

EPISODIC DERMATOLYMPHANGIOADENITIS (DLA) IN PATIENTS WITH LYMPHEDEMA OF THE LOWER EXTREMITIES BEFORE AND AFTER ADMINISTRATION OF BENZATHINE PENICILLIN: A PRELIMINARY STUDY

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ABSTRACT

Dermatolymphangioadenitis (DLA) is a common and serious complication of obstructive peripheral lymphedema. The clinical characteristics of acute DLA are local tenderness and erythema of the skin, sometimes red streaks along the distribution of the superficial lymphatics and enlarged inguinal lymph nodes. Systemic symptoms include malaise, fever and chills. In its subacute or latent form, only skin involvement is observed. Each episode of DLA is commonly followed by worsening of leg swelling. Numerous clinical studies suggest that administration of antibiotic drugs interrupt the acute episodes and prevent their recurrence. We investigated the clinical course of lymphedema with respect to the prevalence of DLA in patients receiving injections of long-acting penicillin (benzathine penicillin). Forty-five randomly selected patients with obstructive lymphedema of the lower limbs were included in an open clinical trial. The inclusion criteria was stage II-IV lymphedema of postsurgical, posttraumatic, and postdermatitis type with at least 3 previous episodes of DLA. Benzathine penicillin (PCN) was given after the last presenting episode of DLA in a dose of 1,200,000 u, intramuscularly at 3-week intervals, for at least one year. Each patient was reevaluated at 3-month intervals. They

were instructed in early diagnosis of DLA and reported promptly to the responsible senior surgeon with prodrome symptoms of recurrent DLA. The duration of lymphedema before initiation of therapy was 7 months to 40 years and the frequency of DLA was 1-6 episodes per year. PCN administration lasted for at least one year but was extended in all patients because of the tendency for recurrence of DLA after cessation of PCN injections. In 26 of these patients, PCN administration extended to over 5 years and in 2 over 10 years. Recurrent episodes of DLA occurred in the PCN-treated group during one year follow-up in only 4 of the 45 patients (9%). The frequency episodes in 3 patients with recurrent DLA was 1-2/year; in one patient, no positive effect of PCN therapy was observed. There were no apparent side effects of long-term PCN therapy.

These data, although evaluated without a placebo group, suggest that long-term PCN administration decreases the frequency of DLA attacks and furthermore provide justification for carrying out a double-blind randomly placebo-controlled clinical trial of the efficacy of prophylactic antibiotic drug treatment in forestalling DLA episodes.

Dermatolymphangioadenitis (DLA) is a common and serious complication of peripheral lymphedema. Clinical signs of

DLA include circumscribed erythema of the skin in the swollen extremity, sometimes red streaks paralleling the superficial lymphatics and enlarged painful regional lymph nodes. The changes develop first in the skin, then in the lymphatics and lymph nodes. Documentation of this sequence of events prompted us to introduce the term DLA for this condition instead of the common misnomer "cellulitis," the imprecise "erysipelas" and overly narrow "lymphangitis." Constitutional symptoms of malaise, fever, and chills typically accompany the local inflammatory changes. The full-blown clinical picture is nowadays less commonly seen as antibiotic drugs are often administered early in the prodromal stage. In most patients, acute changes are limited to the skin. The inflammatory changes, however, persist after an acute episode at a subclinical level and occasionally undergo overt exacerbation. Chronic inflammatory changes can be demonstrated in histopathologic sections after skin biopsy (1). The mononuclear infiltrates are more dense in the papillary and reticular layers of the skin than in the subcutis, lymphatics, and lymph nodes (1). Bacteria can often be cultured from the tissue fluid, lymph, and lymph nodes of lymphedema limbs (2). So-called cellulitis and erysipelas develop otherwise in both healthy and lymphedematous extremities. Although there may be common features, the term DLA should be restricted to the chronic inflammatory, episodic exacerbated changes that occur in lymphedema with the clinical manifestations as outlined above.

DLA is frequently observed in the post-surgical, posttraumatic, and postdermatitis types of secondary lymphedema as well as in the later advanced stages of congenital or primary lymphedema. Clinical observations suggest that there is a distinct time lag of months or years between the overt appearance of lymphedema and the first episode of DLA. Once DLA occurs, however, its recurrence is almost assured, and the frequency of attacks increases in the course of lymphedema. Each episode of DLA is characteristically followed

by a worsening of limb swelling. Based on reports of 40 investigations from all continents an incidence of at least 50% of lymphedema patients are affected by DLA (3) with a higher occurrence in tropical countries (4). The frequency and duration of these DLA episodes seems to depend on the stage of lymphedema (4).

It is generally agreed that antibiotic drugs are highly effective in treatment of acute DLA. It is also well recognized that with cessation of the antibiotics, that recurrent episodes of DLA are frequent. The question arises as to whether long-term antibiotic administration will prevent recurrence of DLA and accordingly retard progressive lymphatic obliteration and skin fibrosis.

In this preliminary study, we examined the clinical course of lymphedema of the lower limbs with respect to the prevalence of DLA in an open clinical trial in 45 patients given long-acting parenteral penicillin (benzathine PCN). The frequency of pretreatment episodes of DLA were compared with post-treatment episodes.

MATERIAL AND METHODS

Criteria of DLA

The criteria for diagnosis of DLA were established, both for doctors and patients. These included the sudden appearance of circumscribed tender, warm, and erythematous areas on the skin of a lymphedematous extremity either separately or in conjunction with epidermal red streaks paralleling lymphatics, sometimes associated with tender and enlarged inguinal lymph nodes and occasionally with prodromal symptoms of malaise, fever, and chills.

Trial Design

An open pilot trial was used to evaluate the effects of long-term administration of a long-acting penicillin on the recurrence rate of acute episodes of DLA. The inclusion

patient criterion was secondary lymphedema with at least 3 earlier attacks of DLA. The frequency of DLA episodes was 1-6 per patient per year. The treatment observation time lasted at least one year. Patients were informed about the purpose of the trial and gave oral consent.

Subjects

The study group consisted of 45 randomly selected patients, 25 females and 20 males, age 23-65 years. Diagnosis of secondary lymphedema was based on clinical investigation including plain x-rays of soft tissues of the limb (skin and subcutaneous/muscle ratio), and lymphoscintigraphy. Specifically excluded were patients with arterial insufficiency, postthrombophlebitic syndrome, congenital malformations, lipedema, recent limb trauma, and unrelated dermatological diseases.

Etiology of Lymphedema

Extirpation of inguinal lymph nodes was the cause of secondary lymphedema in 4 patients, hip operation with immobilization in 2, limb trauma in 6, radical hysterectomy and radiotherapy in 2, severe dermatitis in the past in 15, and no clearly identified factor in 16 patients.

Duration and Stage of Lymphedema

Lymphedema was present for 1 year in 6 patients, 2-5 years in 11 patients, 5-10 years in 12 patients, 10-20 years in 7 patients, and 20-40 years in 9 patients; 24 patients were in stage II, 16 in stage III, and 5 in stage IV lymphedema.

Frequency of DLA

Each patient had experienced at least 3 DLA attacks before inclusion in the trial. One attack/year was recorded in 12 patients, 2-3 episodes in 25 patients, and 3-6 DLA attacks

in 8 patients. Patients in more advanced stages of lymphedema had had a greater frequency of DLA episodes.

Penicillin Administration

a) A skin test for allergy to penicillin was routinely made.

b) For prevention of DLA attacks, benzathine penicillin 1.2 million u (Polish trade name Dibeciline) was given intramuscularly, at 3 week intervals. The site of injection was anesthetized with 2% Xylocaine prior to injection.

c) In case of a recurrence of acute DLA during the period of prophylactic administration of benzathine PCN, patients received a supplemental oral antibiotic (Ampicillin, 1.5 g daily, for 5 days).

Each patient received an injection of benzathine PCN at 3 week intervals for at least 1 year. After this period, administration of benzathine PCN was reinstated on a regular 1 year protocol only when there was a tendency for recurrence of DLA. The prodrome of recurrent DLA consisted of malaise with tenderness of skin, sudden exacerbation of skin inflammatory changes, circumscribed erythema, warm skin areas and tender inguinal lymph nodes.

Other Therapy

Patients wore elastic stockings (Sigvaris); no decongestive or other pharmacological therapy was administered.

Follow-Up

Patients reported to the lymphological outpatient clinic every 3 months. Color and tenderness of the skin, lymph leakage, palpation along femoral lymphatics and of inguinal lymph nodes was routinely performed. Measurements of calf and thigh circumference were carried out by each patient at home, at well-established limb

TABLE 1
Effect of Benzathine Penicillin in 45 Patients with Secondary Lymphedema of Lower Limbs and Prevalence of Dermatolymphangioadenitis (DLA) Episodes from 1-10 Years

Duration of penicillin* (years)	Total Patients (#)	Patients With Recurrent DLA	
		(#)	(%)
1	45	4	9
2	28	2	7
3	25	2	8
4	15	1	7
5	14	1	6
6	9	1	11
7	7	0	0
8	5	0	0
9	3	0	0
10	2	0	0

*1.2 million u., i.m., every 3 weeks

levels and time periods. If a recurrence of DLA developed, the patient reported to the outpatient clinical promptly.

RESULTS (Table 1, Fig. 1)

All 45 patients received benzathine PCN for at least 1 year every 3 weeks. Only 4 patients experienced attacks of DLA (9%). The frequency of DLA episodes were from 1-3 per patient. Cessation of PCN administration after 1 year was followed in each of the 45 patients by recurrence of either subclinical or acute DLA. The time interval between stoppage of PCN and recurrence of DLA was from 3 weeks to 6 months. Accordingly, the prophylactic injections of PCN were resumed in all 45 patients and lasted from 2-10 years. Half of the patients deliberately stopped taking PCN with anticipation of no further DLA recurrences. However, all had to resume PCN therapy upon the first symptoms of recurrence.

During the 1 year follow-up period, there

was no dramatic increase in the calf and thigh circumference in any patient.

DISCUSSION

This study documents that after administration of benzathine penicillin (PCN) for 1 year in a group of 45 patients with secondary lymphedema of the legs, recurrent episodes of DLA decreased by 90%. These data confirm earlier reports that PCN is extremely effective in preventing inflammatory complications of lymphedema and infections (5-10). In our study, we were unable to establish a placebo-controlled group because of ethical considerations. Nonetheless, to examine objectively the frequency of DLA episodes, the findings were compared before, during, and after PCN administration in each patient.

We also observed that progression of skin changes and increase in size of the affected limb compared with the pretreatment period seemed to slow. Although not objectively

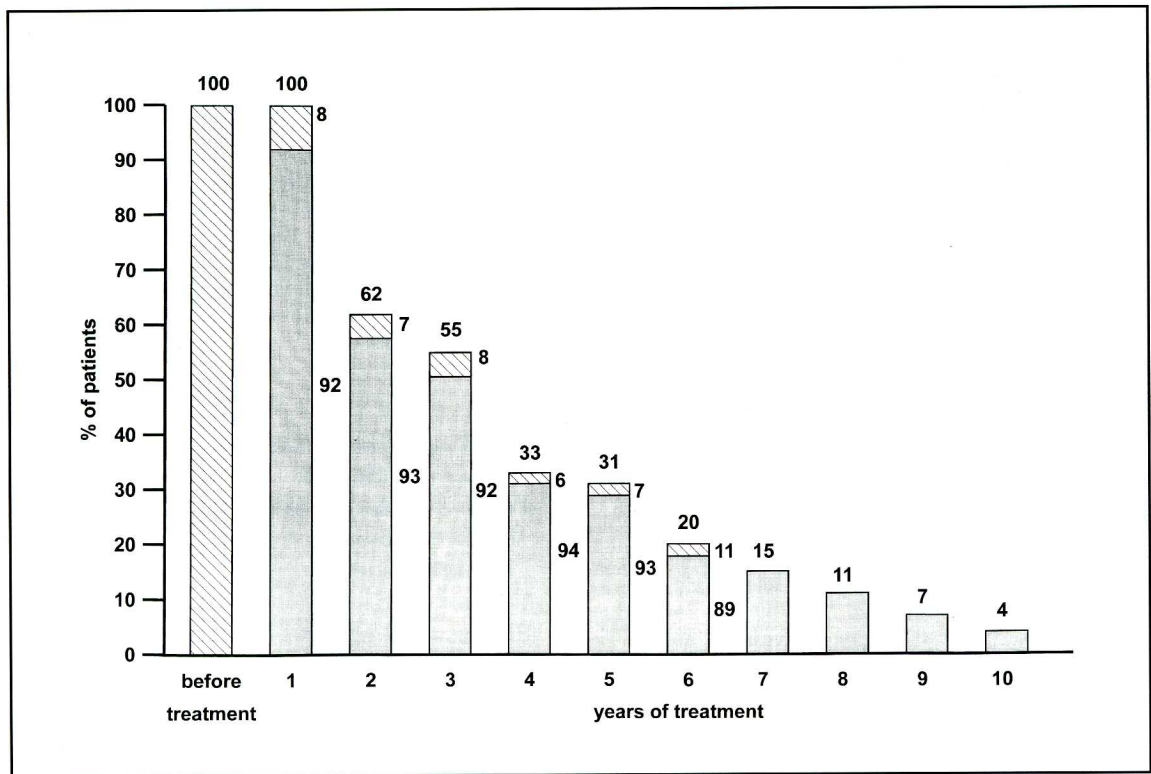


Fig. 1. The incidence of dermatolymphangioadenitis (DLA) attacks in 45 patients with obstructive lymphedema receiving benzathine penicillin and followed for periods from 1 to 10 years. Bars with numbers above show the percentage of patients followed for a given number of years. Shaded areas with side numbers represent the percentage of patients free of DLA attacks; striated areas with side numbers are those with recurrent DLA attacks. Note that the incidence of attacks decreased from 100% in patients prior to benzathine penicillin administration to a mean of 9% after the first year of follow-up.

substantiated, skin biopsies in 3 patients after 3 months of PCN therapy showed on histology resolution of mononuclear infiltrates (unpublished observations). Patients also subjectively reported a subsidence of sensations such as skin tension and tenderness. There was also less limitation of movement at the ankle and knee, and previously erythematous skin gained a more normal skin color.

A 3-week interval between prophylactic PCN injection seemed sufficient for protection after DLA recurrence. Longer periods without systemic PCN administration were complicated by reappearance of inflammatory skin changes and systemic symptoms. Because of subclinical or acute recurrences, the PCN prophylaxis protocol was extended

for longer periods. Twenty-five patients have been receiving PCN; 3 for several years, 14 for more than 5 years, 2 for 10 years. No complications of protracted PCN administration have occurred.

Taken together, these data suggest that benzathine PCN, given periodically at standard dose, is an effective drug preventing recurrence of DLA in patients with lower limb obstructive lymphedema. Moreover, PCN treatment may also slow progression of skin inflammatory changes commonly seen as lymphedema worsens. On the other hand, to reach definitive conclusions on this account, a double-blind placebo-controlled randomized clinical trial is essential.

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