Distinct Autoimmune Syndromes in Morphea

A Review of 245 Adult and Pediatric Cases

Justin J. Leitenberger, BS; Rachael L. Cayce, BS; Robert W. Haley, MD; Beverley Adams-Huet, MS; Paul R. Bergstresser, MD; Heidi T. Jacobe, MD

Objective: To determine the prevalence of extracutaneous manifestations and autoimmunity in adult and pediatric patients with morphea.

Design: A retrospective review of 245 patients with morphea.

Setting: University of Texas Southwestern Medical Center–affiliated institutions.

Patients: Patients with clinical findings consistent with morphea.

Main Outcome Measures: Prevalence of concomitant autoimmune diseases, prevalence of familial autoimmune disease, prevalence of extracutaneous manifestations, and laboratory evidence of autoimmunity (antinuclear antibody positivity). Secondary outcome measures included demographic features.

Results: In this group, adults and children were affected nearly equally, and African Americans were affected less frequently than expected. The prevalence of concomitant autoimmunity in the generalized subtype of morphea was statistically significantly greater than that found in all other subtypes combined ($P = .01$). Frequency of a family history of autoimmune disease showed a trend in favor of generalized and mixed subgroups. The linear subtype showed a significant association with neurologic manifestations, while general systemic manifestations were most common in the generalized subtype. Antinuclear antibody positivity was most frequent in mixed and generalized subtypes.

Conclusions: High prevalences of concomitant and familial autoimmune disease, systemic manifestations, and antinuclear antibody positivity in the generalized and possibly mixed subtypes suggest that these are systemic autoimmune syndromes and not skin-only phenomena. This has implications for the management and treatment of patients with morphea.

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MORPHEA IS CHARACTERIZED by sclerosis of the skin and, in some cases, underlying tissue. It is generally thought to be an autoimmune disorder affecting a single organ—the skin. Consequently, current classification schemes divide morphea into categories based solely on cutaneous morphology, without reference to systemic disease or autoimmune phenomena. This classification is likely incomplete.

Rather, morphea may be a systemic autoimmune condition. For example, case reports describe morphea coexisting with other autoimmune diseases, including systemic lupus erythematosus, vitiligo, primary biliary cirrhosis, autoimmune hepatitis, Hashimoto thyroiditis, and myasthenia gravis. A retrospective review of 750 children with morphea revealed a greater-than-expected prevalence of familial autoimmune disease. The same pediatric study found systemic manifestations outside the area of morphea in 22.4% of children, including arthralgias and esophageal dysmotility. Data in adults are limited, with 1 case-control study of 50 adult white women reporting increased personal and familial autoimmunity, but antinuclear antibody (ANA) status and systemic manifestations were not reported. Many autoantibodies have been reported in patients with morphea, including ANA, anti–single-stranded DNA, antihistone, anti–topoisomerase II, antiphospholipid, and rheumatoid factor. The clinical and prognostic significance of these autoantibodies remains unclear.

Taken together, these reports suggest that morphea is an autoimmune disease with a spectrum of manifestations ranging from only skin to multiple organ involvement. What remains unclear is the prevalence of...
autoimmune and systemic disease in morphea and its subtypes and how these findings correlate with the autoantibody profile. This uncertainty negatively affects patient care because many patients are untreated or are treated only with skin-directed therapy and may require systemic therapy. This study aims to address this gap in knowledge by quantifying the prevalence of autoimmunity and systemic manifestations in adults and children with morphea.

Approval was obtained from the institutional review board to review the medical records of patients with morphea seen from June 1, 2001, to June 1, 2007, at University of Texas Southwestern Medical Center at Dallas-affiliated institutions (University of Texas Southwestern Medical Center at Dallas university-based faculty practice, Texas Scottish Rite Hospital, Children’s Medical Center in Dallas, and Parkland Memorial Hospital). A total of 431 potential adult and pediatric patients were identified on the basis of the International Classification of Diseases, Ninth Revision diagnosis code for morphea/localized scleroderma and lichen sclerosis (code 701.0). If the medical records of patients with morphea seen from June 1, 2001, to June 1, 2007, at University of Texas Southwestern Medical Center at Dallas-affiliated institutions (University of Texas Southwestern Medical Center at Dallas university-based faculty practice, Texas Scottish Rite Hospital, Children’s Medical Center in Dallas, and Parkland Memorial Hospital). A total of 431 potential adult and pediatric patients were identified on the basis of the International Classification of Diseases, Ninth Revision diagnosis code for morphea/localized scleroderma and lichen sclerosis (code 701.0). If the medical records of patients with morphea seen from June 1, 2001, to June 1, 2007, at University of Texas Southwestern Medical Center at Dallas-affiliated institutions (University of Texas Southwestern Medical Center at Dallas university-based faculty practice, Texas Scottish Rite Hospital, Children’s Medical Center in Dallas, and Parkland Memorial Hospital). A total of 431 potential adult and pediatric patients were identified on the basis of the International Classification of Diseases, Ninth Revision diagnosis code for morphea/localized scleroderma and lichen sclerosis (code 701.0).13 Approval was obtained from the institutional review board to review the medical records of patients with morphea seen from June 1, 2001, to June 1, 2007, at University of Texas Southwestern Medical Center at Dallas-affiliated institutions (University of Texas Southwestern Medical Center at Dallas university-based faculty practice, Texas Scottish Rite Hospital, Children’s Medical Center in Dallas, and Parkland Memorial Hospital). A total of 431 potential adult and pediatric patients were identified on the basis of the International Classification of Diseases, Ninth Revision diagnosis code for morphea/localized scleroderma and lichen sclerosis (code 701.0).13 Approval was obtained from the institutional review board to review the medical records of patients with morphea seen from June 1, 2001, to June 1, 2007, at University of Texas Southwestern Medical Center at Dallas-affiliated institutions (University of Texas Southwestern Medical Center at Dallas university-based faculty practice, Texas Scottish Rite Hospital, Children’s Medical Center in Dallas, and Parkland Memorial Hospital). A total of 431 potential adult and pediatric patients were identified on the basis of the International Classification of Diseases, Ninth Revision diagnosis code for morphea/localized scleroderma and lichen sclerosis (code 701.0).13
in 23.6% (29 of 123) of adult patients. The mixed subtype was seen in 4.1% (5 of 123) of adult patients.

Children

The most common subtype was linear in 41.8% (51 of 122) of pediatric patients, followed by plaque and mixed subtypes at 27.9% (34 of 122) and 23.6% (29 of 122), respectively. Among the 33 adults and children with mixed subtypes, 84.8% (28 of 33) had plaque and linear lesions develop over time; the remainder had generalized and linear subtypes of morphea.

CONCOMITANT RHEUMATIC DISEASE AND OTHER AUTOIMMUNE DISORDERS

Table 3 shows the details of rheumatic and other autoimmune disorders present in patients with morphea or their families. Among the 245 patients, 43 (17.6%) reported concomitant rheumatic or other autoimmune disorder. Concomitant rheumatic or other autoimmune disorder was significantly more prevalent among adults (30.1% [37 of 123]) than among children (4.9% [6 of 122]) (P < .001). When analyzed by subtype, the frequency of concomitant autoimmune disorders among adult and pediatric patients with generalized morphea was 45.9% (17 of 37), which was significantly greater (P = .01) than the prevalence in the other subtypes combined (9.6%).

FAMILIAL RHEUMATIC DISEASE AND OTHER AUTOIMMUNE DISORDERS

Among all patients, 16.3% (40 of 245) reported a family history of autoimmune disorders. Significantly more children (23.8%) than adults (10.6%) had a family history of a rheumatic or other autoimmune disorder in a first- or second-degree relative (P < .001). In adults, the generalized subtype had the highest frequency of familial disease (21.6%). In children, those with mixed (24.2%) and generalized (21.6%) subtypes had the highest frequency of family history of autoimmunity. Despite trends in favor of an association of generalized and mixed subtypes with familial autoimmunity, this was not statistically significant (P = .29). Of note, 5 children (2.0% of all patients) reported a family history of morphea in a first- or second-degree relative.

EXTRACUTANEOUS MANIFESTATIONS

Table 4 lists the extracutaneous manifestations of morphea experienced by the study patients. Symptoms outside the areas affected by morphea were common in patients with generalized morphea, with the highest frequency compared with the other subtypes of dysphagia (14.3% [5 of 35], P > .05), dyspnea (20.0% [7 of 35], P = .03), and vascular complaints (Raynaud phenomenon) (31.4% [11 of 35], P = .03). Patients with the mixed subtype had a high level of musculoskeletal manifestations (6.1%-36.4% related to the distribution of the lesions) (6.1%-36.4% related to the distribution of the lesions).
The linear subtype was associated with neurologic (31.4% [27 of 86]) and ophthalmologic (8.1% [7 of 86]) complications related to the affected site on the face or scalp (both \( P = .05 \)) (Table 4).

### ANA AND OTHER ANTIBODIES

Antinuclear antibodies were tested in 36.3% (89 of 245) of patients and were positive (titer \( \geq 1:160 \)) in 39.3% (35 of 89) of those tested (Table 5). The percentage of patients with ANA positivity was highest in the generalized and mixed subtypes (57.9% [11 of 19] and 53.8% [7 of 13], respectively). Adults had a higher frequency of ANA positivity with 52.8% (19 of 36) testing positive compared with 30.2% (16 of 53) of children. The most common ANA patterns observed were speckled and nucleolar.

In contrast to prior reports, only 1 of 26 of patients tested had anti–single-stranded DNA antibodies (generalized morphea). One of 39 patients (with generalized morphea) was positive for anti–Scl-70 antibodies. This patient did not develop any signs or symptoms of scleroderma during a 9-year follow-up period. Three of 19 patients tested (14%) had anti–

### Table 4. Extracutaneous Manifestations in Patients With Morphea Subtypes

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Overall (n=246)</th>
<th>Plaque (n=86)</th>
<th>Linear (n=86)</th>
<th>Generalized (n=35)</th>
<th>Mixed (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fatigue</td>
<td>29 (11.8)</td>
<td>13 (15.1)</td>
<td>7 (8.1)</td>
<td>5 (14.3)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>24 (9.8)</td>
<td>8 (9.3)</td>
<td>5 (5.8)</td>
<td>5 (14.3)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>48 (19.5)</td>
<td>17 (19.8)</td>
<td>8 (9.3)</td>
<td>9 (25.7)</td>
<td>8 (24.2)</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>21 (8.5)</td>
<td>9 (10.5)</td>
<td>1 (1.2)</td>
<td>5 (14.3)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>32 (13.0)</td>
<td>12 (14.0)</td>
<td>6 (7.0)</td>
<td>5 (14.3)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Limb contracture</td>
<td>19 (7.7)</td>
<td>2 (2.3)</td>
<td>6 (7.0)</td>
<td>4 (11.4)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Limited range of motion</td>
<td>48 (19.5)</td>
<td>7 (8.1)</td>
<td>16 (18.6)</td>
<td>10 (28.6)</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision changes</td>
<td>12 (4.9)</td>
<td>3 (3.5)</td>
<td>7 (8.1)</td>
<td>( \ldots )</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td>6 (2.4)</td>
<td>( \ldots )</td>
<td>4 (4.6)</td>
<td>1 (2.9)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Headaches</td>
<td>33 (13.4)</td>
<td>13 (15.1)</td>
<td>14 (16.3)</td>
<td>3 (8.6)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Vascular malformations</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
<td>1 (1.2)</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Calcifications</td>
<td>1 (0.4)</td>
<td>( \ldots )</td>
<td>1 (1.2)</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (6.9)</td>
<td>1 (1.2)</td>
<td>4 (4.6)</td>
<td>7 (20.0)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold fingers</td>
<td>25 (10.2)</td>
<td>8 (9.3)</td>
<td>5 (5.8)</td>
<td>7 (20.0)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>5 (2.0)</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>3 (8.6)</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
<td>( \ldots )</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>

### Table 5. Autoantibodies in Patients With Morphea Subtypes

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Overall (n=246)</th>
<th>Plaque (n=86)</th>
<th>Linear (n=86)</th>
<th>Generalized (n=35)</th>
<th>Mixed (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA(^{a,c})</td>
<td>35/89 (39.3)</td>
<td>8/25 (32.0)</td>
<td>6/21 (28.6)</td>
<td>11/19 (57.9)</td>
<td>7/13 (53.8)</td>
</tr>
<tr>
<td>Anti–Scl-70</td>
<td>1/39 (2.6)</td>
<td>0/12</td>
<td>0/9</td>
<td>1/8 (12.5)</td>
<td>0/7</td>
</tr>
<tr>
<td>Anti–dsDNA</td>
<td>3/19 (15.8)</td>
<td>0/4</td>
<td>1/3 (33.3)</td>
<td>1/6 (16.7)</td>
<td>1/3 (33.3)</td>
</tr>
<tr>
<td>Antiphospholipid(^d)</td>
<td>3/8 (37.5)</td>
<td>2/3 (66.7)</td>
<td>0/1</td>
<td>0/2</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Anti–centromere</td>
<td>1/11 (9.1)</td>
<td>0/4</td>
<td>0/3</td>
<td>1/2 (50)</td>
<td>( \ldots )</td>
</tr>
<tr>
<td>Anti–ssDNA</td>
<td>1/26 (3.8)</td>
<td>0/8</td>
<td>0/6</td>
<td>1/6 (16.7)</td>
<td>0/2</td>
</tr>
<tr>
<td>Anti–snRNP</td>
<td>1/21 (4.8)</td>
<td>0/6</td>
<td>0/5</td>
<td>1/5 (20.0)</td>
<td>0/2</td>
</tr>
</tbody>
</table>

Abbreviations: ANA, antinuclear antibody; anti–dsDNA, anti–double-stranded DNA; anti–ssDNA, anti–single-stranded DNA; anti–snRNP, anti–small nuclear ribonucleoprotein particle; ellipses, not calculated.

\(^{a}\)Six patients with lichen sclerosus morphea overlap were not included owing to small numbers.

\(^{b}\)Statistically significant association between linear morphea and visual changes, seizures, and headaches (\( P = .009 \), \( P = .04 \), and \( P = .03 \), respectively).

\(^{c}\)Association with generalized subtype statistically significant (\( P = .03 \) for both dyspnea and vascular manifestations).

\(^{d}\)No patient tested had a diagnosis of antiphospholipid syndrome.
double-stranded DNA antibodies: 1 each for linear, generalized, and mixed subtypes (prior reports link the presence of anti–double-stranded DNA to the generalized subtype). None of these patients developed any signs or symptoms of systemic lupus erythematosus after 1 year of follow-up.

**COMMENT**

This study represents the largest collection of adults and children with morphea to address the prevalence of autoimmune and systemic disease with stratification by morphea subtype. As in prior reports, there was a female predominance and age-dependent difference in subtype distributions. Of note, morphea occurred nearly equally in adults and children (with a prior report citing the disease is favored in childhood by 2:1). Although this is not a population-based study, it likely represents a fair estimation of distribution between adults and children because patients were enrolled from all university-affiliated institutions, including 2 children's medical centers, and included patients seen by all specialists. Prior reports may be biased in favor of pediatric patients who present with linear lesions more frequently and are subsequently diagnosed and brought to medical attention more frequently. The racial distribution of morphea has not been widely addressed. In this cohort, morphea was less frequent in African Americans. The percentage affected in this cohort (4.5%) is lower than expected based on the racial distribution of metropolitan Dallas, Texas (20.9% African American, 2005 estimate of the US Census Bureau) and the racial distribution of patients seen at the University of Texas Southwestern Medical Center at Dallas-affiliated institutions. Population-based studies are needed to fully address age and racial distribution in morphea.

Overall, 17.6% of patients had a concomitant rheumatic or other autoimmune disorder, an occurrence 4-fold higher than that in the general population, including all races and socioeconomic strata. But when analyzed by subtype, generalized morphea had a statistically significant association with autoimmune disease, with 45.9% of patients with generalized morphea affected, representing 12 times the risk of the general population. Children with morphea were relatively spared of concomitant autoimmune disease (only 4.9% vs 30.1% of adults). It is unknown whether children with morphea will develop autoimmune disorders at an increased rate as they reach adulthood.

Very little is known whether specific disorders aggregate with morphea. In this cohort, several disorders occurred with greater frequency than expected compared with published population-based prevalence estimates, including psoriasis (1.5- to 4.5-fold increase), systemic lupus erythematosus (38-fold increase), multiple sclerosis (7- to 8-fold increase), and vitiligo (3.5-fold increase).

The statistically significant difference in family histories of autoimmune disorders between children (24%) and adults (11%) with all subtypes of morphea is likely confounded by differences in data acquisition at the study sites (family history was collected more thoroughly in the pediatric patients). Thus, the frequency of a positive family history is likely underestimated in adults. Of note, although not statistically significant, the generalized subtype represented the highest frequency of familial disease in adults and the second highest in children (lack of statistical significance may be the result of relatively low numbers). Zulian et al reported similar findings in a pediatric cohort with a statistically significant association of familial autoimmunity in the generalized subtype (23.5% vs 12.5%, 12.3%, and 8.8% in patients with deep, linear, and plaque-type morphea, respectively). Familial autoimmune diseases also occurred more frequently in the mixed subtype (both adults and children), which was not reported by Zulian et al. Thus, familial autoimmunity is most prevalent in generalized and mixed subtypes.

Similar disorders to those reported in patients with morphea were reported in their family members. Rheumatoid arthritis, systemic lupus erythematosus, and psoriasis were observed with the highest frequency in first- and second-degree relatives of patients with morphea overall. These findings are similar to those reported by Zulian et al. Taken together, the increased frequency of personal and familial autoimmunity in the generalized subtype may indicate a common susceptibility locus for this group of disorders, as was recently described in vitiligo and its association with NALP1.

We found that 1% (4 families) of patients with morphea had first- or second-degree relatives with morphea, representing a higher risk than present in the general population (compared with an estimated prevalence reported by Peterson et al of 0.2% [odds ratio, 6.8; 95% confidence interval, 1.15-40.56; P = .01]). Multifacase families with morphea have been described independently in the literature and, as in our study, were in a non-Mendelian pattern suggestive of a multifactorial, polygenic inheritance. There was no family history of scleroderma in this cohort, although this has been reported in the pediatric group described by Zulian et al.

The systemic symptoms and signs observed in the patients in this study are similar to those in prior reports in terms of organ systems of involvement. A novel observation, however, is that manifestations occurring outside the area affected by morphea (eg, dysphagia, joint pain, and Raynaud phenomenon) are most common in patients with the generalized subtype, while patients with linear disease often have neurologic and ophthalmologic manifestations correlating with the area of morphea involvement. Prior reports describe morphea as a relatively painless disorder; this cohort, however, reported pain in areas affected by morphea, particularly in the generalized subgroup. This underscores the need to address pain as a potential symptom in patients with morphea.

An ANA positivity rate of 39% (of patients tested) is comparable with a prior study. Patients with the generalized and mixed subtypes had the highest frequency (58% and 54%, respectively). In contrast to prior reports linking anti–single-stranded DNA to linear and generalized morphea (50%), only 1 of 26 patients tested had a positive result. Prior reports indicate no clear association between subtype and ANA pattern; this cohort, however, demonstrated a trend toward segrega-
tion by subtype (generalized with a homogeneous pattern, linear and plaque with a speckled pattern, and mixed with a nucleolar pattern). This may indicate that morphea subtypes are distinct phenomena with distinct antigenic targets. Because ANAs were not tested in all patients and may have been tested only in more severely affected patients, conclusions are limited.

Limitations of the study are those inherent in a retrospective review, including ascertainment bias in acquisition of medical and family histories and laboratory testing, as well as recall bias in reporting of information by patients and families. Subtype classification was dependent on the treating physician and may not reflect standard criteria. Conclusions regarding autoantibodies are limited by the relatively low numbers of patients who were tested. Prospective longitudinal studies examining these findings in greater detail are indicated.

In conclusion, there is a strong association between generalized morphea and, to a lesser extent, mixed morphea with markers of a systemic rather than skin-limited autoimmune process (high frequency of concomitant autoimmune disease, systemic findings, and positive ANAs), and plaque-type morphea may represent a single-organ (skin only) autoimmune process. This has implications for the management of these patients. Specifically, results of this study suggest that patients with generalized and mixed subtypes should be aggressively monitored for the presence of autoimmune disorders and systemic manifestations and treated with systemic immunosuppressive agents when indicated. These findings may warrant a reexamination of the current classification of morphea from the perspective of inclusion of extracutaneous disorders.

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Correspondence: Heidi T. Jacobe, MD, JA5.521, Department of Dermatology, UT Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9069. (Heidi.jacobe@utsouthwestern.edu).

Author Contributions: Mr Leitenberger, Ms Cayce, and Drs Bergstresser and Jacobe had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Leitenberger, Haley, Bergstresser, and Jacobe. Acquisition of data: Leitenberger. Analysis and interpretation of data: Leitenberger, Cayce, Haley, Adams-Huet, Bergstresser, and Jacobe. Drafting of the manuscript: Leitenberger, Cayce, and Jacobe. Critical revision of the manuscript for important intellectual content: Leitenberger, Cayce, Haley, Adams-Huet, and Jacobe. Statistical analysis: Haley and Jacobe. Obtained funding: Adams-Huet. Administrative, technical, and material support: Leitenberger, Cayce, Bergstresser, and Jacobe. Study supervision: Haley and Jacobe.

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