Title:

A cross-sectional study comparing paediatric and adult onset linear morphoea in a large tertiary referral centre

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ABSTRACT:

Linear morphoea (LM) is an uncommon and severe subtype of morphoea affecting the trunk, limbs and/or craniofacial sites. It can be potentially debilitating, with extracutaneous manifestations (ECM) and permanent disfiguring scarring. LM is more prevalent in paediatric populations, and our knowledge of disease in adults is limited.

Utilising the unique patient cohort at our tertiary-referral scleroderma service, we conducted a clinico-epidemiological study of patients presenting with LM from January 2014 to April 2017, aiming to characterise our large adult cohort, and compare adult and paediatric-onset disease. Of 298 patients with morphoea, 133 had LM; 78.9% were female; 43.6% had adult-onset LM. Mean age of disease onset was 10.4 years in paediatric-onset vs. 35.5 years in adult-onset. Those with paediatric-onset LM had significantly more cumulative irreversible disease related damage, with a mean peak mLoSDI score of 19.5 (95% CI: 17.0-22.0) vs 8.1 (95% CI: 4.4-11.8) in the adult-onset group (p<0.001). Significantly more patients with adult-onset LM had quiescent disease (controlled on therapy or in remission) than those with paediatric-onset LM (22 (55.0%) vs 9 (29.0%), p=0.0332). ECM were recorded in 76 (57.1%) patients, including Raynaud's in 26 (19.5%). Fatigue, joint involvement and raised eosinophil counts were more prevalent in those with >1 affected body site (p<0.05). ANA was positive in 40.4%, raised ESR in 25.0% and raised immunoglobulins in 27.3%. The most commonly prescribed treatments were methotrexate (73.7%), 0.5% tacrolimus ointment (48.1%) and intravenous pulsed methylprednisolone (45.9%).

To our knowledge, we have described the largest cohort of adults with LM. The prevalence of ECM, joint involvement and raised serological markers, highlights the systemic nature of LM. Cumulative disease damage is of particular concern amongst those with paediatric onset LM; these patients were younger, had longer disease duration and more severe functional impairment. There is hence justifiable need for close monitoring to enable early detection and appropriate treatment of chronic or renewed disease activity in adults with LM, if clinicians are to successfully halt and prevent further irreversible cosmetic disfigurement and loss of function.

INTRODUCTION

Morphoea (also referred to as localised scleroderma) is a connective tissue disease (CTD) characterised by fibrosis of the skin and underlying subcutaneous tissue. It is estimated that two thirds of patients with morphoea develop disease in childhood [1-2]. Linear morphoea (LM) is the most common subtype in the paediatric population, affecting approximately 65% of children with morphoea [3-4].

Linear morphoea may involve any body site, with the limbs most commonly affected in paediatric onset disease [5]. The craniofacial structures can also be affected, manifesting as en coup de sabre (ECDS) or progressive hemifacial atrophy (PHA) (otherwise known as Parry-Romberg Syndrome) [6-7]. When severe, LM can extend to involve the deep structures (including the fascia, muscle, joints / bones), potentially resulting in significant functional impairment. Craniofacial LM may be complicated by ocular and/or cerebral involvement, which requires specific investigation and aggressive treatment. In addition to local complications, LM is associated with extracutaneous manifestations (ECM) in approximately 30% [8]. These are widespread symptoms which are unrelated to the anatomical site of the morphoea and can include arthralgia, myalgia, headaches and gastrointestinal disturbance [9]. Hence ECM suggests systemic inflammatory processes are involved in LM.

Accordingly, LM usually requires systemic treatment, aimed at halting disease progression and preventing ongoing irreversible tissue damage. In paediatric populations, stabilisation of disease can take approximately 5 years [4]. One third of patients have disease activity at 10 years, with some experiencing long periods of quiescence prior to re-activation [5,10]. Disease duration and rate of relapse is higher in paediatric-onset morphoea, and relapse rates appear to be higher still, in paediatric onset LM affecting the limbs [11]. Unfortunately, morphoea is notoriously undertreated and its severity under recognised, which can result in irreversible disfigurement and functional impairment [12].

Compared to paediatric onset LM, less is known regarding the comparative phenotype and trajectory of LM in adult-onset disease [13]. Predictably and logically, adults with paediatric-onset morphoea have been found to have a longer duration of disease, higher disease damage scores, but lower overall disease activity, compared to adults with adult onset LM [14]. Treatment modalities utilised in adult-onset patients are also largely derived from research and guidelines in paediatric populations [15] and there is some discordance in treatment even within the better recognised paediatric group [17]. Further, despite methotrexate being first line in the management of paediatric LM, it is underused in adults [16]. Hence there is a need to compare adult with paediatric versus adult onset LM, as these populations may be heterogeneous, thus requiring a different clinical approach, with the potential to change long term outcomes.

Here, we describe the results of a clinico-epidemiological study of LM in a large adult tertiary referral specialist centre. We aim to identify clinically relevant differences between adults with paediatric versus adult onset disease, which may provide insights into variable clinical approaches needed in these populations.

METHODS

This was a clinico-epidemiological cross-sectional study of adult patients with paediatric or adult onset LM at a multidisciplinary dermatology / rheumatology, adult tertiary referral CTD centre, seen between January 2014 and December 2016.

Demographic, clinical and biochemical parameters were retrospectively obtained from electronic medical records. The anatomical distributions of disease were classified as trunk, limb and craniofacial subtypes, with a maximum of 6 possible affected anatomical sites - trunk, craniofacial (head/neck), left upper limb, right upper limb, left lower limb, right lower limb. Extracutaneous manifestations were defined in accordance with previous literature, to include constitutional symptoms (fatigue, myalgia, arthralgia), gastrointestinal (dyspepsia / gastroesophageal reflux), Raynaud's phenomenon, neurological (seizures, ocular involvement), and/or inflammatory arthritis (not including rheumatoid arthritis which was defined as an associated autoimmune condition). Associated autoimmune diagnoses included autoimmune thyroid disease, rheumatoid arthritis, connective tissue disease, vitiligo, psoriasis, pernicious anaemia and inflammatory bowel disease.

Key clinical characteristics were collected at first presentation to our centre. Disease severity across 18 body sites was measured using the Localised Scleroderma Cutaneous Assessment Tool (LoSCAT), comprising the modified Localised Scleroderma Skin Severity Index (mLoSSI) to denote disease activity, and the modified Localised Scleroderma Skin Damage Index (mLoSDI) for disease damage[18,19]. The mLoSSI scores each body site with a score from zero to three for the presence or absence of new or enlarging areas of skin involvement, as well as severity of erythema and skin thickness (total possible score of 54). The mLoSDI scores each body site with a score from zero to three for the severity of dermal atrophy, subcutaneous atrophy and dyspigmentation (total possible score of 54). Scores were collected at presentation and highest scores noted during follow-up. A subset of patients were analysed with regards to treatment response. Treatment response was defined as

- Active disease; an increasing mLoSSI at the final visit, compared to the preceding visit.
- Controlled disease; stable mLoSSI at final visit, compared to preceding visit, whilst on treatment.
- Remission; no activity on the mLoSSI, while on or off treatment.

Results were expressed as absolute numbers and percentages for categorical data, and mean or median (95% confidence interval, interquartile range) for continuous variables. Independent samples t-tests and Mann-Whitney U tests were used to compare normally and non-normally distributed continuous variables respectively, $\chi2$ test for the evaluation of categorical data, and the Fisher exact test was applied where any cell had a value of less than 5. Associations between disease duration, timing of onset and activity were assessed using logistic regression. A p-value of less than 0.05 was considered significant. Statistical analysis was conducted using IBM SPSS Statistics 24 and Stata 15.

This study was part of a larger audit, registered with the Royal Free Hospital London NHS Foundation Trust.

RESULTS

Demographics

A total of 298 patients were seen with a diagnosis of morphoea during the study period. Of these, 135 (45.3%) had LM. Two were excluded due to insufficient data, leaving 133 study participants. Demographics are further described in Table 1.

Disease distribution and subtype

There were no significant differences in disease distribution or observed subtypes between paediatric and adult onset disease (Table 1). As expected, mean disease duration in patients with paediatric onset was much greater than in those with adult onset (19.9 v 9.5 years). Of all subjects, 54.9% (n=73) had one site affected, 20.3% (n=27) had two, 16.5% (n=22) had three and 7.5% (n=10) had four affected body sites.

A majority of patients (n=89, 66.9%) had limb involvement. Seven patients (5.3%) had LM of the trunk and/or limb(s) along with craniofacial LM, all of whom had adult onset disease (Figure 1).

Thirty-six patients (27.1%) had mixed plaque morphoea and LM. Of these, two had disseminated plaque morphoea (with plaques affecting 3 or more anatomical sites) and the remaining 34 patients (94.4%) had limited plaque morphoea affecting the trunk only. Most with mixed pattern (n=34, 94.4%) had LM occurring on the limb(s) (including two with concomitant craniofacial LM). The remaining two patients (5.6%) had LM limited to the head/neck (no limb or trunk LM involvement), with limited plaque morphoea affecting the trunk.

The classic onset of LM was characterised by skin tightness or thickening in 77.4% (n=103) patients (Table 1). Eighteen patients (13.5%) skipped both the clinical inflammatory and sclerotic phase, demonstrating atrophy and/or dyspigmentation only (Figure 2), including a preponderance of those with craniofacial LM (n=14, 77.8%).

Triggers and associated autoimmunity

A potential triggering event preceding disease onset by 6 months or less was recorded at presentation in 16.5% (n=22) of patients overall, including 20 with preceding local mechanical trauma and 2 cases of reported tick bite with positive Borrellia serology.
No patients reported a known or suspected family history of morphoea or systemic sclerosis.

Associated autoimmune diagnoses were reported in 11.3% (n=15) of patients, with a trend towards a higher prevalence amongst those with adult onset disease, although not significant. Autoimmune thyroid disease was the most prevalent, occurring in 4.5% (n=6) of patients.
ANA was tested in 89 patients and showed reactivity (at a titre of greater than 1 in 1000) in 40.4% (n=40). There was no association between ANA positivity and the presence of an autoimmune disease (P = 0.954).

Blood parameters

There were no significant differences in eosinophil counts, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) or immunoglobulins overall, between those with paediatric and adult onset LM. There was also no significant difference between the mean peak and lowest values of these parameters during follow-up in the combined cohort.

Overall, raised inflammatory markers (CRP >5mg/L, ESR according to age) were present in 27 patients (25.0%), with a raised ESR more prevalent than a raised CRP (P = 0.029).

At presentation, peripheral eosinophil counts were measured in 115 patients. A peripheral eosinophilia (defined as >0.5x10^9/L) was present in 18 (15.7%) patients. Those with more than one body site had significantly higher peripheral eosinophil counts compared to those with one body site affected (P = 0.056).

Immunoglobulins were tested in 44 patients. A raised IgG and/or IgM was present in 12 (27.3%).

Cutaneous symptoms

Pruritus, pain, swelling, tightness, tingling and/or numbness, were present at time of presentation in a total of 89 patients (66.9%), with similar prevalence in adult and paediatric onset LM.

Local cutaneous symptoms were more prevalent amongst those with LM of the trunk/limbs compared to craniofacial LM (P = 0.001, OR 3.4 [95%CI: 1.4-7.5]). In particular, pruritus was significantly more prevalent in those with LM of the trunk/limbs compared to craniofacial LM (38.5% (n=30) vs 16.4% (n=9), P = 0.006), as was pain (including headache as reported by those with craniofacial LM) (52.7% (n=29) vs 33.3% (n=26), P = 0.025).

Extracutaneous manifestations

In total, ECM were recorded in 76 (57.1%) patients (Figure 3), with similar prevalence in adult and paediatric onset groups.

Fatigue was more prevalent amongst those with more than one body site affected (25.0% (n=15) vs 8.2% (n=6), P = 0.008), compared to those with only one involved site.

Gastrointestinal symptoms (dyspepsia / reflux) were somewhat more common in those with LM of the trunk/limbs compared to craniofacial LM (15.4% (n=12) vs 5.5% (n=3), P = 0.075).

Excluding local skin tingling, neurological manifestations were exclusively noted in those with craniofacial LM (n=9, 6.8%). This included seizures in 2 patients (1.5%) and ocular involvement (including localised visual symptoms, adnexa abnormalities of the eyelid or eyelashes and/or anterior segment inflammation (episcleritis, anterior uveitis)) in 8 (6.0%).

Inflammatory arthritis was confirmed in 6 (4.5%) patients, with an overlap rheumatoid arthritis (with positive serology, and hence noted as an associated condition) in 2 cases.

Functional impairment

There was a trend towards an increased prevalence of functional impairment amongst those with paediatric onset disease, compared to those in the adult onset group, however this trend was not significant. Functional impairment was also more prevalent in those with multiple affected body sites compared to those with only one affected site (33.3% (n=20) vs. 17.8% (n=13), P = 0.045).

89 patients had LM of the limb(s), with a total of 130 limbs affected (62 upper limbs and 68 lower limbs), 109 (83.8%) of which involved morphoea crossing one or more joints. This resulted in limited range of movement / contractures in 28 (32.2%) patients.

6 patients (10.9%) with craniofacial LM (n=55) had recorded jaw / dental complications.

Disease severity scores

Amongst all LM patients, DLQI scores were serially recorded in 53 (39.8%). Amongst these, the mean peak DLQI score (at presentation or during follow-up) was 9.5 (95% CI: 7.7-11.4), with no significant difference in quality of life disease impact between adult and paediatric onset disease (9.8 vs 9.3, P = 0.526) (Table 1).

Objective disease severity scores were serially recorded in 55 patients (41.4%), with a mean peak mLoSSI (at presentation or during follow-up) of 10.7 (95% CI: 8.5-12.9) and mLoSDI of 14.9 (12.4-17.5). There was no significant difference in mean peak mLoSSI scores between those with adult and paediatric onset disease; however those with paediatric onset LM had significantly more cumulative

damage as reflected by a mean peak mLoSDI score of 19.5 (95% CI: 17.0-22.0) compared to 8.1 (95% CI: 4.4-11.8) in the adult onset LM group (P < 0.001).

There was a weak but significant linear association between mLoSSI and DLQI scores (r = 0.39, P = 0.023).

Treatment

Prescribed treatments were similar between adults with paediatric and adult onset LM groups.
The most commonly prescribed treatments were methotrexate (73.7%), 0.1% tacrolimus ointment (48.1%) and intravenous pulsed methylprednisolone (45.9%). In total, 78.9% were treated with systemic therapy (Figure 4).

After methotrexate, mycophenolate mofetil (MMF) was the next most commonly prescribed steroid sparing agent (23.3%), and 96.8% of these patients also received methotrexate either concurrently or preceding a switch to MMF.

A total of 43 patients (32.3%) required more than one systemic steroid-sparing agent to obtain disease control. All but 3 of these patients also received systemic corticosteroids. In addition to methotrexate, MMF and hydroxychloroquine, other systemic agents included ciclosporin, cyclophosphamide and tacrolimus.
Combination or multimodal systemic treatment with steroid sparing agents was more likely to be required amongst those with more than one body site affected, compared to those with only one involved site (43.3% vs 23.3%, P = 0.014, OR = 2.5 [95% CI: 1.2-5.3]).

Phototherapy was utilised in a minority of cases (n=18, 13.5%), of whom the majority (72.2%) were concurrently or subsequently treated with a systemic agent. Ultraviolet-A1 was the most commonly utilised phototherapy modality (55.6%), followed by topical or bath psoralen (P)-UVA (50%).

Topical therapies were prescribed in the majority of cases (63.9%). Topical treatments were utilised in isolation in 23 patients.

Outcomes

Excluding those with only craniofacial LM, at the last recorded visit during the study period, outcome data on disease control and remission were available for 71 (53.4%) patients. Nineteen (26.8%) had disease that was controlled on treatment, and a further 12 (16.9%) had disease which was in remission off therapy; all but 3 had required systemic therapy to achieve these outcomes. The remaining 40 patients (56.3%) had active disease, with increasing mLoSSI scores, requiring escalating therapy.

Univariable analysis demonstrated some evidence for association between activity and timing of disease onset with significantly more patients with adult onset LM having quiescent disease (controlled on therapy or in remission) than those with paediatric onset LM (58.6% vs 33.3%, p = 0.035). There was no evidence for effect of disease duration on activity (OR 1.03, 95%CI 0.98, 1.07; p=0.227). Even after adjusting for disease duration, there was still some weak evidence for association of onset timing and activity with subjects with paediatric onset LM having over 2.5 times greater odds to have active disease (OR 2.59, 95%CI 0.9, 7.6; p=0.083).

DISCUSSION

We have described a unique and large cohort of adult patients, with paediatric and adult-onset LM, from a single site, adult tertiary referral centre. Overall, our data confirms LM to be a severe disease, regardless of age of onset. This was reflected by the prevalence of cutaneous symptoms (66.9%), extracutaneous manifestations (57.1%), functional impairment (24.8%), high peak DLQI scores, findings suggesting the presence of systemic autoimmunity (such as ANA positivity in 40.4% and an associated autoimmune condition in 11.3%) and the need for multiple systemic therapeutic agents to achieve disease quiescence in many. Previous published cohorts largely describe paediatric populations, but all confirm the systemic nature of LM [3,4,24], recognised extracutaneous manifestations (including Raynaud's phenomenon and gastrointestinal symptoms) [3,11,20,24], ANA positivity, [3,20,28] and the need for systemic treatment with Methotrexate +/- corticosteroids as first line therapy [8,17,24]. Mazori et al also recently demonstrated the significant functional impairment, presence of associated autoimmune conditions and need for methotrexate systemic therapy in a cohort of adults with adult onset LM [10].

However, as well as being younger, there were other clinically relevant differences between those with paediatric and adult onset LM in our adult cohort.

Predictably, a higher peak mLoSDI was seen in those with paediatric onset LM compared to those with shorter duration adult onset disease. This no doubt reflects longer-term on-going accumulation of damage over time. However this occurred despite regular review and treatment, suggesting a lack of overall disease control, and hence ongoing activity over time. Similarly, Martini et al reported a more aggressive disease-course in paediatric onset disease, with more relapses and activity after 10 years, compared with other morhoea subtypes [25]. Whilst the nature of the disease course specifically in LM is largely unpredictable, chronic disease activity and/or recurrent relapses are not uncommon, and appear to be more prevalent in paediatric onset disease [4, 7-8, 10-11]. Accordingly, longer duration systemic therapy of up to 4 to 5 years is now often recommended [8].

Interestingly, Condie et al found higher disease damage, as noted by physician global assessment scores, but not mLoSDI, in adults with adult onset compared to paediatric onset morphoea of all subtypes [14]. This was in a very large cohort of over 300 patients. This slight discrepancy in findings may reflect the true severity and on-going accumulation of damage in LM, compared to other morphoea subtypes, in adults with paediatric onset disease.

Despite the difference in mLoSDI scores between sub-groups, the number of body sites affected was similar. This suggests that clinically significant tissue damage in each body site becomes more severe over time in these patients, rather than more body sites necessarily becoming involved.

Notably, and as a consequence of greater damage, there was a trend towards higher functional impairment in the paediatric-onset group (although not statistically significant). This finding is perhaps predictable, and has been replicated in a large group of patients with paediatric-onset morphoea [11].

Also in keeping with the lower mLoSDI scores recorded in those with adult onset LM, significantly more patients in this group had quiescent disease; either on treatment or in remission off treatment. This could be interpreted as surprising, as one may predict less disease activity and better disease control in the paediatric onset group who are in some case a great many years further from disease onset. Hence this finding may potentially imply that adult-onset disease is easier to clinically control, and, in keeping with anecdotal and expert opinion, that adult onset LM might simply have a shorter natural history overall, hence becoming quiescent sooner after diagnosis. Notably however, other authors have not necessarily confirmed this result [10, 14], and we did not study patients with paediatric onset LM whose disease did not extend into adulthood.

Interestingly, there were similar peak DLQI scores between groups, despite higher mLoSDI scores amongst those with paediatric onset disease. Of note, DLQI did however appear to correlate with mLoSSI scores, suggesting DLQI perhaps reflects disease activity rather than damage. Somewhat similarly, Condie et al

described more favourable health-related quality of life scores in adults with paediatric onset compared to adult onset morphoea (all subtypes), with less disease activity and higher damage scores in the former [14].

As reported by others[21], there was a trend towards more autoimmune diagnoses in the adult-onset sub-group in our cohort; particularly autoimmune thyroid disease. Associated autoimmunity is well recognised amongst patients with morphoea[29,] and our findings again confirm both the systemic nature of LM, and the need for clinically guided active screening for autoimmune conditions, amongst all patients with LM.

Despite the disease's severity and the need for early systemic therapy to prevent irreversible tissue damage, delayed diagnosis is unfortunately well reported in morphoea[12]. Our data demonstrated a mean delay to diagnosis for all patients of 24 months, which has been similarly corroborated in a study of adult-onset patients[10]. Despite LM being better recognised in the paediatric population, we did not note a difference in time to diagnosis between sub-groups, however this may reflect selection bias of severe disease seen in our specialist centre. Milder disease may be more difficult for referring clinicians to recognise.

In our cohort, large numbers in both sub-groups required systemic agents to gain disease-control and hopefully prevent functional impairment. Despite this, and the fact that approximately one third of our patients were on multimodal systemic therapy, over half of our cohort had ongoing disease activity with mLoSSI scores trending upwards. This again reflects the severity of LM, findings in previous studies [4,11, 21], the latest clinical guidelines [8,17,26] and perhaps the specialist tertiary referral setting of our study.

Unfortunately however, despite evidence to firmly suggest the severity of LM and need for systemic therapy as first line therapy in all LM (aside from mild superficial, adult onset disease, that does not cross joints)[8], there remains reticence amongst clinicians to actively treat LM with early systemic therapy [14-22]. Studies have demonstrated significant variability in treatment decisions between dermatologists and rheumatologists, with dermatologists more likely to prescribe topical treatments and phototherapy[12]. Thus, under-treatment of morphoea undoubtedly allows active disease to progress in an irreversible fashion, and may account for some of the functional impairment seen in our paediatric-onset group. Increased dissemination of published treatment guidelines [8,17, 26-27] and larger published cohorts will hopefully improve this with time.

Finally, we found that in patients with more than one involved body site, there was a higher prevalence of elevated ESR, eosinophilia, fatigue, functional impairment and requirement for multimodal systemic therapy. These parameters can all be rationally linked with increased disease severity. Thus at presentation, more than one body site involvement should flag the need for early and more aggressive treatment. Interestingly, cutaneous symptoms were less prevalent in craniofacial disease, thus adding to the challenges of monitoring this group, where local symptoms may be a less helpful marker of disease activity and progression, and clinical monitoring can be most challenging overall.

It is important to interpret the results of this study with a number of limitations in mind. Notably, the study's retrospective nature means there is missing data, especially relating to treatment and outcomes. Consequently we have been unable to assess time to remission, despite this being an important clinical characteristic which may vary between paediatric and adult onset disease, and may be associated with disease activity at any given time. Many clinicians were involved in the care of our patients, resulting in inter-observer variability with regards documentation of disease morphology, activity and damage. The patients in our cohort may also have had greater disease severity due to referral and selection bias, as the study was conducted at a highly specialised single site tertiary referral adult scleroderma centre. This work emphasises the need for further prospective studies looking at adult morphoea populations, who are less well studied compared to their paediatric counterparts.

In conclusion, LM in adults is a severe disease, regardless of age of onset. Cumulative disease damage is of particular concern amongst those with paediatric onset LM; these patients were younger, had longer disease

duration and more severe functional impairment. There is hence justifiable need for close monitoring to enable early detection and appropriate treatment of chronic or renewed disease activity in adults with LM, if clinicians are to successfully halt and prevent further irreversible cosmetic disfigurement and loss of function.

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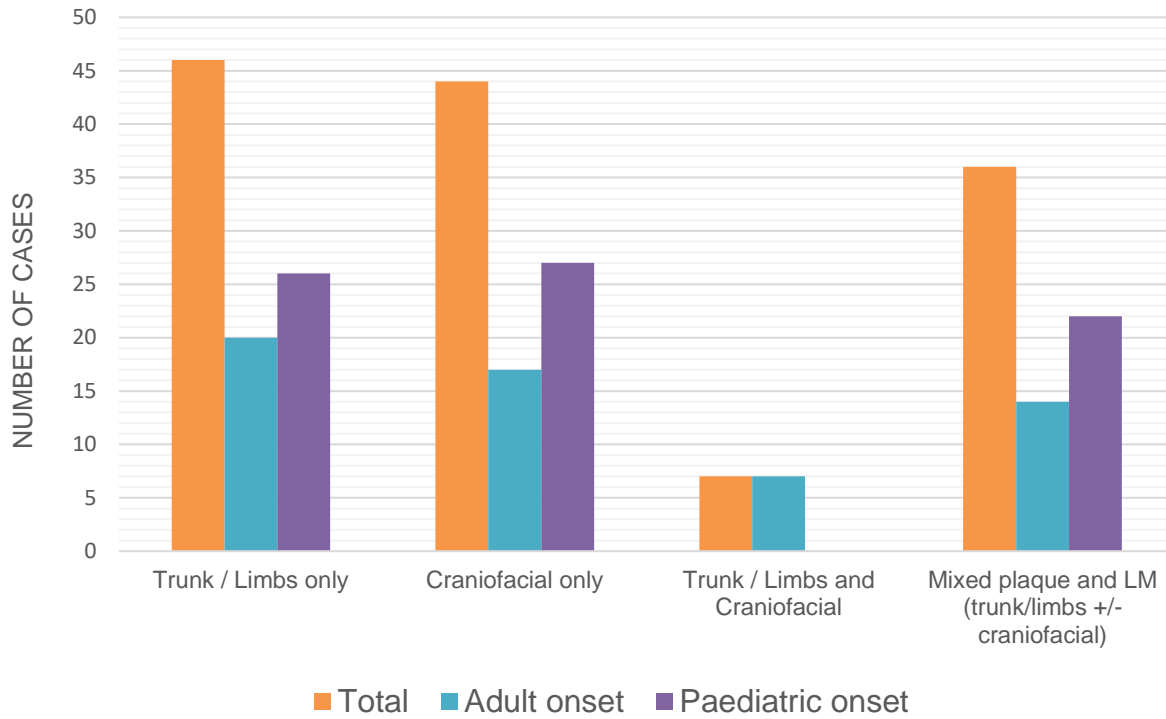
Figure 1. Linear morphoea anatomical distribution; anatomical subtype prevalence amongst total cohort, those with adult and paediatric onset disease.

Figure 2a: LM affecting the right arm causing brown dyspigmentation and atrophy of the underlying muscle resulting in a guttering appearance.

Figure 2b: Craniofacial LM showing a linear atrophic band with sclerosis extending from the right mid-eyebrow to the scalp with associated alopecia

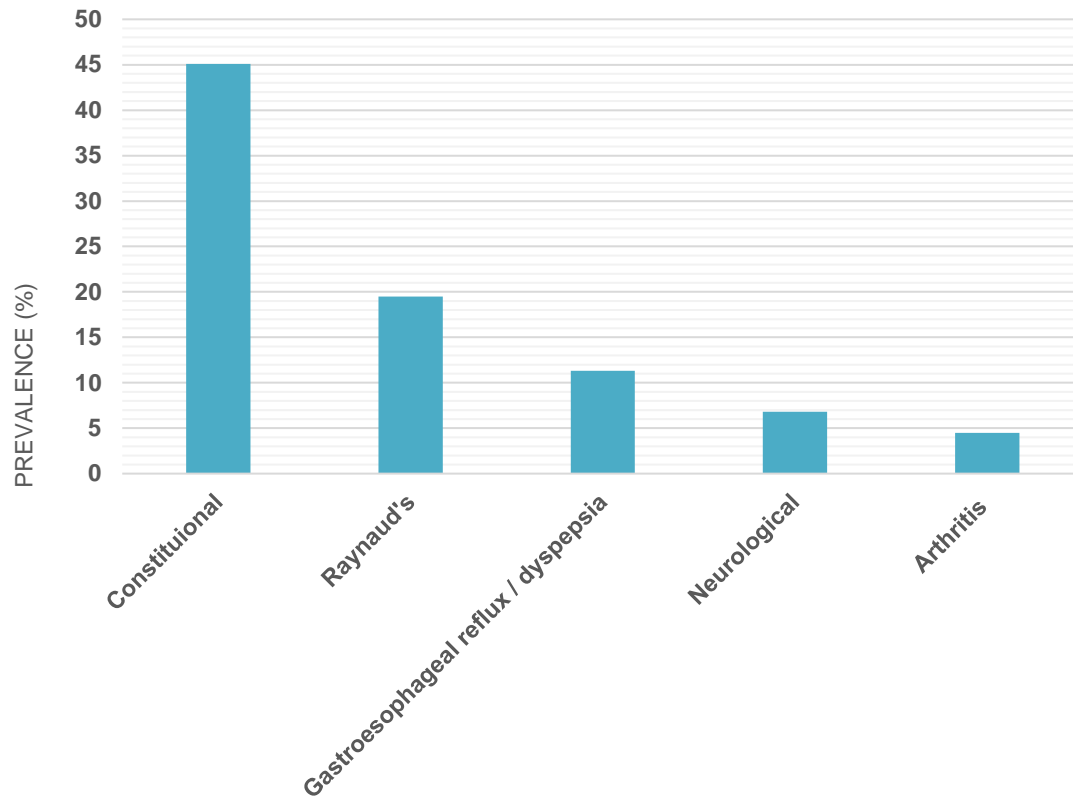**Figure 2c:** Craniofacial LM showing patchy dyspigmentation affecting the left side of the face

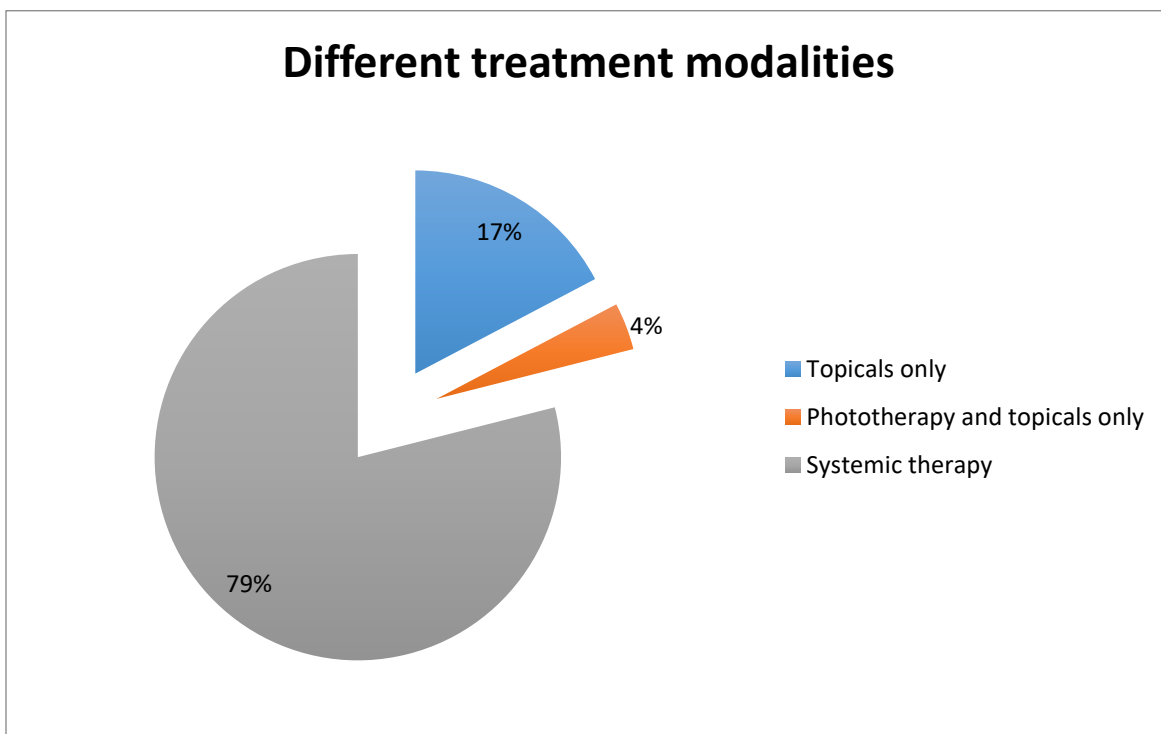**Figure 3.** Prevalence of reported extracutaneous manifestations (% of total cohort, n=133)

Figure 4. Treatment modalities utilised amongst LM patients

Table 1. *Clinical characteristics; overall linear morphoea cohort, and differences between adult and paediatric onset populations.*

	Overall Cohort	Adult onset	Paediatric onset	Significance, p-value~
Demographics				
Overall cohort; n (% of total LM cohort)	133 (100)	58 (43.6)	75 (56.4)	N/A
Female; n (%)	105 (78.9)	49 (84.4)	56 (74.7)	0.169
Caucasian background; n (%)	116 (87.2)	52 (90.0)	64 (85.3)	0.459
Age at time of study; mean (95% CI)	36.5 (34.0-39.5)	43.3 (39.0-47.6)	27.0 (23.2-30.8)	< 0.001
Age at onset of disease in years (known in 84 patients); mean (95% CI)	21.0 (18.5-23.5)	35.5 (31.6-39.5)	10.4 (9.0-11.7)	< 0.001
Delay to diagnosis in years (known in 84 patients); mean (95% CI)	2.0 (1.5-2.5)	2.1 (1.5-2.8)	1.8 (1.1-2.6)	0.568
Disease Subtype and Distribution				
Craniofacial LM; n (%)	55 (41.4)	24 (41.4)	31 (41.3)	0.996
Number of patients with limb involvement; n (%)	87 (65.4)	41 (70.7)	46 (61.3)	0.261
Mixed LM and plaque morphoea; n (%)	36 (27.1)	15 (25.9)	21 (28.0)	0.658
Sclerotic morphology; n (%)	103 (77.4)	41 (70.7)	62 (82.7)	0.453
Damage (dyspigmentation and/or atrophy); n (%)	126 (94.7)	54 (98)	72 (96.0)	0.699
Triggers, Associations, Autoimmunity				
Preceding trauma; n (%)	20 (16.5)	9 (20.9)	11 (14.7)	0.892
Associated autoimmune diagnoses^; n (%)	15 (11.3)	9 (15.5)	6 (8.0)	0.174
Positive ANA[#] (tested in 99 patients); n (%)	40 (40.4)	20 (41.7)	20 (39.2)	0.149
Extracutaneous markers of disease severity:				
Functional impairment; n (%)	33 (24.8)	12 (20.7)	21 (28.0)	0.444
Limited joint ROM / contractures (limb LM (n=87)); n (%)	28 (32.2)	10 (24.4)	18 (39.1)	0.161
Dental / jaw complications (craniofacial LM (n=55)); (%)	6 (10.9)	2 (8.3)	4 (12.9)	0.689
Extracutaneous manifestations; n (%)	76 (57.1)	35 (60.3)	41 (54.7)	0.632
Constitutional symptoms (fatigue, myalgia, arthralgia; n (%)	60 (45.1)	28 (48.3)	32 (42.7)	0.519
Gastrointestinal (dyspepsia/gastroesophageal reflux); n (%)	15 (11.3)	8 (13.8)	7 (9.3)	0.420

Raynauds; n (%)	26 (19.5)	13 (22.4)	13 (17.3)	0.464
Neurological (seizures, ocular); n (%)	9 (6.8)	4 (6.9)	5 (6.7)	0.991

Disease severity scores:				
Highest recorded DLQI (recorded in 53 patients); mean (95% CI)	9.5 (7.7-11.4)	9.8 (6.9-12.6)	9.3 (6.8-11.9)	0.452
Highest recorded mLoSSI (recorded in 55 patients); mean (95% CI)	10.7 (8.5-12.9)	10.1 (6.3-13.8)	11.2 (8.3-14.0)	0.628
Highest recorded mLoSDI (recorded in 55 patients); mean (95% CI)	14.9 (12.4-17.5)	8.1 (4.4-11.8)	19.5 (17.0-22.0	< 0.001

Treatment				
Topical therapies; n (%)	85 (63.9)	38 (65.5)	48 (64.0)	0.734
Phototherapy; n (%)	18 (13.5)	7 (12.1)	11 (14.7)	0.664
Systemic corticosteroids; n (%)	74 (55.6)	32 (55.2)	42 (56.0)	0.924
Steroid sparing agents; n (%)	102 (76.7)	44 (75.9)	58 (77.3)	0.842

*Body sites = head/neck, right upper limb, left upper limb, right lower limb, left lower limb, trunk

^Rheumatoid arthritis, connective tissue disease, autoimmune thyroid disease, vitiligo, inflammatory bowel disease.

Abbreviations: LM – linear morphoea, ANA – antinuclear antibody (positive if titre of greater than 1:1000)#, ROM – range of movement, DLQI – disease quality life index, mLoSSI – modified Localised Scleroderma Severity Index, mLoSDI – modified Localised Scleroderma Disease Index