Altered reactivity to measles virus in previously vaccinated children

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Summary: In children vaccinated with killed measles vaccine, exposure to natural rubeola within two to four years can result in a clinical syndrome of altered measles reactivity.

During a small epidemic of measles in Edmonton, Alberta, 51 children who had received their last killed measles vaccination 27 to 45 months before, were admitted to hospital with this syndrome.

The syndrome consists of a prodromal cough and high fever followed by a maculopapular rash appearing on the extremities and progressing centrally. Pulmonary consolidations with or without pleural effusions were evident, but these cleared rapidly in four or five days. Initial WBC and ESR values suggested a bacterial etiology, but no pathogens could be isolated.

Complement fixation titres for rubeola are present in acute and convalescent sera and indicate a definite measles infection.

Previous killed measles vaccination excites a delayed hypersensitivity which is activated by the natural measles infection to account for this syndrome.

It is recommended that killed measles vaccine be no longer used in routine vaccinations.

Measles vaccination for children susceptible to measles is an accepted procedure in Canada and the United States. The initial recommended schedule of immunization suggested three doses of killed measles vaccine at monthly intervals followed by a live measles vaccine.

After five years' use of this schedule in the United States, many reports began to appear suggesting an altered reactivity in the measles vaccine recipients on exposure to natural measles infections.[1-4] The altered reactivity consisted of a symptom complex of high fever, atypical rash, penumonia and eosinophilia.

No such reports have appeared in the Canadian literature. Because the syndrome should be readily recognized, this paper presents the findings in 51 children who had been previously vaccinated by either the KKKL* or KKK† regimen and who developed the altered reactivity. A recent epidemic of measles (during the first four months of 1970) made possible a study of the efficacy of measles vaccine in the young at varying times after the last killed measles vaccination. Some of the children had also received a live measles vaccine which apparently failed to protect them.

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* Three monthly injections of killed measles vaccine followed by one of live measles vaccine.
†Three monthly injections of killed measles vaccine.

Methods and materials

The 51 children were private patients admitted to the Royal Alexandra Hospital in Edmonton, Alberta between January and April, 1970.

Owing to the short stay in hospital of most of these children, viral serology was completed in only 10 (Table I).

The children studied had previously been vaccinated according to the accepted regimen of three doses of killed measles vaccine at monthly intervals followed by one dose of live measles vaccine. All but one of the children had received a killed vaccine (Pfizer-Vax Measles-K—monkey kidney) which was discontinued early in 1968 when another strain of killed measles vaccine was substituted. The live measles vaccine used throughout was Rubeovax (Lyovac Rubeovax—chicken embryo).

During the hospitalization of these patients, hematology testing included leukocyte counts and differentials, ESR and hemoglobins. Blood and sputum were cultured for bacterial, Mycoplasma and viral pathogens. Testing for cold agglutinins and investigation of viral serology complement fixation were also attempted.

Clinical particulars

Generally, the children were admitted with high fever, an exanthem and extensive bronchopneumonia. The diagnosis of atypical measles was not considered initial-

TABLE I
Relating disease in months after last injection of killed measles vaccine and the measles titres

Case No.	*Age (years)*	*Disease (months after K.M.V.*)*	*Measles titres*	
			Acute	*Convalescent*
1	4½	42	64	>1024
2	4½	42	64	>1024
3	7½	28	256	512
4	4½	45	8	1024
5	4	42	64	>1024
6	4½	44	16	>1024
7	6	44	<8	256
8	4½	43	<8	512
9	6	44	64	512
10	3	27	64	256

*KMV — Killed measles vaccine.
The measles titres are expressed as the inverse of the complement-fixation dilutions.

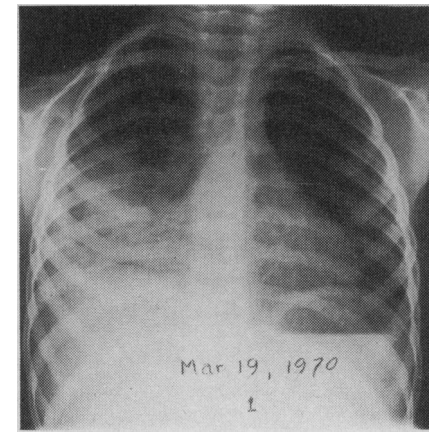

FIG. 1—Posteroanterior projection. Extensive interstitial consolidation in the right lower lobe associated with a large pleural effusion.

ly owing to the variety of presenting signs and symptoms (Table II).

Prodromata

Most of the children had a history of exposure to natural measles seven to 14 days prior to onset of their disease. The illness began with cough, coryza and high temperatures often rising to 104° to 105°F. In two cases the temperature was recorded as 107°F. Cervical lymphadenopathy was minimal and Koplik spots were not apparent.

Exanthem

Within 48 to 72 hours of the prodromal fever, a rash usually became evident on the hands and feet. This was light pink, fine, discrete and morbilliform, rapidly spreading centrally to the trunk to become more erythematous and confluent. In some cases the rash was vesicular and in many it became itchy. Often the rash became confluent over large areas of the thighs and trunk. In a few cases it was purpuric.

Pulmonary involvement

The respiratory complaint of the majority of cases was a dry nonproductive cough. Fine rales could often be heard in various lung fields, and elsewhere clinical signs of consolidation and pleural effusion were found. The latter cleared rapidly, both radiologically and clinically, so that day-to-day examination revealed pronounced changes. In one case, intrapulmonary shunting was present with oxygen desaturation, but radiologically only patchy consolidation was noted.

Radiological findings

When cases of pulmonary involvement as a manifestation of the altered measles imune response began to appear in our hospital early in 1970 it was immediately recognized that this was a different radiologic entity from the usual bacterial bronchopneumonia. The cases bore such a resemblance to each other that they were recognizable from the admission chest radiographs.

All cases showed extensive confluent interstitial consolidation, usually bilateral, frequently lobar but consistently non-segmental. In 10 cases the pneumonic consolidation was associated with significant pleural effusion. The most striking feature was the rapidity with which the consolidation resolved and the effusions were reabsorbed. No bacterial bronchopneumonia could resolve so rapidly and the homogeneous interstitial appearance was not consistent with a simple bronchopneumonia.

The pulmonary manifestations in these children were produced by an interstitial pulmonary edema, and in many cases dilated pulmonary interlobular lymphatics could be identified during resolution. The appearance most closely resembled that of Loeffler's syndrome or the pulmonary edema produced by aspiration of irritants such as chlorine gas.

Representative radiographs of four cases are presented in Figs. 1 to 10.

Laboratory investigation

Initial hematology studies revealed a leukocyte count in excess of 13,000 per c.mm. with a polymor-

TABLE II
Diagnostic criteria of altered measles reaction

A. HISTORY
1. Prior measles vaccination with killed measles vaccine
2. Contact with natural measles within 7 to 14 days prior to symptoms

B. PHYSICAL FINDINGS
1. Prodromal symptoms of cough and coryza
2. High temperature to 104° - 105°F.
3. Maculopapular erythematous rash beginning on hands and feet
4. Clinical signs of pulmonary consolidation and bronchopneumonia
5. Rapid clearing of symptoms in four to five days

C. RADIOLOGICAL
1. Pulmonary consolidation involving entire lobes with or without pleural effusions
2. Rapid clearing of pulmonary complications with other symptoms

D. LABORATORY
1. Initial high WBC counts and high ESR values
2. Subsequent low WBC counts with marked eosinophilia of 10 to 30%
3. Negative cultures of blood and sputum for bacterial, Mycoplasma and viral agents
4. Rising titres of measles virus indicating a recent measles virus infection

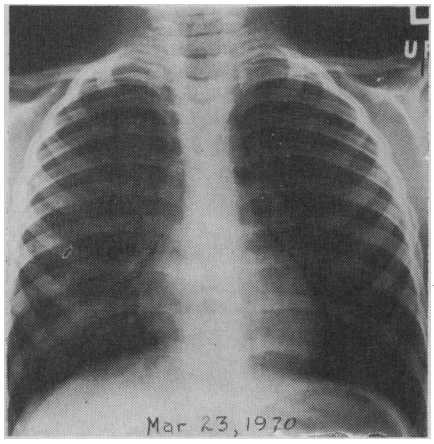

FIG. 2—(Same case as Fig. 1.) Projection four days later. The effusion has been reabsorbed; a little interstitial consolidation remains in the right lower lobe, but dramatic improvement has occurred.

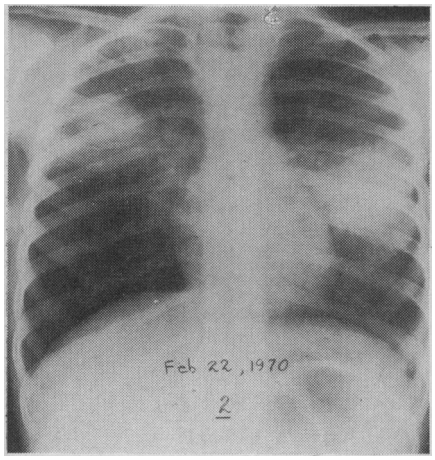

FIG. 3—Posteroanterior projection. Confluent interstitial consolidation is present in the left mid-lung and in the right upper lobe, neither of which conforms to a segmental distribution.

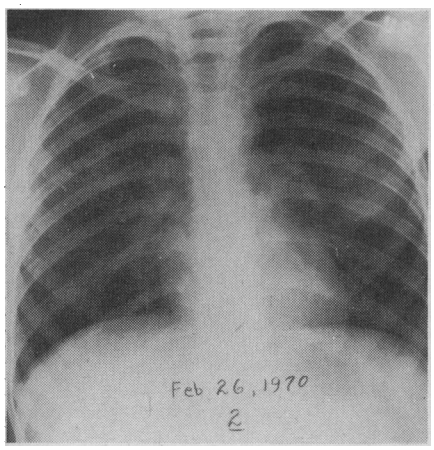

FIG. 4—(Same case as Fig. 3.) Projection four days later. Almost complete resolution has occurred.

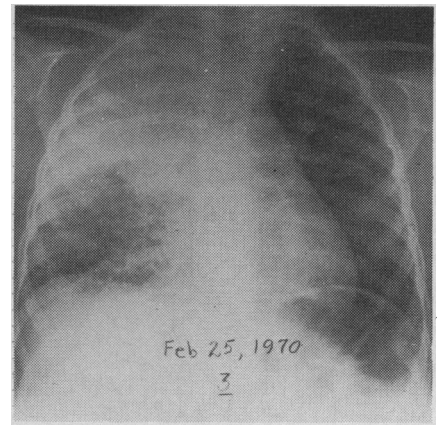

FIG. 5—Posteroanterior projection. Extensive interstitial consolidation is present, most confluent in the upper lobe but involving the entire right lung. No significant effusion.

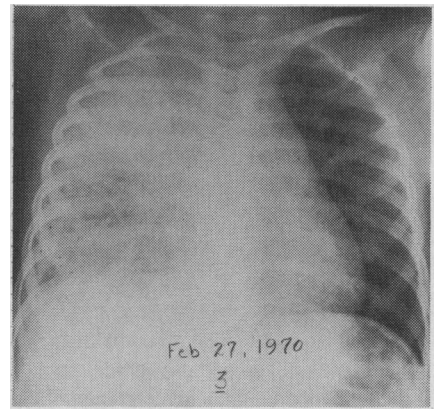

FIG. 6—Projection two days later (see Fig. 5). There is now a very large right pleural effusion. The consolidation in the lung is little changed.

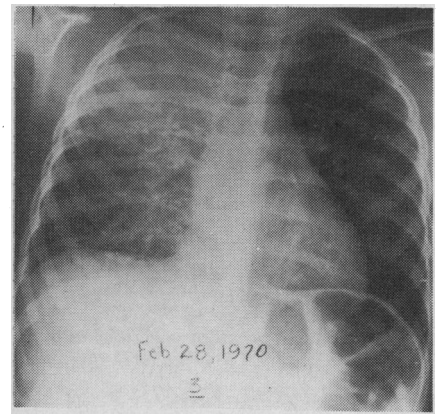

FIG. 7—Projection one day later (same case). Almost complete clearing of both effusion and consolidation.

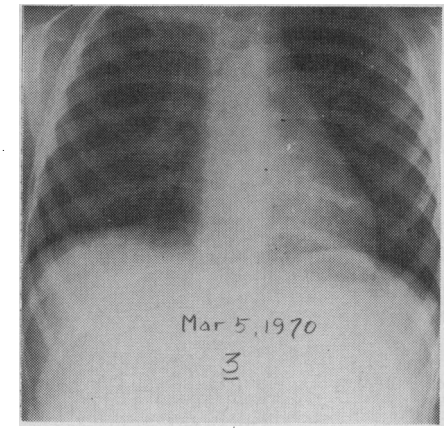

FIG. 8—Projection one week later (same case). Almost complete clearing of both effusion and consolidation.

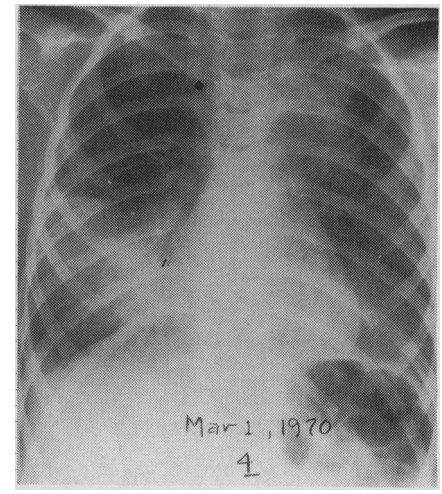

FIG. 9—Case 4. Posteroanterior projection. Confluent interstitial lobar consolidation in the right middle lobe. Nonsegmental consolidation in the left upper and lower lobes. Small bilateral effusions.

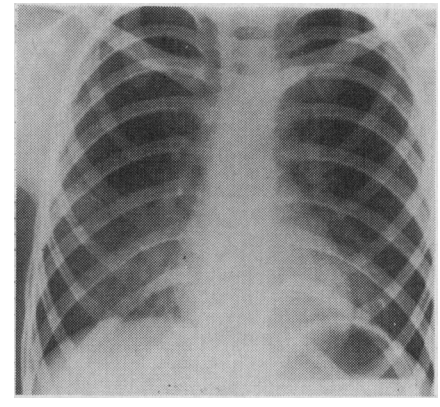

FIG. 10—(Same case as Fig. 9.) Projection four days later. Marked but not quite complete resolution of the pulmonary consolidations.

phonuclear response greater than 70%. ESR values varied from normal to greater than 50 mm. after one hour. By the fourth or fifth day the leukocyte count was normal with a lymphocytosis and eosinophilia of 10 to 30% and normal ESR values.

Although initial blood counts suggested a bacterial infection, as did the elevated ESR values, cultures of blood and sputum were repeatedly negative. Cold agglutinins and viral isolation studies were also negative for pathogens.

Serology on collected specimens is not routinely done for rubeola, and it was only after a considerable number of similar cases had been admitted that the measles titres were documented.

In the cases presented in Table I, complement fixation tests were performed on acute and two-week

convalescent sera. The interval in months since the last killed measles vaccine injection is tabulated, the shortest time being 27 months and the longest being 45 months. The rise in the measles titres in the interval between the two tests indicates a recent rubeola injection.

Discussion

Beginning in 1960-61 some vaccination programs in the United States recommended three doses of killed measles vaccine at monthly intervals beginning at 6 months of age. Following many reports which suggested an altered reactivity to measles virus infection in previously vaccinated children[1-4] the Academy of Paediatrics issued a newsletter in November 1967 urging discontinuation of the use of killed measles vaccine.

To date, various provinces in Canada still use the KKKL regimen of measles vaccination although the original Pfizer-Vax alum-precipitated killed vaccine has been replaced with a newer type of vaccine using no metal as a precipitant.

Many papers have proposed explanations of the altered reactivity to the measles virus infection.[5, 6] The most probable explanation is that killed measles vaccine imparts a short-lived immunity to the recipient 2 years of age or younger and in addition excites a delayed hypersensitivity response (Fig. 11).[5, 6] When the recipient contracts natural measles infection at a time when his immunity is low, the result is the delayed hypersensitivity reaction which has been termed atypical measles and which produces high fever, rash, pulmonary consolidation and eosinophilia. The diagnostic criteria of the altered reactivity are set forth in Table II; these were assembled following the study of the 51 cases presented in this paper.

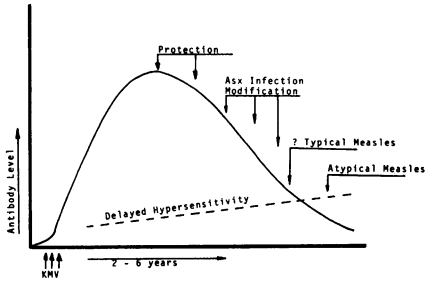

FIG. 11—Schematic representation of the possible responses of recipients of killed measles virus upon natural exposure. A full range of responses, from total protection to typical and atypical measles illness, is related to the decline in serum antibody and the persistence of delayed hypersensitivity. (Reproduced with permission, from Fulginiti, V. A. and Arthur, J. H.: *J. Pediat.*, **75**: 609, 1969.)

Fulginiti *et al.*[3] published 10 cases with the above symptoms, but noted peripheral edema. The cases we present are very similar except that no peripheral edema was evident and the majority of children had live measles vaccine in addition to the killed measles vaccine. The patients of Fulginiti and those described in this paper were vaccinated by an alum-precipitated formaldehyde-killed measles virus. Alum has since been shown to greatly enhance delayed hypersensitivity reactions to many antigens. Since January 1968, the killed measles vaccine used in the Province of Alberta has not been precipitated with alum. If the above hypothesis is correct, the incidence of atypical measles may lessen with the use of this vaccine but the disease will not disappear.

The purpose of this paper is to point out the possibility of an altered measles reaction to measles virus occurring in children receiving killed measles vaccine, and to urge that the use of this vaccine be discontinued. The protection provided by live measles vaccine is reduced by previous use of killed vaccine. In order to protect children from measles infection and from the altered reactivity syndrome in those who have had live measles vaccine, further live measles vaccination is recommended. It is expected that more cases of the altered reactivity syndrome will be seen in the next few years as more natural measles is encountered by the previously vaccinated population.

Résumé

Réactivité modifiée de la rougeole chez des enfants antérieurement vaccinés

Chez des enfants antérieurement vaccinés avec un vaccin anti-rougeoleux à virus tué, un contact avec la rubéole naturelle dans un délai de deux à quatre ans peut se traduire par un syndrome clinique de réactivité modifiée de la rougeole.

C'est ainsi que, durant une petite épidémie de rougeole survenue à Edmonton (Alberta), 51 enfants qui avaient reçu leur dernière vaccination à virus tué entre 27 et 45 mois auparavant, présentaient ce syndrome et furent hospitalisés.

Ce syndrome est annoncé par une toux et une forte fièvre, suivies d'une éruption maculopapulaire qui débute aux extrémités et qui progresse vers le centre. Des consolidations pulmonaires, accompagnées ou non d'épanchement pleural, étaient manifestes mais ont disparu rapidement, soit en quatre ou cinq jours. La formule blanche et la vitesse de sédimentation érythrocytaire permettaient de croire à une étiologie bactérienne, mais on n'a pu isoler de germes pathogènes.

Des titres de fixation du complément de la rubéole, présents dans le sérum de malades en phase aiguë et le sérum de convalescent, indiquent nettement une infection rougeoleuse.

La vaccination antirougeoleuse à virus tué stimule une hypersensibilité retardée, laquelle est activée par l'infection rougeoleuse naturelle, ce qui peut expliquer le syndrome.

On conseille de ne plus employer couramment le vaccin antirougeoleux à virus tué.

References

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