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Juvenile-onset localized scleroderma activity detection by infrared thermography

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Abstract

Objective. The aim of this study was to define the clinical utility of infrared thermography in disease activity detection in localized scleroderma (LS).

Methods. We retrospectively reviewed 130 thermal images of 40 children with LS and calculated the sensitivity and specificity of thermography, comparing clinical descriptions of the lesions and contemporary thermographs. The reproducibility of thermography was calculated by using the weighted kappa coefficient to determine the level of agreement between two clinicians who reviewed the thermographs independently.

Results. The sensitivity of thermography was 92% and specificity was 68%. Full concordance between the two clinicians was observed in 91% of lesions, with a kappa score of 0.82, implying very high reproducibility of this technique.

Conclusion. Our results demonstrate that thermography is a promising diagnostic tool when associated with clinical examination in discriminating disease activity, as long as it is applied to lesions without severe atrophy of the skin and subcutaneous fat. Further evaluation is needed to determine whether thermography can predict the future progression of lesions.

KEY WORDS: Juvenile localized scleroderma, Thermography, Assessment.

Localized scleroderma (LS) or morphoea is a rare disorder in children. In a study of adults and children the incidence of LS was 2.7/100 000 population per yr over a study period of 33 yr [1]. The severity of the disease varies widely from isolated plaques of morphoea to generalized morphoea, and to extensive linear lesions involving the limbs, the trunk and/or the face.

The course of LS is characterized by an initial phase of inflammation followed by progressive fibrosis, which can affect both the skin and the underlying tissues, and ultimately by atrophy. Involvement of deep subcutaneous, muscular and periosteal tissues is particularly important because it interferes with the growth of affected areas. This process potentially leads to irreversible structural deformities, particularly when the lesions affect the face, as in the *en coup de sabre* form, or the limbs, as in the linear form, resulting in joint contractures and limb length discrepancy [2, 3]. Therefore the aim of therapy is to arrest the disease early in its course in order to prevent the development of cosmetic and functional complications. This objective presupposes reliable and reproducible methods to detect disease activity and evaluate treatment efficacy.

Various treatments have been suggested for LS, such as oral steroids, UV light, γ-interferon, methotrexate, d-penicillamine, intravenous steroids and vitamin D_3, but most of the reports are anecdotal or case collections and only two double-blind controlled studies are available [4–7].

Thermography is a non-invasive technique that detects infrared radiation to provide an image of the temperature distribution across the body surface (Fig. 1). The skin temperature, under carefully controlled environmental conditions, is influenced primarily by the state of the skin vasculature or by the conduction to the skin surface of heat generated in deeper tissues. Some of the clinical applications of thermography in rheumatology reported so far are the assessment of inflamed joints [8, 9], the response to cold challenge of

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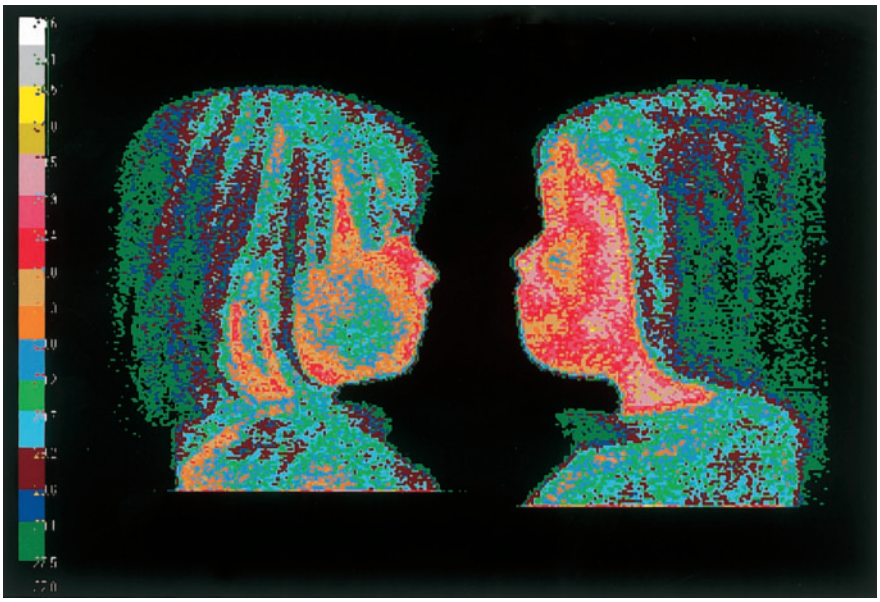

FIG. 1. Area of hyperthermia over the left side of the face (image on the right) in a patient with active *en coup de sabre* scleroderma. Temperature range 27–36°C.

the hands in Raynaud's phenomenon [10–12] and the evaluation of skin surface temperature in Paget's disease [13] and algodystrophy [14, 15].

The aim of this study was to determine if thermography has a potential role in detecting activity of LS lesions. Furthermore, the sensitivity and specificity of this technique were calculated and its reliability was investigated by analysis of the reproducibility between different physicians.

Methods

We retrospectively reviewed all the thermal images of children with juvenile LS managed at London's three collaborating centres: the Rheumatology Department at the Royal Free Hospital and the Paediatric Rheumatology and Dermatology Units at Great Ormond Street Hospital for Children.

All patients with onset of the disease before the age of 16 yr and who were examined between 1993 and 2000 were included in the study. The diagnosis of morphoea was based on the typical clinical appearance of the skin and soft tissues and associated deformity, confirmed when necessary by histopathology. The patients were separated into different disease subsets on the basis of the clinical appearance of the lesions. Morphoea was diagnosed when a single or few circumscribed sclerotic plaques with hypo- or hyperpigmentation were present on the skin. When there were multiple patches of morphoea (more than three or four) the condition was diagnosed as generalized morphoea. Linear scleroderma was defined when a sclerotic area had a band-like appearance over the limbs, often in an asymmetrical distribution, with subcutaneous fat and muscle bulk loss and often with impaired bone growth. The *en coup de sabre* subset was diagnosed when linear morphoea affected the face or the scalp, involving underlying subcutaneous tissues, muscle, periosteum and bone. Combinations of the different subtypes were noted.

All the thermographs were performed at the Royal Free Hospital by the same thermographer (KJH) with the same infrared camera (StarSight pyroelectric infrared imager; Insight Vision Systems, Great Malvern, Worcs, UK). Image processing and production were performed with Thermosoft software (EIC, Jenison, MI, USA) running on a 486–66 IBM-compatible PC.

All the patients were scanned in a temperature-controlled room at 23 $\pm$ 1°C, 10–15 min after acclimatization, wearing underwear only. Acclimatization is the time required to achieve stability in skin temperature and is considered to average of 15 min [16]. The technician was unaware of the clinical description of the lesions.

The lesions were considered positive to thermography when a substantial area more than 0.5°C warmer than the matching opposite limb or body area site was visible (or 0.5°C warmer than the surrounding skin if bilateral sites were involved or comparison was impossible for technical reasons).

The sensitivity and specificity of thermography in disease activity detection were examined by comparing the thermal imaging result with the clinical assessment derived from the medical records. To be included in the study, the clinical report had to be contemporary with the thermograms and contain extensive clinical description.

To improve the reliability of clinical descriptions, we elected to include only those written by four of the

TABLE 1. Clinical characteristics of patients

Type	*n*	F:M	Mean age at onset (yr)	Mean age at diagnosis (yr)	No. ANA-positive	Treatment
Morphoea	5	4:1	10	11.3	1/5	MTX (2), d-pen (1), IVS (3), MMF (1)
Generalized morphoea	2	2:0	7.5	8	1/2	MTX (2), d-pen (2), IVS (2), OS (1), none (1)
ECDS	8	3:5	3.8	6.6	6/8	MTX (3), IVS (2), OS (2), none (3)
Linear	11	8:3	5	5.5	9/10	MTX (4), d-pen (3), IVS (5), OS (2), CyA (1), none (2)
Linear + morphoea	14	9:5	5.4	5.6	6/7	MTX (9), d-pen (5), IVS (13), none (1)

ECDS, *en coup de sabre* scleroderma; MTX, methotrexate; d-pen, d-penicillamine; OS, oral steroids; IVS, intravenous steroids; MMF, mycophenolate mofetil; CyA, cyclosporin A.

authors, JH, DA, PW and CMB, who are all clinicians experienced in the assessment and management of patients with scleroderma.

To date there are no universally recognized criteria for activity and damage definition, so we defined the lesions as 'active' or 'inactive' depending on the clinical description, particularly on skin colour, texture, temperature and lesion size measurements. Lesions with the contemporary presence of hyperaemia, violaceous edge, warmth to touch, oedema with thickening of the skin and progressive extension were defined as 'active'. Lesions were defined as 'inactive' when described as having a pale or brownish colour, without thermal changes, of static size, and with softening and/or atrophy of the skin.

Disease-related deformities mentioned in the medical records, such as skin atrophy, subcutaneous fat loss, muscle bulk reduction, contractures and limb growth failure, were also noted.

To evaluate the inter-observer reproducibility of the technique, two paediatric rheumatologists (GM and KJM), experienced in thermography and blinded to both the clinical description of the lesions and to the thermography report, reviewed all the thermal images independently. Pair data were then analysed using the weighted kappa coefficient (κ) to determine the level of agreement between the two clinicians [17, 18]. The following scores indicate the relative agreement for values of the κ score defined according to the criteria of Landis and Koch [19]: >0.8 = almost perfect agreement; 0.6–0.8 = substantial agreement; 0.4–0.6 = moderate agreement; 0.2–0.4 = fair agreement; 0.0–0.2 = slight agreement, <0.0 = poor agreement.

Results

Patients

Forty-eight children with morphoea were identified and a total of 227 thermal images were reviewed. The thermographs were included only when accurate information on the features of examined lesions were available from the medical notes. After this selection, 40 patients and 130 thermograms were included in the study. Thirty-five patients were Caucasian, two Afro-Caribbean, two Asian and two Asian/Caucasian. The mean age at onset was 5.7 yr (range 0.5–15 yr) and the female to male ratio was 1.8 (26 females, 14 males). The clinical characteristics of the patients are shown in Table 1.

The most frequent subgroup was linear scleroderma, isolated or associated with one or more plaques of morphoea (11 and 14 patients respectively). Eight patients had *en coup de sabre* scleroderma, two of them having patches of morphoea over the rest of the body as well; five patients had localized morphoea and two had generalized morphoea. The characteristics of the different subtypes of scleroderma patients are presented in Table 1.

Twenty-three out of 32 patients (72%) tested for antinuclear antibodies (ANA) were positive.

Fifty per cent of the patients had developed more than two deformities because of the disease: the most frequent were subcutaneous fat loss and tissue atrophy (35 and 30 patients respectively) and muscle bulk reduction (19 patients). Twelve patients presented with severely impaired growth of the affected limb and 11 had developed joint contractures.

Lesions and thermograms

Sixty-eight clinically separable and independently assessed lesions were identified. The sites of the lesions were mainly the limbs (33 lesions on lower limbs, 16 on upper limbs). Ten lesions affected the face and scalp and nine were on the trunk.

Four lesions were present on similar aspects of opposite limbs; in these cases the temperature of the affected area was compared with that of the surrounding skin. For all the other lesions the temperature evaluation was performed by comparing the two matching opposite sites.

Among the 227 thermographs examined, 130 were included in the study, each of them having a contemporary detailed clinical description of the corresponding lesion derived from the medical notes. Fifty per cent of the lesions had been examined by thermography and recorded more than once, 25% being examined three or more times over the disease course.

Clinical–thermography agreement

The thermographic activity of all lesions assessed by GM and KJM is shown in Table 2. The sensitivity and specificity reached by GM were 92 and 68% respectively

Table 2. Clinical–thermography comparison by two observers (GM and KJM)

	GM		KJM	
	Thermography-positive	Thermography-negative	Thermography-positive	Thermography-negative
Clinically active	47/51	4/51	44/51	7/51
Clinically inactive	25/79	54/79	25/79	54/79

(positive predictive value 0.65), with full agreement between the clinical report and thermography in 47/51 active lesions and 54/79 inactive lesions.

KJM achieved a sensitivity of 86% and a specificity of 68% (positive predictive value 0.55). This observer found agreement between the clinical description and the thermography result in 44/51 active lesions and 54/79 quiescent lesions.

All the 11 lesions described as new according to the clinical descriptions were also positive on thermography. In 25 out of 79 examinations, lesions described as inactive were positive on thermography for both observers. We noticed that this phenomenon appeared to depend on lesion duration. The average duration of so-called false positive lesions was 58.6 months compared with 45 months in all the others. We observed that lesions that were warm on thermography but described as quiescent were in general older lesions with a severe degree of atrophy and subcutaneous fat and muscle bulk loss.

In order to confirm this observation, we calculated the sensitivity and specificity of thermography in lesions with duration 2 yr. We found that they were 81 and 87.5% respectively (positive predictive value 0.87), with full agreement between the clinical description and the thermography result in 42/50 lesions, 21/24 clinically active and 21/26 inactive.

Furthermore, the site of the lesion influenced the disagreement between the clinical description and the thermography result. Thirty-nine per cent of thermograms performed on lesions affecting the face and the scalp were falsely positive in comparison with 17 and 12% of those performed on limb and trunk lesions respectively.

Inter-observer agreement

GM and KJM performed an independent review of 112/130 thermograms: both were unaware of the thermal image report and the clinical description of the corresponding lesion. The result of the comparison is shown in Table 3. There was full concordance between the two observers in 102/112 (91%) lesions examined and the κ score was 0.82 (95% confidence interval 0.714–0.926), which implies almost perfect agreement between the two physicians in thermography interpretation.

Table 3. Clinical observer (GM–KJM) agreement

	KJM positive	KJM negative	Total
GM positive	56	7	63
GM negative	3	46	49
Total	59	53	112

Discussion

Disease activity detection in LS is a fundamental problem, both in the evaluation of the need for treatment and the assessment of its efficacy over time. Unfortunately, there are no objective methods of assessing disease activity and laboratory tests are not helpful for this purpose.

Several skin scoring systems have been proposed and validated for systemic sclerosis based on skin thickening extension and its changes over time [20], but these scores are not applicable to isolated lesions. The serial measurement of the lesions is often unreliable because of the difficulty in defining the exact border of the lesion itself. Similarly, the sensation of warmth to touch, suggesting activity of the lesion, is a subjective finding.

The use of thermography for activity detection was described for the first time by Allen *et al.* in 1987 [21]. The authors reported a case of a patient with rapidly progressive generalized morphoea and they monitored the response to treatment with pulse intravenous methylprednisolone by clinical assessment, laboratory tests and thermography examination. They showed that clinical improvement after therapy was confirmed by cooling of the lesions on thermography.

Birdi *et al.* [22] examined once by thermography 18 lesions in 11 children with linear scleroderma. In that study, all three extending lesions were positive and all three resolving lesions were negative on thermography, while three out of 12 clinically unchanged lesions were thermography-positive.

Such reports, suggesting a possible role for thermography in the assessment of morphoea, do not give any information on its use over time, nor do they indicate either its reproducibility between different observers or the factors possibly affecting its reliability.

In our study we compared thermographic assessments with clinical descriptions of lesion activity recorded at the time of imaging, and we found that thermography had a sensitivity of 92% and a specificity of 68%. Specificity was even higher in new and recent lesions (87.5% in lesions examined within 2 yr of onset), with a high positive predictive value (0.87). This observation suggests that thermography is helpful in investigating the blood flow changes occurring in the initial stages of the disease.

The rate of false positivity of thermal images increases in old lesions characterized by skin atrophy, loss of subcutaneous fat and reduction of muscle bulk. Similarly, the thermograms performed on lesions of the face or scalp, where the skin and subcutaneous tissues are thinner and thus more rapidly altered by the atrophic process occurring in the disease, are more frequently positive despite the clinical features of inactivity. An intact subcutaneous fat layer constitutes an insulating barrier against metabolic heat conduction towards the skin surface. Therefore we could suggest the hypothesis that these observations may be explained by an alteration in heat transfer through the atrophic subcutaneous fat layer, resulting in skin hyperthermia detected by the infrared camera. On the other hand, hyperthermia observed over an area without lipoatrophy is likely to be caused by the microcirculatory changes occurring during the inflammatory process taking place within the dermis [23].

In the present study we evaluated the level of agreement between different observers in interpreting thermal images in order to calculate the reproducibility of this technique as a measure of its reliability. Our results show very high reproducibility between observers ($\kappa = 0.82$), strongly suggesting the value and reliability of the technique in assessing LS lesion activity.

As with all diagnostic tools, thermographic examination of the area of interest has to be applied in the appropriate clinical context, with the purpose of either confirming or excluding a suspected clinical diagnosis or narrowing the diagnostic possibilities.

Our results demonstrate that thermography is a promising diagnostic modality when associated with clinical examination in discriminating disease activity, as long as it is applied to lesions without a severe degree of skin and subcutaneous fat atrophy. Further investigations are necessary to study the relationship between dermal thickness, subcutaneous fat loss and the degree of hyperthermia observed with thermography.

Thermography is likely to have application in monitoring the response to treatment, as suggested by Allen *et al.* [21]. The retrospective nature of our study does not allow us to speculate on this issue or to evaluate the possible role of thermography in predicting the disease course. For this purpose, prospective studies are required with serial thermographic examinations in order to evaluate disease progression or arrest, to develop methods to quantify the degree of hyperthermia and to define the lesion extension clearly.

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