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Clinical and Serological Diagnosis of Measles

By

G. Nyerges, Z. Gálfi, Éva Csonka, Tamara Kubászova and E. Farkas

Third Section of Paediatrics, László Central Hospital for Infectious Diseases, Budapest, and National Institute of Public Health, Budapest

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Clinical and serological (HI test) findings in 89 children admitted with the diagnosis of measles are compared.

Subsequent to admission all the serologically verifiable cases were diagnosed correctly on the basis of the clinical symptoms. Although in 19% the exanthem was atypical, the eruptive phase had always been preceded by a typical prodromal stage lasting at least three days.

The importance of early blood sampling is emphasized. The frequency of equivocal serological results increases steeply if the first sampling is delayed.

In could neither be proved or excluded that some of the serologically unverified but clinically typical cases of measles had been caused by some other virus.

Measles is a clinically well-defined disease with little variability in its natural course. A regular incubation period is followed by a 3 to 4 day, febrile catarrhal period and a subsequent characteristic rash which differentiates measles from the other diseases displaying exanthems. The view based on epidemiological observations that measles is a disease of common viral aetiology, appeared to be proved by the virological and serological studies [1, 2, 4, 7, 8, 9, 12, 14, 15, 19, 20] that followed the first isolation of the measles virus [6].

However, in the course of systematic aetiological investigations [21, 23] cases of clinically characteristic measles were observed in which the role of the measles virus could not be verified, whereas other viral infections appeared to simulate the clinical picture of measles [3, 11, 16, 21—24].

Some authors [5, 17, 21, 23], on the other hand, have observed virologically and serologically verified measles virus infections which clinically were different from measles.

In the present work we have attempted to estimate the frequency by which a serologically verifiable measles virus infection can be recognized clinically and, further, how the aetiological diagnosis can be supported by serological testing. As serological method, the haemagglutination-inhibition (HI) test was chosen.

Materials and Methods

Eighty-nine children admitted with the diagnosis of measles were examined.

Blood was taken from each patient on the day following admission and on the

day before discharge. The HI antibodies were titrated in each serum sample according to Rosen's method [14]. If the case appeared to be atypical, the HI antibodies to German measles were determined as described by Halonen et al. [10].

During the period of study the clinician was not aware of the serological results, nor the virologist of the clinical diagnosis. If later the serological test failed to verify the clinical diagnosis, the HI test was repeated. In the meantime the serum samples were stored in the frozen state.

Results

Although all the patients had been admitted with diagnosis of measles, a careful analysis of their history, clinical symptoms, and course of illness made it possible to divide them into three groups.

1. *Typical measles.* The criteria of typical measles were as follows. *a)* A rash preceded by a three-day febrile catarrhal period. *b)* Typical maculopapulous morbilliform exanthem tending to be confluent, visible for at least four days, and extinguished with pigmentation. The rash appeared first on the head and extended towards the extremities. *c)* Simultaneously with the spread of the rash the patient had a temperature. *d)* If the patient was seen on the first or second day of the rash, conjunctivitis, pharyngitis, rhinitis and buccal enanthems were also present. In this period, Koplik's spots were often absent, but as a remnant of the enanthem, buccal hyperaemia was observable. *e)* Patients admitted because of a complication were classified as typical measles provided the morbilliform character of their exanthem was still obvious and their history consistent with measles.

Sixty-eight patients belonged to this group. The serum HI titres for these patients are plotted against the time elapsed from the onset of the rash

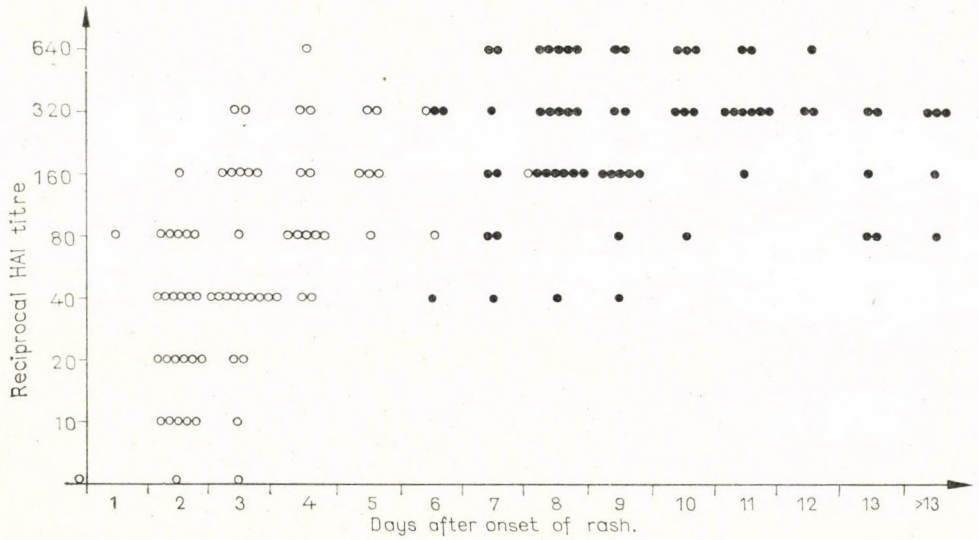

Fig. 1. HI titres in patients with clinically typical measles, as related to the day of appearance of the exanthem

in Fig. 1. Two blood samples were examined from each patient. From one child a sample from the pre-eruptive stage was also available; this proved to be seronegative. Most of the acute-phase samples were taken on the 2nd to 4th day of the eruptive stage. Of these, two proved to be negative, the HI titre for the others ranged between 1 : 10 and 1 : 640, without any characteristic peak. After the 7th day the titre ranged from 1 : 40 to 1 : 640. No patient remained seronegative.

Fig. 2 shows the changes in titre for each patient. The rise was four-fold or greater in 38 patients, whereas it was non-significant or even absent in 30 patients. However, from 15 of the latter the first blood sample had been taken after the third day of the eruptive phase. If the first blood sample was taken in the first three days (47 cases) the rise in titre was demonstrated in 32 cases, whereas if it was taken later (21 cases) the respective figure was 6 cases. In general, the rise in titre expressed in dilution steps was the greater the lower the acute stage titre had been.

To the category "typical measles" belonged three siblings who had become ill on the same day. Blood was taken from the children on the 2nd and 8th days following eruption. In two of them the initial titre, 1 : 40 and 1 : 80, respectively, increased to 1 : 160, whereas the 1 : 40 titre of the third sibling remained at the same level.

In this group, two children had been immunized against measles with a vaccine prepared from the Schwarz

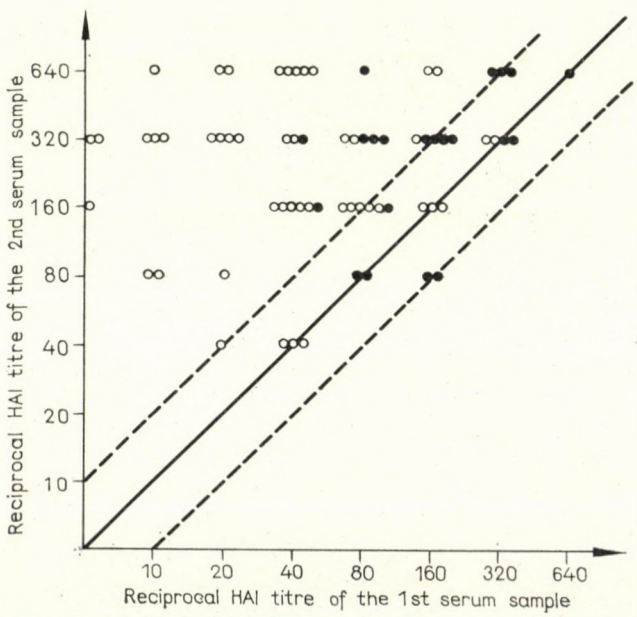

FIG. 2. HI titres in the course of clinically typical measles

strain, 7 and 9 months before the onset of illness, respectively. HI titre of the first child, which was 1 : 80 on the 4th day, was at the same level on the 18th day, whereas the titre of the second patient, 1 : 20 on the 2nd day, rose to 1 : 320 by the 11th day.

2. *Abortive measles.* The illness of the children classified into this group was preceded by more or less defined prodromal fever and catarrh, which lasted at least three days. The rash was not typical of measles in character and course; the exanthem did not tend to become confluent, and was sometimes reminiscent of German measles; pale morbilliform exanthems also occurred, but these did not extend to the whole body and disappeared in one or two days, simultaneously with the defervescence.

One of the 12 children belonging in this group had been given prophylactic gamma globulin. Nine children showed an at least four-fold rise in HI titre, in two cases the titre remained unchanged (1 : 80 and 1 : 320, respectively), and one child failed to develop antibodies.

None of the children developed HI antibodies to rubella virus.

3. *Non-measles cases.* The children classified in this group displayed a short or no prodromal phase. The catarrhal symptoms, if present, and the exanthems were not characteristic of measles, or if the exanthems were morbilliform, they were not accompanied by fever and catarrhal symptoms. Thus, in these cases measles could be excluded clinically.

Among the 9 children classified in this group, four remained seronegative, in the other cases the HI titre persisted at the same level. In two cases the rubella antibody titre increased from 1 : 20 to 1 : 320 and 1 : 640, respectively.

A comparison of the clinical and the serological findings is shown in Table I.

Discussion

The above data allow some conclusions concerning the diagnostic value of the clinical symptoms and serodiagnostics in measles.

Table I

Clinical and serological examination of 89 children admitted with the suspicion of measles

Clinical picture	Anti-measles HI titre during illness			Total
	negative	positive		
		no change	increased	
Typical measles	—	30	38	68
Abortive measles	1	2	9	12
Non-measles	4	5	—	9
Total	5	37	47	89

First of all, in the present study an unchanged anti-measles HI titre was neither proving nor excluding a measles virus infection. Nevertheless, a convalescence titre of 1 : 640 or 1 : 320 as measured by the method applied by us strongly supported the diagnosis of measles even in the absence of a significant rise in titre. In these cases (see the 13 cases in the rhombus in Fig.2) the acute-phase titres ranging from 1 : 160 to 1 : 640 could hardly be expected to increase four-fold, as convalescence titres above 1 : 640 are infrequent in healthy children except after natural measles or vaccination. Even unchanged titres at the level of 1 : 160 or lower did not exclude measles virus infection, *e.g.*, in the case of the two siblings whose clinically typical measles was proved by the simultaneous serologically verified measles of the third sibling.

Accordingly, out of the 68 "typical measles" cases 38 were verified, and 13 were strongly supported, by the HI test; in two cases the sibling verified the diagnosis indirectly, and in 15 cases serological testing supplied no appreciable information. In no case was the clinical diagnosis disproved.

Of the 12 "abortive measles" cases, 9 were verified, in two cases serological testing supplied no information, and in one case the diagnosis was disproved.

Of the 9 "non-measles" cases 4 remained seronegative and two gave a significant antibody response to the rubella virus. Therefore, in these six cases the serological result harmonized with the clinical finding. In three cases the HI test in itself failed to exclude measles.

Accordingly, the clinical diagnosis was correct in all cases but one. However, in 20 cases the serological result was equivocal and in 13 cases the positive information was not quite convincing.

The high frequency of equivocal results was due first of all to the late withdrawal of the first serum sample. Fig. 1 shows that if the first sample was taken on the 4th day or later after the onset of rash the titre was already so high that a further significant rise could hardly be expected. In a number of cases the initial titre was too high even if the first samples had been taken on the first three days of the eruptive phase. It is therefore important to take blood as early as possible. It would be most advantageous to take blood during the prodromal stage; this is, however, usually impossible when hospitalized patients are examined. In these cases attempts should be made to demonstrate IgM-type measles antibody which seems to be an appropriate indicator of acute measles [18].

Nine out of the 47 verified cases of measles were clinically abortive, *i.e.*, the eruptive phase was short and the exanthem was atypical. However, in all of these cases the prodromal phase was typical: the fever lasted at least three days and catarrhal symptoms were well-defined. Nevertheless, if such cases are first seen in the eruptive phase and thus the characteristic prodromal phase escapes attention, false negative results often

occur. On the other hand, lack of the typical prodromal phase speaks against measles. In the present material the false diagnoses were mostly due to neglecting the lack of the characteristic prodromal stage.

It is, of course, possible that some of the clinically typical but serologically unverified cases were caused by some other virus, and supposedly the relative frequency of such cases will increase as the bulk of the children population will have been vaccinated. This view is supported by the observations of Schaffner et al. [18]. Thus, from the aspect of the correct field evaluation of measles vaccination, serological verification seems to be necessary.

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Dr. G. Nyerges
Gyáli út 5—7
Budapest IX., Hungary