Acute Arthritis Complicating Rubella Vaccination

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After a field trial of rubella virus vaccine (HPV-77 DK 12 strain), 329 children (2.8%) developed joint symptoms. Forty had complete rheumatologic evaluation and constitute the basis of this report. Twenty children (50%) had predominantly knee complaints; 13 (33%) had symptoms suggesting the carpal tunnel syndrome; and 7 (17%) had polyarthritis. The mean duration of arthritis was 18.4 days, and the mean interval between vaccination and onset of arthritis was 30.6 days.

Rubella is considered the leading cause of congenital malformations and fetal death in the United States. Gregg's original observations (1), in 1941, relating congenital cataracts and other abnormalities to maternal rubella, have been amply confirmed. The incidence of fetal abnormalities after maternal rubella in the first trimester of pregnancy has been estimated at 7 to 70% by prospective studies (2) and as high as 100% by retrospective studies (3).

The consequences, to the fetus, of maternal rubella include spontaneous abortion and stillbirth, deafness, heart disease, cataract, glaucoma, and psychomotor retardation. In the neonatal period, a frequent, and often severe, complication is thrombocytopenic purpura. Aside from the humanitarian aspects, the cost of the total program to treat and provide special education for children damaged by the 1964 epidemic in New York alone has been estimated at 2.2 billion dollars (4). Thus, there has been great interest in the development of a program for the prevention of congenital rubella. This has become a reality with the isolation of the rubella virus in 1961 (5, 6) and the subsequent development of an attenuated strain for vaccination (7, 8).

Arthritis is a frequent complication of naturally occurring rubella, particularly in adults, but also, occasionally, in children (9–11). Rubella virus has been recovered from the synovial fluid of a 1-year-old child (12). Arthritis has been observed frequently in adults after vaccination with HPV-77, Candehill, and RA 27/3 strains (13–18). In one series of 35 adult women, 15 developed arthritis or arthralgias, and rubella virus was isolated from synovial fluid in one case (15). Arthritis has also been observed in children after vaccination (13, 19), but the incidence is much less frequent.

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After a large field trial of rubella vaccine in schoolchildren, we had the opportunity to carefully study 40 children who developed arthritis. Our observations on these children constitute the basis of this report.

MATERIALS AND METHODS

In the Spring of 1969, a large field trial of live rubella virus vaccine was conducted in Southeastern Michigan.* The vaccine used was the HPV-77 strain, additionally passaged 12 times in dog kidney cell cultures.† Previous studies had indicated that this vaccine was highly immunogenic, inducing high antibody titers (20).

A total of 11,758 school children were vaccinated. On the basis of rubella hemagglutination-inhibition (HI) antibody titers (21), 6172 children, or 52.5% were susceptible, no rubella antibody or a titer less than 1:4 had been demonstrated in serum samples obtained prior to vaccination. Similarly, 4485 children were immune; rubella antibody was present prior to vaccination. Prevaccination specimens were not obtained from 1101 children. A seroconversion rate of 99% was obtained based on the development of an HI antibody titer of 1:16 of greater.

Careful follow-up was conducted by means of a 30-day parental reporting form and a telephone reporting system which was maintained throughout the entire study. Three hundred and twenty-nine vaccinees, or 2.8%, were reported to have joint complaints. Of these 329, 80.7% were in the susceptible group, and 17.9% were immune. If classified by their prevaccination immunologic status, 251 (4.1%) of the susceptible children were reported to have experienced arthritis or arthralgias, as did 59 (1.3%) of the immune children, and 19 (1.7%) of those whose serologic status was not determined. Further, those in the immune group had much milder symptoms, experiencing arthralgias and not arthritis, with only one child judged to have mild arthritis.

Based on this follow-up system, 49 of the 329, or 0.4%, were classified as having arthritis, the remainder had arthralgias.

Subsequently 40 of the children with more severe symptoms were referred to us for complete evaluation of their joint complaints. This included a careful history and a complete physical examination, with particular attention to the musculoskeletal system. Blood was obtained for a complete blood count, Wintrobe sedimentation rate, serum protein electrophoresis, and rubella HI antibody titers. Also done were a battery of serologic studies, including the Veneral Disease Research Laboratory (VDRL) test, C-reactive protein, latex test for rheumatoid factor, a fluorescent test for antinuclear antibody using human leukocytes as substrate and antistreptolysin-O antibody titers.

Complete follow-up of these 40 children was done by telephone conversation with one of the parents by the authors approximately six weeks after initial examination. Further follow-up information was obtained by mailed questionnaire or by telephone five months later. Some of the children also had second examinations.

RESULTS

The age distribution of these children is depicted in Fig 1. The age range was from 4 to 12 years, with a median age of 7 years and mean age of 7.6 years. This is the same as the mean age of the susceptible group for the whole study population. Twenty-one were female and 19 male. There were four sets of siblings. The interval between vaccination and onset of articular symptoms ranged from 14 to 55 days, with a mean of 30.6 days. Table 1 gives the distribution of patients over this time span,

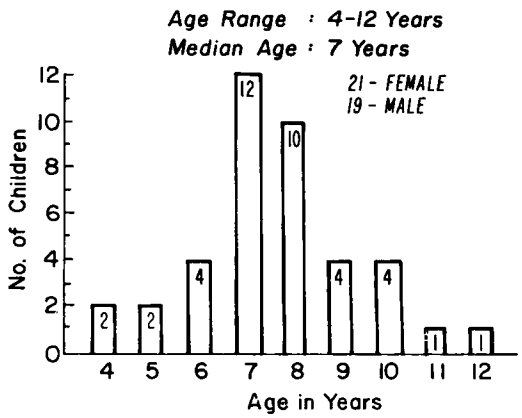

Fig 1. Age distribution of the 40 children studied.

*This study was conducted by Parke, Davis and Company.

†Produced by Phillips Roxane, Inc, St. Joseph, Missouri.

Table 1. Interval Between Vaccination and Onset of Arthritis

Interval (days)	No. of patients
14	2
15–20	5
21–25	7
26–30	8
31–35	5
36–40	6
41–45	4
46–50	1
51–55	2
Total	40

from which the mean value was obtained.

For the purposes of this study, arthritis was defined as either joint pain or stiffness on motion. Arthralgias were defined as only mild articular aching without functional impairment. By these criteria, 37 of the 40 children had arthritis and 3 had only arthralgias.

The joints involved are listed in Fig 2. The knee was the most commonly involved joint, producing symptoms in 26 children (5 of whom, however, had only arthralgias of the knee). The next most frequently involved joint was the wrist, occurring in 20 patients. The metacarpophalangeal and interphalangeal joints were involved in 7 each, the elbow in 5, ankle in 2, and hip in 2 patients. Tenosynovitis, as manifest by swelling of the dorsum of the hand, was present in 5 children. Definite joint effusion was observed in none of the 40 children examined.

The duration of symptoms in these 40 children ranged from 1 to 46 days, with mean of 18.4 days. All joint symptoms cleared without residual impairment. However, on follow-up contact, it was found that 2 patients had had monthly recurrence of knee pain, with limping and inability to fully extend the knee, typical of their early symptoms. This would last two or three days and clear, only to recur the next month. This persisted thru the fourth month after vaccination, but has not subsequently recurred. Another patient had intermittent arthralgias thru the fourth month. Three other children were reported to have recurrence of some musculoskeletal complaints, all of which were mild, and dissimilar to their earlier, acute symptoms. It is of interest that 2 of these 3 were the only children in the study who had a past history of articular complaints.

Three patterns of symptoms were observed to occur in these children. The patterns could be characterized as predominantly knee complaints, which occurred in 20 (50%) cases; symptoms suggestive of carpal tunnel syndrome occurred in 13 (33%) and polyarticular complaints occurred in 7 (17%) of the cases.

The knee symptoms usually consisted of stiffness, with pain on motion and inability to fully extend the leg because of pain in the knee. The knee was the only joint involved in 15 patients, and in 5 of these the involvement was monarticular. Three others experienced only arthralgias in addition to their knee arthritis. The remaining 2 patients had, in addition, involvement of the wrist in 1 and the elbow in the other. Of the 20 patients with knee complaints, half were male and half were female. The average duration of knee symptoms was 17.5 days. However, if one excludes 3 patients who had symptoms for 45, 43, and 35 days respectively, the mean duration of symptoms for the remaining 17 patients was only 7.4 days, with a range of 4–34 days. Knee problems also tended to be recurrent and, as noted above, the 2 patients with monthly recurrence of joint complaints both had knee symptoms. An example of this symptom complex is illustrated in the following case:

*Knee	-	26 (5 arthralgias only)
*Wrist	-	20
*MCP	-	7
*PIP/TIP	-	7
*Elbow	-	5
*Ankle	-	2 (1 arthralgias only)
*Hip	-	2 (1 arthralgias only)
"Tenosynovitis"	-	5

Fig 2. Joints involved in the 40 children studied.

SC, an 8-year-old boy, received his rubella vaccine on April 18, 1969. Approximately one week later he developed coryza with intermittent low grade fever. These symptoms persisted for three weeks. For two days on May 28 and 29, 1969, his mother noticed an erythematous macular skin eruption on his chest, abdomen and back. On June 9, 1969, 52 days post vaccination, he awoke with pain and stiffness in his right knee. No swelling, redness, or warmth was noted, and after he was up and about, it improved markedly. However, these symptoms gradually became worse, with stiffness lasting into the day; by June 15 he was unable to straighten the right knee and required crutches for ambulation. His parents felt there was minimal swelling and increased warmth in the knee. He had no other joint symptoms.

He was seen at Wayne County General Hospital on June 18, 1969. At that time, the examination was all normal exept for the right knee, which appeared slightly swollen, measured ¼ inch larger in circumference than the left, and was warm and tender to palpation. No definite effusion was present. Motion of the knee was painful and lacked 20° of full extension.

Laboratory studies revealed a hemoglobin concentration of 14.0 g/100 ml, a white blood cell count of 7200/cu mm and a Wintrobe sedimentation rate of 6 mm/hr. Serologic studies were all negative. Antistreptolysin-O titer was 12 Todd units. Serum protein electrophoresis showed 6.7 g/100 ml total protein with 4.29 g albumin (64%), 0.34 g α_1 globulin (5%), 0.60 g α_2 (9%), 0.71 β (11%); and 0.75 g γ globulin (11%). The rubella HI antibody titer, which was negative before vaccination, was 1:256 at the time of examination.

The patient was treated with aspirin and local heat to the knee and his symptoms gradually cleared completely 21 days after onset. He has had no recurrence.

The most annoying group of symptoms were those simulating the carpal tunnel syndrome. Characteristically, the child would awaken at night with pain, numbness, and tingling sensations in the wrist and hand, often traveling up the forearm to the elbow. This would usually keep the child awake and crying most of the night. The symptoms cleared with activity during the day, only to recur at night waking the child from sleep. These symptoms occurred in 13 (33%) of the 40 children and included 7 boys and 6 girls. The average duration of symptoms was 18.6 days with a range of 3–44 days. If one excludes the patient whose symptoms lasted 44 days and were less marked than those in others, the average duration for the remaining 12 was 16.5 days, with a range of 3–25 days. Nerve conduction studies were done on 2 of these patients at the time of their examination, and both were normal. The following case report illustrates this problem:

RG an 8-year-old boy, received his rubella vaccination on May 1, 1969. He was well until 26 days post vaccination, when he awoke with pain in the left knee. The pain cleared by the time he had finished breakfast, and he had no further difficulty until June 1, 1969, when he developed pain and aching in the right wrist, metacarpophalangeal and proximal interphalangeal joints of the right hand associated with a tingling sensation, as if his hand were "asleep". The paresthesias often extended up his arm toward the elbow. Characteristically, the symptoms would occur at night, awaken him from sleep and keep him awake most of the night. On one occasion he was taken to a hospital emergency unit at 4:00 AM for help. However, in the morning his symptoms would clear and he did not miss school.

He was seen at Wayne County General Hospital on June 12, 1969. Examination disclosed a healthy appearing boy. Physical findings were within nor-

mal limits, except for a questionably positive Tinel's sign on the right and some tenderness to palpation of the left third metacarpophalangeal joint, and the right hip.

Laboratory studies showed a hematocrit of 38%, a white blood cell count of 8200 cells/cu mm and a sedimentation rate (Wintrobe) of 5 mm/hr. Routine serologic studies were negative. Antistreptolysin-O titer was 166 Todd units. Serum protein electrophoresis showed a total protein of 6.1 g/100 ml, with 3.87 g albumin (59.5%), 0.39 g α_1 globulin (5.9%) 0.62 g α_2 (9.5%), 0.73 g β (11.3%), and 0.89 g γ-globulin (13.7%). Nerve conduction velocities were measured in both the right and left upper extremities and were all within normal limits. Rubella HI antibody titer was negative before vaccination and 1:128 at the time of examination at Wayne County General Hospital.

He was started on aspirin therapy on June 11; and symptoms gradually improved, completely clearing within 21 days after onset. He has had no recurrence.

The symptom-complex least commonly seen could be classified as polyarthritis. This occurred in 7 (17%) of cases. Five were females and 2 males. The duration of these symptoms ranged from one to 46 days, with a mean of 20.4 days. Both large and small joints were involved, and morning stiffness was a frequent complaint. A typical case is described below:

KM, a 10-year-old girl, received her rubella vaccination on May 6, 1969. On May 19, 1969 she developed a sore throat and burning of the eyes, but no fever or other symptoms. Two days later, she noticed an erythematous macular skin eruption on her upper thighs, which lasted until May 26. On May 25, for one day only, she had a generalized eruption over her entire body which was described as "hives". She was then asymptomatic until 23 days post vaccination, when she developed aching in her joints. By June 2 this became worse with definite pain, tenderness and stiffness involving the knees, wrists, and subsequently the hands. Morning stiffness of one hour's duration was present, but no night pain.

She was seen at Wayne County General Hospital on June 10, 1969. The complete examination was normal except for the joints. There was tenderness and swelling of the right wrist, and possibly some effusion. The left wrist was normal. The left third metacarpophalangeal joint was tender and swollen as were the left first, third and fourth proximal interphalangeal joints. The grip on the left was weak. Tenosynovitis of the extensor tendon sheaths was thought present on the dorsum of the right wrist. Both knees were tender and painful to move, but not swollen, and could be taken through a full range of motion.

Laboratory studies showed a hemoglobin of 13.2 g/100 ml; a white blood cell count of 8100, and a sedimentation rate (Wintrobe) of 12 mm/hr. Serologic studies were negative. Anti-streptolysin-O titer was 100 Todd units. Total serum proteins were 7.12 g/100 ml, with 4.29 g albumin (60%); 0.40 g α_1 globulin (5.7%); 0.44 g α_2 (6.2%); 0.99 g β (13.9%); and 0.99 g γ-globulin (13.9%). At the time of examination her rubella HI titer was 1:32 (it was negative before vaccination).

She was treated with aspirin and heat to the involved joints, and her symptoms gradually cleared, completely 19 days after onset. She has not had recurrence.

In these 40 children, a history of coryza was elicited in 10, occurring some time between vaccination and the time of examination. Similarly 9 children had experienced cough, and 8 a minor sore throat. Whether these symptoms were related to the rubella vaccination or to an intercurrent infection was impossible to ascertain. Eight children similarly were reported to have had a skin rash, though only one patient had a rash at the time of examination. No correlation between the reported rash and arthritis was observed. Fever was described in 5 of the children, but no temperature over 100.5° F, was observed at the time of the examination. Lymphadenopathy was reported in 4 children at some time between vaccination and examination. Similar data from the entire group of susceptable children vaccinated, computed from returned questionnaires, indicated fever in 11.5%; rash in 6%; and cervical lymphadenopathy in 5.6%. However, rubella immune children were also reported to have fever in 8.7%; rash in

3.3% and lymphadenopathy in 4%. In weighing these differences it must be taken into account that the immune were slightly older than the susceptibles.

All of the 40 patients studied had negative rubella HI antibody titers prior to vaccination (ie, were susceptible), and all developed significant antibody titers following vaccination. At the time of examination, the mean HI titer was 1:151.7, and the median titer was 1:128. The range of antibody titers was 1:32 to 1:512. Antibody titers in these patients when obtained at the routine bleeding 4-6 weeks post vaccination were similar. This represents a very good antibody response and is not significantly different from that obtained for the total study population.

Generally, the laboratory studies done were unremarkable. None of the patients were anemic, and white blood cell counts ranged from 5150–11,600 cells–cu mm, with only 5 over 10,000 cells/cu mm. The battery of serologic tests included the VDRL test, C-reactive protein, latex slide test for rheumatoid factor, and a fluorescent test for antinuclear antibodies. All were negative except for a positive test for antinuclear antibodies, a speckled pattern, occurring in an 11-year-old girl with polyarthritis. Aside from a protracted course (46 days), nothing was unusual about this girl, and all of the remainder of her laboratory studies were normal. She has remained well through the period of follow-up.

Antistreptolysin-0 titers were generally negative or in low titer. One child had a titer of 1:500 (the highest observed); 2 had titers of 1:333, and 2 of 1:250. The remainder were all lower. These elevated ASO titers were thought to represent intercurrent streptococcal infection. Two of the highest titers observed (1:500 and 1:333) were in siblings. Clinically, these children did not differ from the others.

The Wintrobe erythrocyte sedimentation rate ranged from 3.5 to 21 mm/hr, with a mean of 9.6 mm/hr. Only 3 patients had sedimentation rates over 15 mm/hr. Serum protein electrophoresis was essentially normal. The only remarkable finding was some elevation of the α_2 globulin over 0.8 g/100 ml in 10 children. The highest of these was 1.08 g/100 ml. Eight of these 10 children had knee complaints, and 2 had symptoms suggesting the carpal tunnel syndrome.

DISCUSSION

It seems reasonable to consider the arthritis observed to be secondary to rubella vaccination. It would be most unusual to observe 40 new cases of juvenile rheumatoid arthritis all within one month's period of time. Also, the lack of elevation of the sedimentation rate, and the benign course with complete clearing without recurrence, are all against rheumatoid arthritis. Similarly, the benign course, absence of cardiac abnormalities, normal sedimentation rate and low serum antistreptolysin-0 titers are against rheumatic fever. Besides arthritis, other manifestations to support a diagnosis of serum sickness were absent. In addition to rubella, other viruses may cause acute arthritis. However, this is rare, and there was little evidence to suggest another viral infection. Finally, it has been established that the HPV-77 rubella virus vaccine can produce arthritis in the adult, and the virus has been recovered from synovial fluid (15). Thus, we feel confident that the arthritis observed in these children was secondary to rubella virus vaccination.

Comparison with the arthritis following naturally occurring rubella is interesting. In a series of 11 patients (9), the youngest of whom was 10 years and the mean age of 32 years, the duration of arthritis ranged from 3 to 28 days, with a mean of 9 days. The

arthritis occurred with the acute illness, and appeared no later than the sixth day after the rash. The most common joints involved were the metacarpophalangeal; proximal interphalangeal, knee and wrist. One patient had symptoms of the carpal tunnel syndrome, bilaterally. Tenosynovitis of the extensorpollicis longus tendon secondary to rubella has also been described (22).

While arthritis after rubella vaccination is distressing, it appears to be a self-limited complication. All of the children eventually cleared without residual, although in a very few it tended to be recurrent. Further continued surveillance of these children is planned.

It is important to recognize that arthritis may occur nearly two months after vaccination. Often the vaccination is forgotten, and the physician is not given this information unless he specifically inquires. By remembering that self-limited arthritis may occur after rubella vaccination, both the parents and physician may be spared a great deal of anxiety when faced with a child so afflicted.

Aspirin in adequate doses usually afforded relief, as did local heat to the involved joint. In some cases mild sedation (such as elixir of diphenhydramine) proved helpful. Short courses of adrenocorticosteroids have been used by others and reported of benefit (15). One of our patients received one 10 mg dose of prednisone from a relative with apparent improvement. However, we feel aspirin is sufficient in most cases, and in view of the self-limited nature of the illness, therapy should be conservative.

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