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Clinical Manifestations of Erythema chronicum migrans Afzelius in 161 Patients

A Comparison with Lyme Disease

EVA ÅSBRINK and INGEGERD OLSSON

Department of Dermatology, Södersjukhuset, Stockholm, Sweden

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Clinical symptoms were studied in 161 consecutive patients with erythema chronicum migrans Afzelius and in a follow-up study signs of late manifestations were investigated. General symptoms such as headache, fever, myalgia and/or arthralgia were found in about half of the patients with a disease duration of ≤3 weeks. Three patients had coexisting lymphadenosis benigna cutis. Two untreated patients developed meningitis/meningoradiculitis and one untreated patient arthritis. The importance of a sufficient antibiotic therapy to prevent late manifestations is stressed. Although there are many similarities between erythema chronicum migrans Afzelius and Lyme disease, the results of the present study also point to differences. Multiple skin lesions, pronounced general symptoms, laboratory abnormalities and major symptoms from the joints were less common in patients with erythema chronicum migrans Afzelius than reported in patients with Lyme disease, but a prolonged course of the skin eruption was more common. *Key words: Spirochetes.*
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E. Åsbrink, Department of Dermatology, Södersjukhuset S-10064 Stockholm, Sweden.

At a meeting of the Dermatological Society of Stockholm in 1909, Afzelius demonstrated the first patient with erythema chronicum migrans Afzelius (ECMA). In his opinion the disease should be regarded as tick-borne (1). ECMA is not uncommon in Northern Europe and is usually characterized by an annular erythema which enlarges centrifugally. Without antibiotic therapy the skin eruption may persist for months. An association with meningitis was reported by Hellerström in 1930 (2). In 1941 and 1944 Bannwarth (3, 4) described a syndrome with intense, often migrating pain, cerebrospinal fluid pleocytosis and in a few patients an erythema. During the last years there have been case reports of erythema chronicum migrans and arthritis (5, 6) in Europe.

In the United States erythema chronicum migrans was described for the first time in 1970 (7). In addition an epidemic form of arthritis, named Lyme arthritis, has been noted in Lyme in Connecticut at least since 1972. In 1976 this arthritis was linked to a preceding annular skin lesion, reminiscent of erythema chronicum migrans in Europe, and other manifestations such as neurologic and cardiac abnormalities were also described (8). The epidemic disorder was called Lyme disease (LD). In 1982 Burgdorfer et al isolated a spirochete from Ixodes (J.) dammini, the incriminated tick vector of LD (9). In 1983 Steere et al reported on a rise in specific antispirochetal antibodies in most Lyme patients and recovered the spirochete from 3 patients (10).

Patients with ECMA and acrodermatitis chronica atrophicans (ACA) have also shown increased serum antibody titers against Ixodes spirochetes (11, 12) and spirochetes have been demonstrated in (13) and isolated from (11, 12) skin lesions. ACA has been described in untreated ECMA patients after a latency of a few years, which may be consistent with ACA as a late spirochetal manifestation (12). Coexisting ECMA and lymphadenosis

benigna cutis (LABC) (14, 15) and coexisting ACA and LABC (15) have also been described.

The aim of the present study was to report on clinical manifestations in consecutive ECMA patients examined at a dermatological Department in Sweden. A follow-up was also carried out to investigate the frequency of late manifestations in order to compare the results with the clinical symptoms reported in LD.

MATERIAL AND METHODS

Patients

During a 6-year period (1978–1983) 161 patients with ECMA were investigated at the Department of Dermatology, Södersjukhuset, Stockholm. ECMA was defined by its gross appearance and course. Histological examination of lesional skin was also performed in some of the patients. The history was taken and clinical symptoms were noted at the time of diagnosis. Arthritis was defined as pain on motion and swelling of a joint. Patients with neck and/or back pain were referred to the group with neurological symptoms, as in lymphocytic meningoradiculitis (Bannwarth's syndrome) there may be focal pain located in the cervical and/or lumbal regions.

Therapy

Antibiotic therapy was prescribed at the time of diagnosis. Our standard treatment for adults with uncomplicated ECMA has been phenoxymethyl penicillin 1.95–2.4 g a day for 10 days. Patients with a penicillin allergy were treated with tetracycline or erythromycin 1 g a day for 10 days.

Follow-up

Two to 4 weeks after the beginning of the antibiotic therapy 114 patients showed up for re-examination. Another 13 patients were interviewed by telephone 2–6 weeks after treatment. Eleven patients who did not wish antibiotic therapy were observed until recovery of the skin lesion. Of the remaining 23 patients all but one later on answered the questionnaire. During the summer of 1983 a questionnaire was sent to the patients, in whom ECMA had been diagnosed during the years 1978 to 1982. The questions concerned recurrences, symptoms of other diseases and especially complaints of the joints, neurological or cardiac manifestations and any medical examinations that might have occurred (in which case medical records were examined). To the patients in whom ECMA had been diagnosed in 1983 the questionnaire was sent half a year after the ECMA diagnosis was established. Patients with a history of symptoms from the skin, the nervous system, the joints or the heart were then interviewed by telephone and/or examined by the authors.

Laboratory tests

At the time of the ECMA diagnosis laboratory tests were performed on 57 arbitrarily selected patients. In all of them erythrocyte sedimentation rate was determined. On 36 of these patients determinations of serum immunoglobulins (by the turbidity technique in I. L. multistat III), cryoglobulins (refrigerated at 4°C for 48 hours) and circulating immune complexes (by the C1q solid phase assay/C1q SPA/ and the conglutinin assay) were performed. Sera from many patients were frozen at −70°C for further serological analyses. Electrocardiograms were obtained from 20 arbitrarily selected patients at the time of the ECMA diagnosis and in these patients physical heart examinations were performed 1–4 weeks later at the Section of Cardiology, Södersjukhuset.

In the follow-up study laboratory tests including sedimentation rate, immunoglobulins and complement, antinuclear antibodies, rheumatoid factor and immune complexes were performed on 15 patients with neurological and/or joint complaints. Sera from these 15 patients were also analysed for antibodies against the *I. ricinus spirochete* using the indirect immunofluorescence (IF) method (11). The results are reported as reciprocal titers. Sera drawn at different occasions were frozen and then analysed simultaneously.

Statistics

The χ^2-test was used in the statistical calculations.

RESULTS

Out of 161 patients investigated 111 (69%) were women. The median age was 53 years (range 1–84 years). Six of the patients had a history of ECMA once before and 1 patient

twice before. Three patients had a family member with ECMA during the same season. The onset of the ECMA was between June 1 and October 31 in 139 (86%) of the patients. The duration of the ECMA at the time of diagnosis was ≤3 weeks in 55 (34%) patients and >2 months in 53 (33%) patients (median 5–6 weeks, range 2 days to 1 year). Eleven patients had a duration of >6 months. A tick bite at the site where ECMA later developed, had been noted by 58 patients (36%) and another 37 (23%) had observed what they called "insect bites". The median time from tick bite to onset of the ECMA was 3 weeks (range 3 days to 3 months) in 25 patients who recalled the time interval.

Skin manifestations

A solitary ECMA lesion was observed in 151 patients (94%). The most common site was the leg (51%), often near the knee. Two types of skin lesions were noted at the first visit. The typical and most common one was the solitary annular erythema, with a central clearing and a red migrating border, which was observed in 121 patients. Thirty patients revealed a solitary homogenous erythema sometimes irregular, sometimes indurated and often of moderate size. In 21 of these 30 patients (70%) the homogenous erythema was seen as an early lesion (ECMA duration ≤3 weeks) compared to the annular erythema where only 31 of the 121 patients (26%) had a disease duration of ≤3 weeks. This difference is statistically significant ($p<0.001$). In 8 of the patients with homogenous erythema common insect bite reactions, contact dermatitis or fixed drug eruptions had been suspected by the examining dermatologist at the first visit and the diangosis of ECMA had not been made until the second visit, when the homogenous erythema had often changed to a typical annular erythema. None of the 161 patients had vesicular or necrotic lesions.

Multiple ECMA lesions were seen in 10 patients. Nine patients had 2–4 lesions and one 6 lesions. Two patients with 2 lesions had observed tick bites at both ECMA locations. One of the patients with 4 lesions was among those who had the most pronounced symptoms of headache, fever, myalgia and arthralgia. She also had an elevated sedimentation rate, the highest elevated serum IgM level seen among our patients and a spirochetal antibody titer of 320 against the Ixodes spirochetes. Her husband developed a classical solitary ECMA lesion during the same season. In 4 of the patients with multiple lesions the diagnosis was not established until the second visit.

A diffuse maculopapular rash on the trunk was seen in 4 of the 161 patients at the time of diagnosis.

Three patients (2 women and 1 man) showed up with a red swollen and tender nipple which in 2 of the patients was surrounded by a migrating annular ECMA on the chest and in the third patient surrounded by a homogenous ECMA. One of these patients had noted a preceding tick bite near the nipple. The histologic examinations of the biopsies from the nipples showed dense lymphocytic infiltrates with plasma cells in the dermis and in 2 of the biopsies reaction centers were found. The clinical and histopathological findings were in agreement with the diagnosis lymphadenosis benigna cutis as described by Bäfverstedt (15). The biopsies from the surrounding erythemas showed a light perivascular infiltrate with a few plasma cells. One patient, who had a typical ECMA on the right leg with a duration of half a year and an acrodermatitis chronica atrophicans on the left hand and arm with a duration of >2 years, has been described earlier (12).

Symptoms at the time of the ECMA diagnosis

Nine of the 161 patients were excluded here because of incomplete data.

Symptoms at the location of the ECMA, such as burning, itching, a painful sensation and/or dysesthesia, described as an increased, unpleasant sensitivity to touch, were found

in 34 (62%) of the 55 patients with an ECMA duration of ≤3 weeks and in 56 (58%) of the 97 patients with a duration of >3 weeks. Two patients had intense neuralgiform pain in the same extremity as the ECMA. The pain disappeared with oral penicillin treatment and a spinal tap was not performed.

General symptoms such as headache, myalgia, arthralgia, low-grade fever, profound fatigue, a sore throat, nausea and/or gastrointestinal complaints were found in 29 (53%) of the 55 patients with an ECMA duration of ≤3 weeks, compared to in only 22 (23%) of the 97 patients with a disease duration of >3 weeks. The difference is statistically significant ($p<0.001$). The general symptoms were usually mild or moderate and many patients did not relate the symptoms to their ECMA and did not mention them spontaneously but only after direct questioning. Several patients with a duration of the ECMA of >3 weeks remembered "flu-like symptoms" just before the onset of the ECMA or during the first weeks of the skin eruption. In patients with a disease duration of ≤3 weeks headache was the most common general symptom and was found in 33%.

One patient with a seropositive rheumatoid arthritis exhibited an exacerbation of her arthritis during the ECMA infection. Arthritis was not found in any of the other patients at the time of the ECMA diagnosis.

Laboratory findings before treatment

Two (4%) out of 57 patients investigated had an elevated (>20 mm/h) erythrocyte sedimentation rate (22 respectively 23 mm/h). Another 8 patients had a sedimentation rate of 18–20 mm/h. Six (17%) out of 36 patients had an elevated (>1.35 g/l) serum IgM level (range, 1.45–2.35 g/l). Immune complexes were found by the C1q SPA in 2 and by the conglutinin assay in 5 of these 36 patients. Tests for cryoglobulins in sera were negative in all the 36 patients investigated.

None of 20 patients examined had electrocardiographic changes suspective of cardiac involvement.

Therapy

Penicillin treatment was given to 132 patients, erythromycin to 9 patients and tetracycline to 4 patients. Sixteen patients, most of whom had a fading erythema and no other symptoms, did not want therapy.

Follow-up

In all the 114 patients re-examined 2–4 weeks after treatment the ECMA lesion had healed. In most patients general and localized symptoms had begun to subside within a couple of days and were gone 1–2 weeks after the beginning of therapy. In a few patients, however, slight local dysesthesia remained. The 13 antibiotic treated patients, who were interviewed by telephone, all reported that they were free of symptoms. None of the 20 patients examined by a cardiologist showed any signs of cardiac involvement.

In the 11 untreated patients followed until healing the median ECMA duration was 10 weeks (range 2 weeks–1 year). One patient (Table I, no. 1) with a 6-week history of ECMA, who showed up with the skin lesion almost healed, was not treated with antibiotics. Three weeks later she got a recurrent ECMA and severe lumbar pain radiating to one leg and profound fatigue. A spinal tap was performed which revealed a mononuclear pleocytosis and a cerebrospinal-fluid-IgG index indicating intrathecal immunoglobulin synthesis. No signs of cardiac involvement were found by auscultation or electrocardiogram. This patient was successfully treated with intravenous benzylpenicillin (3 g every 6 h for 2 weeks). A further spinal tap 2 months later showed normal values. In one untreated

Table I. *Neurologic symptoms in 8 patients with preceding ECMA. Interval from the onset of the ECMA, duration of the neurologic symptoms and indirect IF titers against the I. ricinus spirochete*

If titers were performed on sera drawn A) at the time of the ECMA diagnosis, B) at the time of neurologic symptoms or, in 3 cases, after recovery

Patient no.	Treatment of ECMA	Diagnosis or symptoms	Interval (months)	Duration (months)	IF titer A	IF titer B
1	–	Meningoradiculitis	2.5	0.5	40	160
2	–	Meningitis, facial palsy	0.75	1	160	ND
3	–	Back, neck pain	4	36	40	10[a]
4	Tetracycline	Back pain	2	6	160	80[b]
5	Penicillin	Back pain	4	0.5	80	80
6	Tetracycline	Back pain	23	36	ND	40[c]
7	Penicillin	Neck pain (spondylosis)	13	6	40	10
8	Penicillin	Back pain (spondylosis)	2.5	2	80	40

[a] 5 months, [b] 3 months, [c] 2 months after recovery.
ND = not done.

patient (Table I, no. 2) headache, stiff neck and facial palsy developed 1 week after the healing of the skin lesion (ECMA duration 2 weeks). The spinal tap showed mononuclear pleocytosis and elevated cerebrospinal fluid protein. One patient (Table II, no. 1) with an untreated ECMA that healed after a duration of 4 months, 2 weeks later developed morning stiffness, pain and swelling of the ankle of the extremity where the preceding ECMA had been located. Laboratory tests showed increasing IF-titers, a slightly elevated serum IgM level and circulating immune complexes (C1q SPA). No signs of cardiac

Table II. *Symptoms of the joints in 10 patients with preceding ECMA. Interval from the onset of the ECMA, duration of the joint symptoms and indirect IF titers against the I. ricinus spirochete*

IF titers were determined on sera drawn A) at the time of the ECMA diagnosis, B) at the time of symptoms of the joints or, in 3 cases, after recovery

Patient no.	Treatment of ECMA	Joint symptoms	Interval (months)	Duration (months)	IF titer A	IF titer B
1	–	Ankle arthritis	4.5	1.5	80	320
2	Penicillin	Knee pain	3	4	320	320
3	Penicillin	Migrating arthralgia	3	6	80	80
4	Tetracycline	MCP-arthritis	4.5	4	160	80
5	–	Migrating arthralgia	4	12	40	10[a]
6	–	Knee pain	0	24	ND	10[b]
7	Tetracycline	Migrating arthralgia	25	34	ND	40
8	Penicillin	Knee pain	5	48	ND	20[c]
9	Penicillin	Pain in knee, ankle, wrist (RA)	4	10	80	80
10	Penicillin	Polyarthritis (malignancy)	2	8	80	80

[a] 6 months, [b] 3 months, [c] 6 months after recovery.
ND = not done.

involvement were found by auscultation or electrocardiogram. The symptoms from the joints had continued for 4 weeks when standard penicillin therapy was given and 2 weeks later the joint symptoms had disappeared.

The questionnaire was answered by 150 out of 161 patients. One of the penicillin treated patients and 2 of the untreated patients, all of whom had been followed until healing, reported a recurrent skin lesion at the original ECMA site 2, 3 respectively 7 months later. In none of the patients symptoms of ACA were reported. Twenty-two of the 23 patients who had not participated in the previous follow-up answered the questionnaire. In the 5 untreated patients of this group the skin lesion had a duration of 3 to 12 months. The remaining 17 patients reported that their ECMA had healed after antibiotic treatment.

Neurologic symptoms. In answer to the questionnarie 6 patients described periods of moderate to severe pain in the back and/or neck radiating to the extremities (Table I, nos. 3–8). No other patients reported on medical consultation for neurologic symptoms and none mentioned paralysis or periods of severe headache. Patients 3, 4 and 6 had symptoms of the joints as well. One patient (no. 3), who had refused to take penicillin for her ECMA, 4 months later had developed symptoms suspective of meningoradiculitis, namely severe intermittent lumbar pain radiating to the legs, intermittent pain in the neck and shoulders, as well as profound fatigue and migrating arthralgia. Two years later the patient had been treated with phenoxymethyl penicillin 4 g a day for 10 days and the symptoms then gradually disappeared within 1 year.

Symptoms of the joints. Eighteen patients reported on symptoms of the joints, starting after the ECMA diagnosis. One patient had a 3-year-history of recurrent arthritis in the metacarpophalangeal and interphalangeal joints, verified by a physician's examination. The patient did not wish to participate in further follow-up as she had been free of symptoms for >1 year. Four patients mentioned articular symptoms (one had had migrating arthralgia, one pain in the finger joints and two pain in the knees), but had never consulted a physician. As the symptoms were slight and inconstant these patients were not interested in any consultation. Four elderly patients with pain in the knee or hip had received the diagnosis osteoarthrosis. The remaining 9 patients (Table II, nos. 2–10) were examined by the authors and laboratory tests were performed. Patient no. 9, with joint pain without swelling, initially had a low positive test for rheumatoid factor which, 4 months later, had changed to a high titer indicating an early rheumatoid arthritis. Patient no. 10 had a positive test for serum antinuclear antibodies (1/100) and was diagnosed by a rheumatologist as having a seronegative rheumatoid arthritis. The joint symptoms later disappeared after the operation for a chondrosarcoma. Except for patient no. 10 and a patient with osteoarthrosis of a hip, none of the patients had been hospitalized for symptoms of the joints.

Cardiac symptoms. Six patients described cardiac symptoms appearing after the ECMA. All patients had consulted physicians and electrocardiograms had been performed. Atrioventricular block or changes compatible with acute myopericarditis had not been found in any of the patients. One patient had received the diagnosis infarctus cordis, one angina pectoris, two incompensatio cordis, one mitralis vitium and the last patient had periodical tachycardia but no electrocardiographic changes.

Laboratory findings in the follow-up study. On examination of sera from 15 patients who had got neurologic symptoms and/or symptoms of the joints after their ECMA, antinuclear antibodies and elevated IgA was found in one, elevated serum IgM in one, circulating immune complexes (C1q SPA) and low C3 in one and one had a positive test for rheumatoid factor. With the exception of patient no. 1 (Table I), who developed a meningoradiculitis and patient no. 1 (Table II), who developed an arthritis increasing IF titers were not found in any of the patients tested. In patients 7 and 8 (Table I), with

decreasing IF titers, X-ray had shown spondylosis, which probably can explain their symptoms.

DISCUSSION

The solitary annular ECMA is usually easy to recognize, but the homogenous erythema, particularly occuring in the early phase of the disease, can, as well as the relatively uncommon multiple lesions, cause diagnostic problems. In this study slight to moderate general symptoms, mostly appearing early in the course of the ECMA, were not uncommon, but many patients do not relate such general symptoms to the ECMA and the symptoms may therefore be overlooked.

Among the 145 antibiotic-treated patients no late manifestations from the nervous system, the joints or the heart could be proven. In some patients with a history of mild to moderate arthritis or arthralgia a connection with the previous ECMA can not be excluded, but increasing IF titers were not found in any of the patients tested, as described in some patients with late manifestations of LD (16).

Among the 16 untreated patients in this study 2 patients (Table I, nos. 1–2) developed meningitis/meningoradiculitis. Another patient (Table I, no. 3) was found to have had symptoms suspective of meningoradiculitis, but the low IF titer found at the time of follow-up did not support the presumption of a late spirochetal manifestation. One untreated patient (Table II, no. 1) developed an arthritis and had increasing IF titers, which is in accordance with a late manifestation of ECMA. The complications found among the untreated patients in this study emphasize the importance of early antibiotic therapy in ECMA patients.

Comparison with Lyme disease

Recent studies indicate that both LD (9, 10) and ECMA (11) are tick-borne spirochetoses. Serologic results (11, 12, 17), studies with monoclonal antibodies, protein studies and electron microscopy (17) have shown that spirochetes isolated from American I. dammini ticks are closely related to the spirochetes isolated from European I. ricinus.

In Northern Europe ECMA has been known since the beginning of this century and has been described as a usually benign disease with slight or absent subjective symptoms (2, 18, 19). The association with neurologic manifestations is well-known, but has been regarded as fairly rare. In a recent study from Germany Weber et al (20) followed 30 erythema chronicum migrans patients for >2 years. They emphasized the similarities to LD as they found symptoms such as arthritis in 5 patients, arthralgia in another 5, cardiac symptoms in 3, symptoms suspective of meningitis in 3 and in 7 patients an increased sedimentation rate. In most patients these manifestations occurred despite antibiotic treatment.

In the US the clustering of arthritis found in Lyme in Connecticut during the last decade has led to the clinical description of LD which often starts with one or multiple annular skin lesions, called erythema chronicum migrans.

Sex and age. The present study showed that there was a female predominance (69%) among ECMA patients, which is in agreement with earlier reports (20, 21). A female predominance has also been found among ACA (12, 22) and LABC (15) patients. In early LD no sex difference was reported (23). The median age of the ECMA patients was 53 years compared to 28 years of the LD patients (23).

Duration, skin manifestations and early symptoms. In 55 untreated LD patients the skin lesions faded within a median of 28 days (23). In the present study the median time from the onset of the ECMA to diagnosis was 5–6 weeks and in the 11 untreated patients followed until healing, the median ECMA duration was 10 weeks. This indicates that the

duration of ECMA may be longer than the duration of the skin manifestations in LD. Multiple skin lesions were seen in only 6% of the ECMA patients. None of the patients had more than 6 lesions. In LD 48% of the patients (150/314) had multiple annular lesions, 13% had more than 20 lesions (23). In this investigation LABC was found in 3 of the 161 examined patients and as has been reported earlier there is probably also a connection between ECMA and ACA (12). To our knowledge no association between LD and LABC or ACA has been reported. In early LD most patients reveal general symptoms such as malaise, fatique (80%), headache (64%), fever (59%), arthralgia (48%), stiff neck (48%) and myalgia (43%) (23). General symptoms were noted in about half of the patients (53%) with an ECMA of short duration (≤3 weeks), but the course was as a rule milder than that described in LD (22).

Laboratory findings. In this study an elevated sedimentation rate was found in only 4% (2/57), an elevated serum IgM level in 19% (7/36) and circulating immune complexes tested by the C1q SPA in sera from 2 out of 36 ECMA patients. In the early phase of LD with skin lesions an elevated sedimentation rate has been reported in 53% of the patients and an elevated serum IgM level in 33% (23). Serum C1q binding activity has been described to be present in nearly all cases of early LD and patients with neurologic or cardiac involvement continue to have abnormal C1q binding activity (24). Although difficulties may arise in the comparison of data from different laboratories the results indicate that nonspecific laboratory abnormalities are more common in early LD than in ECMA.

Late neurologic, articular and cardiac manifestations. The skin manifestations in LD may weeks to months later be followed by neurologic involvement (14%) or cardiac involvement (4%) and weeks to years later by arthritis (43%) (8, 25). In 69% of the patients who developed arthritis the first attack had occurred within 6 months (25). In the present study none of the patients had developed arthritis at the time of ECMA diagnosis, when 11 patients had had ECMA for >6 months. Two untreated patients later developed meningitis/meningoradiculitis and one untreated patient arthritis. During the follow-up period some more patients got symptoms from the nervous system or the joints in whom a connection with the preceding ECMA can not be excluded. As one part of the investigation was a retrospective study mild symptoms and symptoms of short duration may also have been forgotten by some patients. The results, however, indicate a lower frequency of major late manifestations in this material compared to LD (25).

Risk factors for the development of "late disease" in LD are according to Steere et al, severe initial symptoms, such as marked arthralgia, multiple skin lesions, an elevated serum IgM level and a late start of therapy (26). Except for a late start of therapy these risk factors were rare or infrequent among our ECMA patients compared to LD.

Antibiotic therapy

Ever since the report of Hollström (27) about the successful penicillin treatment of ECMA and of its neurologic complications, there is a tradition of antibiotic treatment of ECMA patients in Scandinavia. Antibiotic therapy of LD was first begun in the summer of 1977. A marked reduction of subsequent late manifestations in LD has been reported since the change of treatment from penicillin G (25), the absorption of which is uncertain after oral administration, to phenoxymethyl penicillin (1 g a day) or tetracycline (1 g a day) (26). Compared to the penicillin dose used in the present study Weber et al (20), on a majority of patients, also used a lower phenoxymethyl penicillin dose and this may be one of the explanations for the higher frequency of late manifestations in their study compared to the present one. A treatment of 2 g phenoxymethyl penicillin a day for 10 days seems to be beneficial in most patients, but it is possible that even higher doses may be needed in some patients to prevent late manifestations.

Although there are many similarities between LD and ECMA the results of the present study also point to differences. Multiple skin lesions, pronounced general symptoms and laboratory abnormalities were less common in ECMA than reported in early LD and major late manifestations were also less common. A female predominance, a higher median age and an often more prolonged course of the skin eruption were found among the ECMA patients. Differences in patient selection and in therapy may explain some of the dissimilarities but probably not all.

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