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Risk Factors for Morphea Disease Severity: A Retrospective Review of 114 Paediatric Patients

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Abstract

Background—Morphea is a rare fibrosing disease of the skin and subcutaneous tissue with an unpredictable disease course, running the spectrum from mild skin involvement to severe disfigurement or extracutaneous complications.

Objectives—Our objective was to describe the natural history of paediatric morphea and determine patient variables that were associated with severe disease.

Methods—We conducted a retrospective chart review of morphea patients seen in one paediatric hospital system. Information about demographics, clinical characteristics, disease course, and treatment were collected. Statistical analysis was performed using appropriate univariate tests and a multivariable model.

Results—One hundred fourteen patients met study inclusion criteria. The female:male ratio was 2.6:1, and the median age of onset was 7 years old. There were 55 patients (48%) with linear morphea, 38 patients (33%) with circumscribed morphea, 12 patients (11%) with generalized morphea, and 9 patients (8%) with mixed morphea. Neurologic symptoms and joint involvement were present in 27 subjects (24%). Extracutaneous manifestations occurred in 38% of linear morphea subjects, compared to 15% of generalized morphea and 3% of circumscribed morphea ($p = 0.0001$). Thirty-six percent of children with disease onset prior to 10 years and 5% of children with disease onset after 10 years had extracutaneous manifestations ($p = 0.0002$). Both linear morphea and early disease onset were significantly associated with extracutaneous involvement in a multivariable model.

Conclusions—Children with linear morphea and disease onset before 10 years should be closely monitored for extracutaneous manifestations and need early treatment with systemic medications to prevent disease complications.

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Introduction

Morphoea, also known as localized scleroderma, is a rare fibrosing disease with an estimated incidence of 2.7 per 100,000 individuals.¹ Morphoea causes significant morbidity through atrophy and fibrosis of the skin, soft tissues, muscle, and bone, resulting in scarring and disfigurement. Treatment may prevent further progression of the disease but is not fully effective in reversing all disease damage; therefore, early intervention is needed. In some children with morphoea, the autoimmune process eventually abates, but the disease course is highly variable. Although most lesions are asymptomatic, in some patients, especially those with linear morphoea, extracutaneous complications can result, including joint contractures, arthralgias, seizures, nerve palsies, and migraine headaches.²

Clinicians face many difficulties when treating children with morphoea. One of the most challenging decisions is differentiating active disease from inactive damage. Systemic immunosuppressants with potential risk for adverse effects may be inappropriately initiated when the disease process has already abated. Alternatively, therapy may be withheld or prematurely discontinued in active lesions, resulting in further disfigurement. Additionally, physicians cannot predict which patients will progress to extracutaneous manifestations and may require aggressive therapy before complications develop. The objective of this retrospective study is to describe the natural history of morphoea and isolate clinical features that could help predict disease severity.

Materials and Methods

This retrospective chart review study was approved by the Children's Hospital of Wisconsin Institutional Review Board. The International Classification of Diseases, 9th Revision code of 701.0 (circumscribed scleroderma) was used to identify patients treated at our institution from 2000 to November 2011. Patients were included if they had onset of their morphoea prior to 18 years of age. Subjects with lichen sclerosus, systemic sclerosis, and erroneous diagnoses were excluded, and after review, there were 114 patients with a diagnosis of morphoea made by a paediatric dermatologist or paediatric rheumatologist.

Patient demographics were recorded; race, ethnicity, and age of onset of disease were by patient self-report. We defined morphoea subtypes using the Zulian et al. classification system including: circumscribed, linear, generalized, pansclerotic, and mixed.³ Personal and family history of other autoimmune disorders was noted. Extracutaneous manifestations were defined as joint involvement (arthritis, arthralgias, joint contractures, leg length discrepancy causing functional impairment) or neurologic involvement (neurologic signs or symptoms) attributed to morphoea by the treating clinician. Anti-nuclear antibody (ANA) values were documented. Details of treatment methods, including topical and systemic therapy, were recorded.

Subjects' disease courses were included in the analysis if 2 or more visits occurred during the study period. We defined a patient's duration of disease as self-reported initial onset of signs or symptoms until end of treatment, including periods of remission and relapse if applicable. Patients were determined to have entered remission when therapy was

discontinued. Relapse was defined as enlarging, worsening, or new lesions after therapy was discontinued.

All statistical analyses were performed using SAS 9.2 statistical software. Chi square test was performed to evaluate associations between patient variables (age of onset, race, gender, presence of ANA, personal history of autoimmune disease, and family history of autoimmune disease) and presence of extracutaneous manifestations. Significant variables at $p < 0.05$ from the univariate analysis were selected for multivariate analysis to evaluate the association between age, subtype, and extracutaneous manifestations. The log rank test was used to compare time to relapse of the morphoea subtypes and other patient-related covariates as listed above. The two sample t test was used to compare length of systemic treatment between those subjects who relapsed and those who did not.

Results

Clinical Characteristics and Natural History

One hundred fourteen subjects met study inclusion criteria. Demographic features of the study population are summarized in Table 1. The female:male ratio was 2.6:1. The median age of onset was 7 years old (range, 10 months to 17 years). The median age of presentation to our clinic was 10.5 years old. The study population was predominately white (73%).

Clinical features of the subjects are summarized in Table 2. There were 55 patients (48%) with linear morphoea, 38 patients (33%) with circumscribed morphoea, 12 patients (11%) with generalized morphoea, and 9 patients (8%) were mixed morphoea subtype. All patients with the mixed subtype had linear morphoea in combination with circumscribed or generalized morphoea and were included in the linear morphoea group for the statistical analyses. In total, linear morphoea was present on the head (en coup de sabre or Parry-Romberg) in 32 and on the trunk or extremity in 35 (including 3 subjects with multiple areas of involvement and 9 subjects with mixed subtype). There were no patients with pansclerotic morphoea.

In our study population, 11 patients (10%) had another autoimmune disease, including juvenile idiopathic arthritis, systemic lupus erythematosus, vitiligo, Raynaud's disease, Hashimoto's thyroiditis, coeliac disease, and alopecia areata. Twelve patients (11%) had a family history of an autoimmune disease, including systemic lupus erythematosus, autoimmune hepatitis, ulcerative colitis, Raynaud's disease, psoriasis, vitiligo, Hashimoto's thyroiditis, juvenile idiopathic arthritis, and Crohn's disease. Of the 37 patients with ANA tested, 14 of them had a positive ANA (38%).

Extracutaneous manifestations were present in 27 subjects (24%). Seventeen had joint involvement in the form of arthralgias (2), arthritis (1), or contracture (14), the majority of whom had linear morphoea of the trunk or extremity. No subject had leg length discrepancy causing functional impairment. All of the subjects with contracture and arthritis had morphoea overlying their affected joint(s), while the 2 subjects with arthralgias had involvement of joints that were distant from their morphoea. Ten children had neurologic involvement, most commonly seizure present in 4 patients, followed by headache in 3

patients. Nine of the patients with neurologic involvement had linear morphoea of the head; one subject with linear morphoea of the leg had a generalized tremor attributed to the morphoea after evaluation by a paediatric neurologist. Additional details of the neurologic involvement and neuroimaging findings in our en coup de sabre and Parry-Romberg population have been previously reported.⁴ No patients in our study progressed to systemic sclerosis.

Table 3 describes the treatment details in our population. Topical treatments alone were used in 64 patients, systemic treatments alone were used in 10 patients, a combination of topical and systemic treatments were used in 32 patients, and eight patients did not receive medical therapy. Subjects with linear morphoea, isolated or as part of a mixed subtype, were treated with systemic therapy at a higher rate (54%) compared to subjects with circumscribed (8%) or generalized (38%) morphoea. Among topical therapies, corticosteroids and vitamin D analogues were most commonly prescribed, used in 74 (65%) and 69 (61%) patients respectively. The median duration of topical treatment was 8.5 months. The most common systemic treatment used in 24 patients was methotrexate combined with pulsed intravenous methylprednisolone (intravenous methylprednisolone at 30 mg/kg [maximum 1000 mg] on each of 3 consecutive days a month for 3 consecutive months, combined with long-term oral or subcutaneous methotrexate once weekly). Ultraviolet A1 phototherapy administered at another center was used in one patient with linear morphoea. The median duration of systemic treatment was 14 months.

Ninety-seven patients were seen for 2 or more visits and their disease course is detailed in Table 4. The median duration of follow up was 20 months. Sixty subjects were lost to follow-up while undergoing treatment or were still undergoing treatment, either for clinically active or clinically inactive disease, at the time of chart review. In total, 37 patients achieved remission of their morphoea during the time period of this study: 4 with no intervention, 18 with topical therapy alone, 2 with systemic therapy alone, and 13 with combination topical and systemic therapy. Of the 37 patients achieving remission, 10 patients (27%) experienced relapse with one patient relapsing twice. The 10 patients with relapse were treated with topical therapy alone in 2 cases, systemic therapy alone in 1 case, and combination therapy in 7 cases; this corresponds to relapse rates of 11%, 50%, and 57%, respectively. Overall, the median time to relapse was 16 months in these 10 patients. In the 27 patients without relapse, the median follow-up time was 18 months. The mean systemic treatment duration was 25 months in the non-relapse cases ($n = 7$) and 19 months in the relapse cases ($n = 7$, treatment duration missing for one case; $p = 0.4$). Overall, median disease duration was 54 months in the 27 patients that achieved remission.

Risk Factors for Disease Severity

Extracutaneous manifestations were most likely to occur in the setting of linear morphoea. Thirty-eight percent of subjects with linear morphoea, either isolated or as part of a mixed subtype, had joint or neurologic involvement, compared to 15% with generalized morphoea and 3% with circumscribed morphoea ($p = 0.0001$). Of children with linear morphoea on the head, 28% had neurologic involvement ($p = 0.01$). Of children with linear morphoea on the trunk or extremity, 43% had joint involvement ($p < 0.0001$). Children with disease onset <10

years old were more likely to have extracutaneous manifestations, occurring in 36% as compared to 5% of children with disease onset ≥ 10 years old ($p = 0.0002$).

Race/ethnicity ($p=0.5$), gender ($p=0.6$), personal history of autoimmune disease ($p=0.3$), and family history of autoimmune disease ($p=0.5$) were not associated with risk of extracutaneous manifestations. Presence of an ANA did not differ substantially between the subtypes and was not associated with extracutaneous manifestations ($p=1.0$). Duration of systemic therapy ($\leq$ or > 18 months) was not associated with relapse rate ($p=0.6$) or time to relapse ($p=0.1$).

Table 5 summarizes the odds ratio estimates from the multivariate analysis. Patients with linear involvement were more likely than those with circumscribed morphoea to have extracutaneous manifestations (OR 22.3, 95% CI 2.8–178.5, $p = 0.0035$). The association between age and extracutaneous manifestations remained significant in the multivariable model; subjects with an age of onset <10 years old were much more likely to have extracutaneous manifestations than older children independent of subtype (OR 10.0, 95% CI 2.1–47.6, $p = 0.0036$).

Discussion

In this paper, we describe the natural history of morphoea in a large population of paediatric patients and examined risk factors that may or may not be associated with severe disease. The demographic characteristics of our study population are in line with previous studies.^{5–8} We confirmed that linear morphoea is much more likely to be associated with extracutaneous manifestations, but also identified age of onset as a novel and independent association.

Children with onset of disease prior to 10 years of age were 10 times more likely to have extracutaneous manifestations. Zulian et al. performed a retrospective study of 750 children with morphoea.² The authors found no difference in the mean age of onset between those children with and without extracutaneous involvement. The reason for the discrepancy between our studies is unclear though the other study had a broader definition of extracutaneous manifestations, including concomitant autoimmune diseases such as diabetes mellitus and thyroid disease, and their larger series may have captured children with rare overlap syndromes as their series included cardiac, renal, and respiratory involvement, which are rarely seen in morphoea. It is perhaps not surprising that early onset paediatric morphoea may result in more severe disease than later onset disease. The developing musculoskeletal system and brain in a younger child may be more prone to complications such as contractures or seizures, explaining the higher rates of extracutaneous manifestations in the younger age group. It is also possible that like many other autoimmune diseases, morphoea represents an interplay between genetic predisposition and environmental factors where early disease onset suggests a stronger genetic predisposition. Ultimately, it is particularly important to have a high degree of suspicion for extracutaneous involvement in a younger child who may not be able to verbalize symptoms.

Linear morphoea was the most common subtype in our population, comprising nearly half of patients. Other studies have suggested up to 86% of children have linear morphoea, though those reporting a higher prevalence of the linear subtype may suffer from referral bias as this variant is generally more severe and more likely to be referred to a tertiary centre for treatment.^{5–8} Not surprisingly, linear morphoea was the subtype with the highest association with neurologic and joint complications, occurring in 38% consistent with a prior study.⁵ Linear morphoea on the head was strongly associated with neurologic involvement, and linear morphoea of the trunk and extremity was strongly associated with joint involvement. Our multivariate analysis determined that children with the linear subtype had a 22 times increased odds of having joint or neurologic disease. Given the risk of developing extracutaneous manifestations, children with linear morphoea should be treated early with systemic agents to prevent complications.

An ANA was checked in 37 patients, of whom 38% were positive, comparable with prior reports.^{6,7} ANA positivity was not associated with the presence of extracutaneous manifestations in our study. Arkachaisri et al found that the presence of anti-single stranded DNA, anti-histone, and anti-chromatin antibodies, but not ANA, was associated with joint contractures in their population of patients with childhood onset morphoea.⁹ As ANA and other autoantibodies were not systematically checked in all patients, firm conclusions cannot be drawn from our results.

A variety of topical and systemic therapies were used in our subjects. Although linear morphoea has traditionally been known to carry a higher risk of complications, 36% of these subjects were treated with topical agents alone. Prospective studies have been performed that demonstrate the effectiveness of methotrexate and systemic corticosteroids in the treatment of morphoea, but the efficacy of systemic immunosuppressants in preventing or reversing extracutaneous manifestations is unknown.^{10,11} It would stand to reason, however, that systemic therapies would be more effective than topical therapies at preventing or treating joint or neurologic disease and should be the treatment of choice for most children with linear morphoea. Consideration for systemic immunosuppression should be given for children with early onset disease prior to age 10 as well. The risk of extracutaneous manifestations and severe disfigurement in superficial circumscribed morphoea is low, and most children, even those with onset prior to age 10, likely do not require systemic therapy. Those children with linear morphoea, and perhaps generalized morphoea, developing before 10 years warrant the strongest consideration for systemic therapy to treat extracutaneous manifestations.

The relapse rate in those treated with systemic therapy, alone or in combination, was 53%. We had a slightly higher relapse rate than the 29–44% reported by other studies, though the reason for this cannot be gleaned from the retrospective data.^{12,13} The lower relapse rate of 11% seen with topical therapy alone was likely due to selection bias; patients with milder disease were more likely to be treated with topicals alone. It should be noted that many cases of relapse may not represent true disease recurrence, but rather discontinuation of therapy too early before remission was achieved. This is a common problem facing clinicians as it is difficult to distinguish morphoea that has entered remission from active disease that is

effectively suppressed by treatment. The median time to relapse was 16 months, very similar to prior studies.^{12,13}

We were unable to determine an effect of treatment duration on disease relapse, though our numbers were small and those subjects who experienced disease relapse were on systemic therapy for a shorter duration (mean 19 months) compared to those who did not relapse (mean 25 months). A study of 90 children found patients who relapsed received methotrexate for a shorter duration than those who did not.¹² The results from other studies have been conflicting, but some authors have suggested that shorter treatment courses result in higher relapse rates.^{10,13,14}

The median disease duration in the 27 subjects with available data was 54 months, suggesting that children may have active disease and require treatment for several years. This number may underestimate true disease duration as children with on-going disease, which may include a subset of children with longer-lasting disease, were not included in the disease duration analysis.

As with any retrospective review, this study was limited by the retrospective nature and missing data; however, it was strengthened by the relatively large number of subjects given this rare disease. There was a high rate of follow-up as 85% of patients returned for 2 or more visits, allowing us to describe the natural history of the disease over time. Of note, we were unable to differentiate superficial and deep involvement of circumscribed and generalized morphea in our study; it may be that children with deeper involvement by these subtypes have a higher risk of joint involvement that was not detected in our statistical analyses.

Our study describing the natural history of paediatric morphea and evaluating risk factors for disease severity found that children with linear disease and those with disease onset at a younger age were at higher risk of developing extracutaneous involvement. Because of the morbidity associated with joint and neurologic complications, these children need to be regarded with an additional degree of vigilance and early intervention with systemic therapies is necessary. Larger studies, ideally conducted prospectively, are necessary to corroborate the findings from this study.

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Bulleted Statements

- Paediatric morphoea has an unpredictable disease course with self-limited mild disease in some children and unremitting severely disfiguring disease in others.
- Linear morphoea and age of onset less than 10 years are significantly associated with extracutaneous manifestations.
- Children with linear morphoea and those with onset of disease prior to 10 years should be treated with systemic therapy to prevent neurologic and joint complications.

TABLE 1

Demographics of 114 patients with paediatric-onset morphoea.

Number	114
Median age of onset (years [range])	7 [1–17]
Sex	
Female	82 (72%)
Male	32 (28%)
Ethnicity	
Caucasian	83 (73%)
African American	8 (7%)
Hispanic	15 (13%)
Other	8 (7%)

TABLE 2

Clinical features in 114 patients with paediatric-onset morphoea.

	Circumscribed	Linear	Generalized	Mixed	Total
Number	38	55	12	9	114
Location of lesions					
Head	4 (11%)	28 (51%)	0	0	32 (28%)
Trunk	20 (53%)	2 (4%)	1 (8%)	0	23 (20%)
Arm	1 (3%)	5 (9%)	0	0	6 (5%)
Leg	7 (18%)	11 (20%)	1 (8%)	0	19 (17%)
2 sites	6 (16%)	9 (16%)	10 (83%)	9 (100%)	34 (30%)
Autoimmune disease					
Personal history	1 (3%)	7 (13%)	2 (17%)	1 (11%)	11 (10%)
Family history	4 (11%)	5 (9 %)	2 (17%)	1 (11 %)	12 (11%)
Positive anti-nuclear autoantibody	1/3 (33%)	7/23 (30%)	3/6 (50%)	3/5 (60%)	14/37 (38%)
Extracutaneous manifestations					
Joint involvement	1 (3%)	10 (18%)	2 (17%)	4 (44%)	17 (15%)
Neurologic involvement	0	10 (18%)	0	0	10 (9%)

TABLE 3

Treatment of 114 patients with paediatric-onset morphoea

	Circumscribed	Linear	Generalized	Mixed	Total
Number	38	55	12	9	114
Treatment					
Topical only	33 (87%)	20 (36%)	8 (67%)	3 (33%)	64 (56%)
Median topical only duration (months [IQR])	10 [12]	7 [6]	16 [22]	1 [11]	8.5 [12]
Systemic only	0	6 (11%)	2 (17%)	2 (22%)	10 (9%)
Median systemic only duration (months [IQR])	0	16.5 [8]	12	22.5 [11]	14 [12]
Topical and systemic	3 (8%)	23 (42%)	2 (17%)	4 (44%)	32 (28%)
Median topical and systemic duration (months [IQR])	21 [16]	29.5 [35]	18 [10]	36.5 [25]	28 [32]
Overall median treatment duration (months [IQR])	10 [13]	14 [23]	12 [19]	23.5 [20]	12 [20]

IQR = interquartile range

TABLE 4

Disease course of 97 patients with paediatric-onset morphoea

	Circumscribed	Linear	Generalized	Mixed	Total
Median length of follow-up (months [IQR]) ¹	12 [19] (N = 31)	21 [35] (N = 50)	13 [36] (N = 9)	59 [48] (N = 8)	20 [35] (N = 97)
Remission					
Patients with remission ²	13/31 (42%)	20/50 (40%)	1/9 (11%)	3/8 (38%)	37/97 (38%)
Treatment duration for patients with remission (months [IQR])	18.5 [16.25]	19.5 [23]	46	33 [13]	21 [23]
Median length of follow up after remission (months [IQR]) ³	10.5 [18.75]	21 [27]	31	18 [5]	18 [26]
Relapse ⁴	3/13 (23%)	6/20 (30%)	1/1 (100%)	1/3 (33%)	10 (27%)
Median time to relapse (months [IQR])	12 [7.5]	19 [12]	8	25	16 [13]
Median disease duration (months [IQR]) ³	32.5 [51] (N = 10)	59 [17] (N = 13)	75 (N = 1)	47 [27] (N = 3)	54 [35] (N = 27)

IQR = interquartile range; N = number of subjects

¹ Only patients with at least 2 visits were included.² Only patients with at least 2 visits were included in the denominator.³ Disease duration was defined as initial onset of signs or symptoms until end of treatment. Patients with active disease or lost to follow-up prior to disease remission were not included in the N. One subject with linear morphea did not have an age of onset recorded and was not included.⁴ Only patients who had a documented remission were included in the denominator.

TABLE 5

Multivariate analysis of factors associated with extracutaneous manifestations in 114 patients with paediatric-onset morphoea.

	Risk of Extracutaneous Manifestations	Odds Ratio (95% Confidence Limit)	p-value
Linear morphoea	38%	22.3 (2.8 – 178)	0.0035
Circumscribed morphoea	3%		
Age of onset < 10 years	36%	10.0 (2.1 – 47.6)	0.0036
Age of onset ≥ 10 years	5%		