were checked. Case reports (8 found) were excluded and only 6 studies were found (Table 1). Only one of these (Moss et al; 2002) directly compared HIV-infected and uninfected measles cases. Only the cases of confirmed measles from this study were included

Results

1. Single study comparing measles between HIV-infected and uninfected children:

Twenty-nine percent of the HIV-infected children did not have a morbilliform rash; 31% had a desquamating rash but these categories were not mutually exclusive. Children with stunting were more likely to have a desquamating than morbilliform rash. The timing of the appearance and clearance of the rash was not commented on. One HIV-infected and two HIV-uninfected children with confirmed measles had no rash.

No significant differences were detected in the frequency of temperature $>38^{\circ}\text{C}$, rash, conjunctivitis, stomatitis, stridor, pneumonia, watery diarrhoea and death in hospital between HIV-infected and uninfected children. Thrush, wasting and stunting were significantly more common in HIV-infected children.

Among all children with CD4+ lymphocyte percentages $\leq 25\%$, HIV-infected children were less likely to have conjunctivitis or watery diarrhoea on physical examination although this was not statistically significant.

When all children with clinically diagnosed measles were included in the analysis, HIV-infected children had a higher fatality rate than did HIV-uninfected children.

2. Studies of measles in HIV-infected children only:

Five additional studies reported the symptoms and signs of measles in HIV-infected children, but the size of these studies, and the fact that the results were not compared to HIV-uninfected children meant they could not be included in this review (Table 1). However, it is interesting to note the two HIV-infected children who

presented without a rash; neither had been vaccinated and one also did not have any of cough, coryza, conjunctivitis or fever. (Krasinski et al 1989).

Discussion

The available data concerning measles in HIV-infected children is sparse.

Overall, in the comparative study by Moss et al (2002), a smaller number of HIV-infected patients presented with each symptom than HIV-uninfected children and no HIV-uninfected children presented without a rash or fever. However, while measles in HIV-infected children clearly has the potential to present atypically, overall no significant difference in symptoms was seen between HIV-infected and HIV-uninfected children.

Many factors may influence the appearance of the rash. All three HIV-infected patients without a rash in whom vaccination status was known had not been vaccinated. In Moss et al 2002, combining HIV-infected and uninfected patients showed those with a lower CD4 count were significantly more likely to have a morbilliform rash. Also, no difference was found in the presence of morbilliform rash between HIV-infected and HIV-uninfected patients when controlling for CD4. CD4 count did not affect the appearance of rash when looking at HIV patients alone although this was based on categorisation into \leq or $> 25\%$ which may be concealing an overall trend. The effect of immunosuppression is also unclear in the literature; a recent review found no clear correlation between CD4 counts or CD4:CD8 ratios and measles severity or complication rates.¹¹

Moss et al also showed that children with stunting were more likely to have a desquamating than morbilliform rash and this is supported by early studies¹². However, this effect was not shown with wasting and other factors were not controlled for. Also, while a link between severe measles and malnutrition sounds rational, recent research has shown no association and alternative factors such as overcrowding and severity of infectious dose have been proposed,^{13 14 15} suggesting the intensity of exposure or length of contact with an infected individual may have confounded earlier analyses.

The comparative study by Moss et al is based in Zambia, an area of high measles incidence at the time of study.¹⁶ The other studies were based in areas of low measles incidence. Comparing the two regions suggests atypical symptoms may be more likely in areas of low incidence although this is again based on very limited data and separate studies. The differences may be attributable to intensity of exposure, or perhaps greater identification of cases without rash in the developed world. Also, differences between the populations such as age, gender or HIV stage may be confounding the data. Different measles genotypes may also be associated with different antibody responses, severity of disease¹⁷ and variations in symptoms.

There are also weaknesses within the studies. All the research was hospital-based so only included a limited population i.e. those ill enough to be hospitalised but not so severely ill they died before reaching hospital. However, this can also be seen as the desired population as these are the cases where clinical intervention is most needed and likely to be effective. Moss et al acknowledged that those children who were severely ill or died soon after reaching hospital were unlikely to be enrolled in their study. This latter problem is avoided in the retrospective study by Palumbo et al (1992) and the other four studies included all patients. However, in using only one or two hospitals as a base, it is not clear if the population captured is representative; this may be influenced by severity of infection, social class or other factors. Palumbo et al also rely on the completeness of hospital records. The data given for each patient was often incomplete and Moss et al compared many factors leading to a high probability of chance positive results.¹⁸

As measles can appear without the classic signs, cases may easily be missed unless actively sought. Some cases were diagnosed only at autopsy, a practice frequently not carried out and if a diagnosis of measles is not suspected, it may not be discovered. This is also exemplified by interesting recent unpublished research by Moss et al in which 3 out of 160 children diagnosed with pneumonia in a developing country with no clinical signs of measles tested serologically positive for measles IgM and with measles virus confirmed by RT-PCR. Two of these three were HIV-infected.¹⁹ Additional studies on HIV-uninfected patients have found that serologically positive cases of measles have frequently not displayed the typical symptoms.²⁰ HIV-infected

children may be more likely to receive treatment for minor symptoms, while milder cases in HIV-uninfected children, possibly without rash, may be missed. However the converse may be true that mild symptoms may be ignored in HIV-infected children in the face of concurrent high morbidity. Either will result in missed cases and distorted comparisons between HIV-infected and uninfected patients. In low incidence countries clinical experience of measles has declined, so clinicians may not consider the diagnosis or even recognise a typical case. Even when rash is present, there are other diseases which are more common and even conform to the measles case definition themselves such as Rubella, herpesvirus, enterovirus, adenovirus, Dengue fever and Kawasaki disease.^{21 22}

For this analysis, cases had to be serologically confirmed due to the low positive predictive value (PPV) of clinical case definitions. However, as well as limiting the data which could be used, particularly in the developing world, the immunosuppressive effects of HIV may cause true measles cases to test seronegative. This may have influenced data in Moss et al when comparing confirmed cases from HIV and HIV-uninfected children. Concerns have also been raised of the reliability of serological tests with the PPV of any laboratory test also decreasing alongside incidence, increasing the number of false positive results.²³ The studies also used different methods of serological confirmation performed in different laboratories, leading to potential differences in accuracy and reliability of results.

Summary

The data currently available is not sufficient to draw conclusions regarding which clinical signs are most useful for diagnosing measles in HIV-infected children. However, as the proportion of those vaccinated increases and the declining incidence means a lower infective dose, it is likely there are increasing numbers of mild measles cases which are never identified, even in those without HIV. It would seem beneficial to raise awareness of including measles in the differential diagnosis of any child with fever or pneumonia, particularly those with HIV, with the knowledge a typical morbilliform rash and archetypal symptoms may not be present.

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Table 1: Characteristics of Included Studies of Measles in HIV-infected Children

Reference	Dates and Location	Study Type	HIV and measles patients	Evidence Level ²⁴	Study Population	Diagnostic Method	Comment
Moss WJ et al 2002 ²⁵	1998-2000 Zambia	Comparative Prospective Case Control	93	1b	All children hospitalized with a clinical diagnosis of measles in one hospital over a 33 month period. HIV-infected and HIV-uninfected, and confirmed and unconfirmed measles cases compared	Clinical diagnosis (case definition not given) followed by serological testing for virus specific IgM.	Individual case symptoms and characteristics not published. 93 HIV-infected and 453 HIV-uninfected children with confirmed measles.
Palumbo P et al 1992 ²⁶	1990-1991 USA	Retrospective	6	2b	All HIV-infected children with measles from hospital discharge and outpatient records over a two year period	Serological by measles specific IgM, epidemiological or post-mortem	Unclear how many different hospitals were included in the record search
Krasinski K et al 1989 ²⁷	2 year period USA	Cohort	4	3b	All HIV-infected children hospitalized with measles in one hospital over a two year period	Serological by 4x increase in measles haemagglutination inhibition antibody and measles specific IgM or post-mortem	One case excluded as indeterminant HIV status. One case excluded as unclear method of diagnosis
Morbidity and Mortality Weekly Report 1988 ²⁸	1986-1987 USA	Epidemiology Report	6	3b	All cases of measles in HIV-infected patients in the USA in one year as reported to the CDC.	Serological, epidemiological or post-mortem histopathological analysis	3 cases also reported by Krasinski et al. Additional information for one case found from a case report of the same patient. ²⁹
de Carvalho V et al 2003 ³⁰	1997-1998 Brazil	Prospective Cohort	5	3b	Prospective study of 40 children with HIV over 11 months	Serological (presence of IgM antibody) or epidemiological confirmation	
Kaplan LJ et al. 1992 ³¹	1989-1990 USA	Cohort	2	3b	All immunocompromised children hospitalized with a clinical diagnosis of measles within 2 hospitals	Serological confirmation for 4x rise in IgG or presence of IgM antibody	Also one case of measles in an HIV-infected adult reported.

