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Erysipelas as a sign of subclinical primary lymphoedema: a prospective quantitative scintigraphic study of 40 patients with unilateral erysipelas of the leg

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Conflicts of interest

None declared.

Summary

Background Erysipelas is a common skin infection that is usually caused by β-haemolytic group A streptococci. After having had erysipelas in an extremity, a significant percentage of patients develops persistent swelling or suffers from recurrent erysipelas. We hypothesize that in cases of erysipelas without a clear precipitating agent, subclinical pre-existing congenital or acquired disturbances in the function of the lymphatic system are present. The persistent swelling after erysipelas is then most likely caused by lymphoedema.

Objectives We designed a study to examine if erysipelas of unknown origin is associated with a pre-existent insufficiency of the lymphatic system. If our hypothesis is correct, patients with erysipelas of unkown cause without previously evident lymphoedema should have evidence of disturbed lymphatic transport in the unaffected extremity.

Methods A prospective study, in which lymphoscintigraphy of both legs was performed in patients 4 months after presenting with an episode of erysipelas only in one leg. No patient had any known risk factor for erysipelas, such as diabetes mellitus, chronic venous insufficiency or clinical signs of lymphoedema. Lymphoscintigraphy was performed in 40 patients by subcutaneous injection of Tc-99m-labelled human serum albumin in the first web space of both feet. After 30 and 120 min, quantitative and qualitative scans were performed using a computerized gamma camera. During the lymphoscintigraphy, the patients performed a standardized exercise programme. Lymph drainage was quantified as the percentage uptake of Tc-99m-labelled human serum albumin in the groin nodes at 2 h after injection. Groin uptake of $< 15\%$ is pathological; uptake between 15–20% is defined as borderline, and uptake of $> 20\%$ as normal.

Results The mean ± SD percentage uptake in the groin nodes in the affected limbs was 9·6 ± 8·5% vs. 12·1% ± 8·9% in the nonaffected limbs. The mean paired difference in uptake between the nonaffected vs. affected side was 2·5% (95% confidence interval 1·1–3·9%). This indicates that lymphatic drainage in the nonaffected limb was only slightly better than in the affected limb despite the infectious event in the latter. Of 33 patients with objective impairment of lymph drainage in the affected limb, 26 (79%) also had impaired lymph drainage in the nonaffected limb. Agreement in qualitative measurements between affected and nonaffected leg was less pronounced: 21 patients had abnormal qualitative results in the affected leg of whom nine also had impairment of the nonaffected leg (43%).

Conclusions Erysipelas is often presumed to be purely infectious in origin, with a high rate of recurrence and a risk of persistent swelling due to secondary lymphoedema. In this study, we show that patients presenting with a first episode of erysipelas often have signs of pre-existing lymphatic impairment in the other, clinically nonaffected, leg. This means that subclinical lymphatic dysfunction of both legs may be an important predisposing factor. Therefore, we recommend that treatment of erysipelas should focus not only on the infection but also on the lymphological aspects, and long-standing treatment for lymphoedema is essential in order to prevent recurrence of erysipelas and aggravation of the pre-existing lymphatic impairment. Our study may change the clinical and therapeutic approach to erysipelas as well as our understanding of its aetiology.

Erysipelas is a common superficial skin infection with lymphatic involvement and swelling that often persists after resolution of the infection. *Streptococcus pyogenes* or β-haemolytic group A streptococci are the major causative agents, but *Staphylococcus aureus* can also be involved. In erysipelas, erythema and swelling are usually sharply demarcated from intact skin. It usually affects the legs, less frequently the face[1] or arms.

The most common known local risk factors for erysipelas are venous insufficiency, previous or current local injury, fungal skin infections and lymphoedema.[2–4] Systemic risk factors for erysipelas include diabetes mellitus, obesity, immunosuppression, upper respiratory tract infection and alcoholism.[5]

The clinical signs of lymphoedema are pitting and/or nonpitting oedema and a positive Stemmer sign (thickening of the interdigital web space between the second and third toes). In long-standing oedema, the skin shows papillomatous thickening. Fluid-filled 'blebs' can develop and there is an increased risk of lymphangiosarcoma.[6] Lymphoedema is caused by accumulation of protein-rich interstitial fluid due to a deficient capacity for lymphatic fluid transport.[7]

The lymphatic system is not only essential for the maintenance of the interstitial fluid balance, but also has an important immunological function. Therefore, impairment of the lymph system will also lead to a dysfunctioning immunological response.[8] Lymphoedema can be either primary or secondary. The former type is defined as genetically determined dysfunction, malformation or hypoplasia of the lymphatic circulation, and the latter as disruption of previously normal lymphatic circulation, for example due to infection or surgical procedures. De Godoy *et al.*[9] estimated that 77% of patients who have had two or more episodes of erysipelas have scintigraphic abnormalities correlating with lymphatic impairment.

We hypothesized that these patients will often have preexisting primary subclinical lymphoedema, which can also explain the high rate of recurrence. Our hypothesis predicts that patients with erysipelas will have a significantly higher incidence of lymphatic impairment in the nonaffected leg than the general population.

To test our idea, we set up the present study to look for an existing, bilateral lymphatic impairment in the legs without signs of lymphoedema in patients with a first episode of unilateral erysipelas.

Materials and methods

Study design and population

The study was conducted at the Nij Smellinghe Hospital in Drachten, the Netherlands, from 1999 to 2006. The protocol performed is part of the routine pratice for patients with erysipelas in our hospital. The study population consisted of 40 patients (28 men, 12 women) who were hospitalized because of unilateral erysipelas of the lower leg and who met the inclusion criterion. All patients were treated with intravenous antibiotics, wet wrap for the first days, compression therapy and compression hosiery for 4 months after discharge from the hospital. In addition, lymphoscintigraphy was performed.

Inclusion and exclusion criteria

The inclusion criterion for this study was a history of one to three episodes of unilateral erysipelas in one leg. The diagnosis of erysipelas was based on the presence of the following: acute onset of sharply demarcated erythema, swelling and pain in one leg, and fever ($> 38{\cdot}5$ °C).

Excluded were patients with known risk factors for erysipelas, such as clinically evident lymphoedema, chronic venous insufficiency, pressure ulcers, diabetes mellitus, obesity (body mass index > 30 kg m^{-2}) or other skin diseases affecting the legs. Venous duplex ultrasonography was performed in all patients to exclude venous insufficiency.

Data collection and lymphoscintigraphy

The investigator completed a history and examined both legs. At 4 months after hospitalization, a qualitative and quantitative lymphoscintigraphy was performed. We used Tc-99m-labelled human serum albumin microcolloid particles. The colloid size (95% of the particles have a diameter of < 80 nm) is reproducible. The rapid clearance from the injection site makes the

colloid suitable for quantitative studies, and injections are painless.[10–12] Uptake of radioisotope in the groin lymph nodes as measured by lymphoscintigraphy was used as indicator of the degree of lymphatic drainage.

Protocol

In order to perform a reliable and reproducible quantitative lymphoscintigraphy, we used a standardized protocol: 40 MBq per injection is administered subcutaneously in the web space between the first and second and the second and third digits of the foot. A second 40 MBq dose is administered to the contralateral foot. Images are recorded with a dual-detector gamma camera (SKYLight®; Philips, Eindhoven, the Netherlands).

After injection, the first recording phase is static and the activity in the feet is monitored. Then the patient walks on a standardized treadmill (20 times; Buffalo Mini-Stepper®; Quelle, Fürth, Germany) to give maximal stimulation of initial lymphatic transport. In the second, dynamic, phase, time–activity curves are performed during 30 min for both groins when the patient is placed in a supine position between the dual-detector cameras. During the next static phase, the entire body area below the diaphragm is visualized. Then the patient is asked to walk at a brisk pace for 60 min without getting exhausted. The last recording phase is performed in the same way as the former.

Uptake percentages of the radioisotope in the groin lymph nodes and the clearance of the injection site on the feet are measured with the gamma camera. Qualitative and quantitative parameters are measured.

Qualitative and quantitative assessment of the results

Lymphoscintigraphy offers objective evidence to distinguish (late-stage) lymphatic pathology from nonlymphatic causes of peripheral oedema. Criteria for lymphatic dysfunction include delay (> 30 min), asymmetrical or absent visualization of regional lymph nodes, and the presence of 'dermal backflow'. Additional findings include asymmetrical visualization of lymphatic channels (normally three to five vessels per calf and one to two vessels per thigh) and collateral lymphatic channels. All these parameters are correlated to a clinically diagnosed lymphoedema.[13,14] We scored for six criteria as pathological signs of lymphatic impairment: P1, absence of radiotracer transport from the injection site; P2, delayed or absent flow after 30 min (proximal uptake vessels/groin within 30 min); P3, paucity or hypoplastic lymph vessels or absence of regional lymph nodes (normally three to five vessels per calf and one to two vessels per thigh); P4, collateral vessels; P5, hyperplastic or ectatic lymph vessels; and P6, lymphatic leaks and dermal backflow.

Interpretation of qualitative lymphoscintigraphy is highly subjective and it is difficult to quantify. Careful attention to technical performance and image evaluation is essential. It can help to distinguish between swelling of venous and lymphatic origin and may demonstrate an underlying lymphatic system abnormality.[14] We judged a qualitative lymphoscintigraphy to be pathological if one or more pathological signs were present (P1–P6).

Qualitative and quantitative lymphoscintigraphy results are usually in agreement. However, quantitative assessment can detect a reduction in lymphatic drainage capacity before clinical or qualitative lymphoscintigraphic signs appear. Quantitative analysis may thus increase the sensitivity and specificity of the lymphoscintigraphy in the early diagnosis of lymphatic disorders.[15]

In our protocol we measured uptake of radioisotope in the groin lymph nodes at 2 h in a standardized region of interest (ROI). When uptake in the ROI is < 15% there is a clear shortage of lymphatic drainage. An uptake between 15% and 20% is defined as borderline, and an uptake of > 20% as normal.[16] These data were confirmed by 20 scintigraphies in healthy control persons. These controls underwent the same lymphoscintigraphy protocol and were comparable for age and gender. Clearance of radioisotope from the foot was not taken into account in our study because these values are not reliable and are less sensitive for the diagnosis of lymphatic impairment compared with uptake percentages of the lymph nodes.[17–19]

Statistical analysis

The limb in which the diagnosis of erysipelas was made will be referred to as the affected limb, and the limb without erysipelas will be referred to as the nonaffected limb. The mean percentage uptake of Tc-99m-labelled human serum albumin in the groin lymph nodes in the affected limb was compared with the uptake in the unaffected limb and the mean paired difference was tested using the t-test for paired samples. The correlation between the uptakes in the groin lymph nodes in both legs was evaluated using Spearman's correlation coefficient. In additional analyses, both the affected and nonaffected leg were assigned to categories according to percentage of uptake in the groin lymph nodes. In these analyses, impaired lymph drainage was defined as an uptake of < 15%, whereas an uptake between 15% and 20% was considered to be borderline and an uptake of > 20% as normal. Using cross-tabulation we evaluated in which proportion of patients both the affected and nonaffected leg were impaired. All analyses were performed in SPSS (Chicago, IL, U.S.A.) and $P < 0{\cdot}05$ was considered statistically significant.

Results

Forty patients (28 male and 12 female) were included in our study. Their mean age was 39·3 years (range 11–66). A complete lymphatic investigation was performed in all patients. Main clinical characteristics are presented in Table 1.

The mean ± SD percentage of uptake in the groin lymph nodes in the affected limbs was 9·6 ± 8·5% vs. 12·1 ± 8·9% in the nonaffected limbs. The mean paired difference in

Table 1 Patient demographics and clinical characteristics

Age (years), mean (range)	39·3 (11–66)
Gender	28 M/12 F
Affected side (left/right)	21/19
Number of episodes of erysipelas (%)	
One	32/40 (80)
Two or three	8/40 (20)
Groin uptake after 2 h, % (mean ± SD)	
Affected side	9·55 ± 8·52
Nonaffected side	12·07 ± 8·89

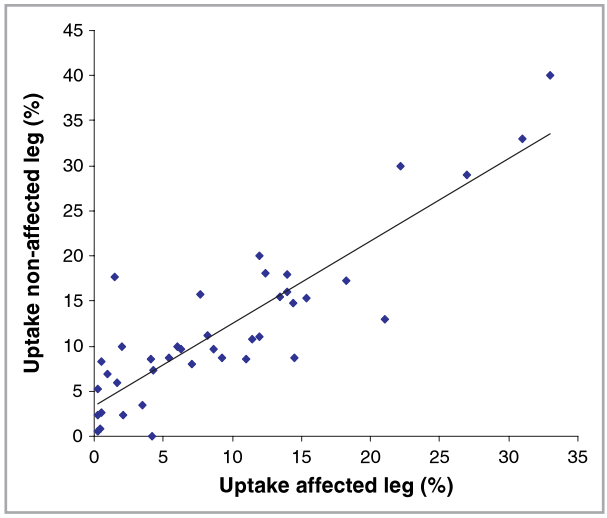

Fig 1. Relation between scintigraphic uptake in affected and nonaffected leg in patients with unilateral erysipelas (n = 40), showing a good correlation between both values (r = 0·81, P < 0·001).

uptake between nonaffected vs. affected side was 2·5% [95% confidence interval (CI) 1·1–3·9%]. This indicates that lymphatic drainage in the nonaffected limb was only slightly better than in the affected limb despite the infectious event in one of them.

There was a strong and significant correlation between percentage uptake in both legs as indicated by the Spearman's correlation coefficient, which was r = 0·81 (P < 0·001). The high and statistically significant Spearman's correlation coefficient implies that the hypothesis that there is no correlation between the two groups can be rejected. Also, in the nonaffected legs there were already signs of a disturbed lymphatic drainage, which was probably pre-existing before the erysipelas.

Figure 1 shows a graphical representation of the relation between the affected and the nonaffected limb. The percentage uptake of the injected radioisotope in the inguinal regions in the affected limb is plotted on the *x*-axis against the percentage uptake in the nonaffected limb on the *y*-axis. The plot clearly shows that the uptake percentage in the nonaffected leg decreases when the uptake percentage of the affected limb decreases. Finally, lymph drainage in both limbs was assigned to one of three categories: impaired (uptake < 15%), borderline (uptake 15–20%) or normal (uptake > 20%). Table 2 shows that there is strong agreement between both limbs: lymph drainage in 33 of 40 (83%) affected limbs was categorized as 'impaired' and in 26 (79%) of these 33 patients the nonaffected limb also fell into this category.

Table 2 Agreement between quantitative measurements in the affected and nonaffected limbs. Lymph drainage was categorized into one of three categories: impaired (uptake < 15%), borderline (uptake 15–20%) or normal (uptake > 20%)

	Affected leg			
Nonaffected leg	Uptake < 15%	Uptake 15–20%	Uptake > 20%	Total
Uptake < 15%	26	0	1	27
Uptake 15–20%	7	2	0	9
Uptake > 20%	0	0	4	4
Total	33	2	5	40

Table 3 Agreement between qualitative measurements (normal vs. pathological) in the affected and nonaffected limbs

	Affected leg normal	Affected leg pathological	Total
Nonaffected leg normal	16	12	28
Nonaffected leg pathological	3	9	12
Total	19	21	40

According to qualitative measurements, abnormal results indicative of lymph drainage impairment were observed in only 21 of 40 (53%) affected legs. Of these 21 patients, just nine (43%) showed qualitative pathology in the nonaffected leg (see Table 3). So the agreement in qualitative measurements between the affected and nonaffected leg was less pronounced than that in quantitative measurements.

Discussion

For a long time, erysipelas has been considered as a purely infectious disease generally caused by group A streptococci and which should be treated with antibiotics. No attention was paid to underlying diseases of the lymphatics. In many studies, it was suggested that the presence of fungal infections is an important predisposing factor for the development of erysipelas.[20–23] From a dermatological point of view, however, fungal infections and dermatosis of the feet are very common while erysipelas in these patients is not frequent at all. For example, in the Achilles project,[24] 13 486 patients visiting a dermatologist were studied and 58% had foot diseases, independent of their presenting medical complaints. Thus, we hypothesized that there must be other predisposing factors. In 1987 Stöberl and Partsch[25] studied retrospectively 16 patients

with erysipelas of the legs. In 11 patients the infection was unilateral and by using indirect lymphography they showed in six patients signs of bilateral abnormalities. They wondered if initial lymphatic impairment could contribute to the cause of the erysipelas.

The recurrence rate of erysipelas is high, up to 30–54%[26,27] after 2 years. Leclerc *et al.*[28] presented 47 patients with recurrent erysipelas, 55% of whom had persistent swelling and 30% local trauma/surgery preceding their erysipelas. They concluded that 77% had venous and/or pure lymphatic insufficiencies. Leclerc *et al.* concluded that antibiotic prophylaxis is indicated for recurrent erysipelas but did not address treatment of the lymphoedema. In a recent study, Cox[29] studied 171 patients with erysipelas and showed a 47% recurrence rate and 46% development of manifest oedema over a period of 3 years. He concluded that oedema is significantly correlated with erysipelas ($P < 0{\cdot}0002$). These results might also be interpreted to mean that several patients had pre-existing lymphoedema and developed permanent swelling due to clinical lymphoedema. Björnsdóttir *et al.*[3] mentioned two study groups (mean age 66·5 years) in which 56% of the 100 patients with erysipelas had swelling, compared with a control group of 200 persons, of whom 66% also had swelling (odds ratio 2·65, 95% CI 1·59–4·42). These figures support the idea that swelling in itself is not the issue, but that the swelling in erysipelas has a lymphatic origin. Vignes and Dupuy,[30] in 48 patients with breast cancer-related lymphoedema, demonstrated a recurrence rate of up to 26% after 1 year, despite the use of prophylactic antibiotics. Although there was a large variation in the severity of the oedema, the amount of oedema was no indicator for the risk of recurrence. Local immunological impairment can be a major factor in the risk of recurrent erysipelas. Mallon *et al.*[31] showed disturbances in efferent as well as afferent immunological pathways in patients with breast cancer-related lymphoedema. In none of the studies is the possibility discussed that locoregional sensitivity for erysipelas can be related to lymphological disturbances such as primary (subclinical) lymphoedema.

However, a study by Brorson and Svensson showed that prolonged use of adequate elastic stockings leads to a dramatic reduction of the recurrence rate.[32] Our own findings support this observation by showing that pre-existing lymphoedema is a significant risk factor for erysipelas. Logically then, prevention of post-erysipelas lymphoedema by compression will reduce recurrence rates.

Quantitative lymphoscintigraphy is a noninvasive, effective and safe technique to determine the functional status of peripheral lymphatic vessels. It does not differentiate between primary and secondary lymphoedema, but enables the physician to show functional deficits of the lymph transport capacity before the appearance of morphological clinical features which will eventually occur, such as nonpitting oedema, suprafacial fibrosis and epidermal changes. The literature provides little useful information about normal radioisotope uptake parameters by a sufficient lymph transport system. The protocol in this study was designed according to recommendations published by the Dutch Society of Nuclear Medicine.[16] We used a standardized lymphoscintigraphy protocol in which 20 healthy persons (20–35 years; no erysipelas or any other exclusion criteria; symmetrical gender distribution) were investigated to confirm the cut-off point of maximal uptake in the groin at 2 h mentioned in this guideline. All patients showed symmetrical uptake values between 20% and 25% after 2 h (M.J. de Haas, unpublished data). We realise that these figures may vary according to the camera equipment and radioisotope used, the method used and some biometric figures. The percentages may therefore differ between hospitals according to the use of different protocols.

In our group 90% (36/40) of patients with an episode of unilateral erysipelas also had demonstrable lymphatic disorders of the contralateral, nonaffected leg on quantitative lymphoscintigraphic examination when using a cut-off point of uptake > 20%. When lowering the cut-off point to 15%, 68% (27/40) still had objective impairment of the lymphatic system in the nonaffected leg. This implies that a significant number of patients, even without previously manifest swelling or signs of lymphoedema, has scintigraphic outcomes suggestive for a clinically compensated primary lymphoedema, that predisposes to erysipelas.

The results of our qualitative measurements show that the agreement in qualitative measurement between the affected and nonaffected leg was less pronounced when compared with the agreement in quantitative measurement. Moreover, when performing qualitative lymphoscintigraphy, the affected leg was less often diagnosed as having deficient lymph drainage. An explanation for these findings may be that qualitative lymphoscintigraphy cannot detect minor defects in lymphatic transport and is more accurate when there are already clinical signs of lymphoedema. On the other hand, abnormal scintigraphic features such as dermal backflow, anatomical changes or absence of lymph nodes would not be expected in patients without clinical signs of lymphoedema.

Because erysipelas is an acute infection spread in the suprafascial compartment by lymph vessels, postinfectious lymphatic impairment can be expected. The results of this study strongly suggest that initial lymphatic impairment already exists before the erysipelas occurs. Therefore we recommend that, after the initial antibacterial treatment of erysipelas, all patients should follow a lymphological therapy protocol including compression, skin care and garments in order to prevent development of significant lymphoedema and recurrence, which has been reported so frequently after erysipelas.

In conclusion, the causative role of lymphatic dysfunction in erysipelas has long been neglected. We show that bilateral impaired lymphatic drainage is strongly correlated with an episode of unilateral erysipelas, and therefore is likely to constitute an important, independent risk factor that may be responsible for the high recurrences rates observed in erysipelas. In support of this notion, we demonstrate significant lymphatic impairment in the affected leg as well in the nonaffected, clinically normal leg in patients with unilateral erysipelas. Quantitative lymphoscintigraphy seems best suited

to diagnose lymphatic impairment in this preclinical stage, in which a qualitative lymphoscintigraphy would not show any defects.

Consequently, treatment of erysipelas should address not only the infection itself but also the underlying lymphological impairment. We recommend that any therapeutic regimen include compression therapy and that patients be fitted with compression hosiery after completion of the initial therapy as is done in lymphoedema treatment. When erysipelas recurs, or occurs without any obvious risk factor such as chronic venous insufficiency, diabetes or pre-existing clinically evident oedema, the diagnosis of primary lymphoedema should be strongly considered and further investigated.

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