Clinical and Demographic Characteristics of Pediatric Patients Diagnosed with Localized Scleroderma: A Retrospective Analysis

Lokalize Sklerodermalı Çocuk Hastalarda Klinik ve Demografik Özellikler: Bir Retrospektif Çalışma

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ABSTRACT

Objective: Localized scleroderma (LS), which is also called as morphea, is a rare skin disease with unknown etiology. LS is typically characterized by sclerosis in the dermis and the subcutaneous tissue. The number of retrospective studies examining the epidemiological, clinical and laboratory data of patients with juvenile LS in Turkey is very limited. The purpose of this study was to investigate the clinical and demographic characteristics of pediatric patients under the age of 18, who were followed up with a diagnosis LS, also to evaluate and compare these findings with available literature.

Material and Methods: The medical records of 39 patients, who had been clinically and histopathologically diagnosed with LS and followed up in our clinic between 2012-2018, were retrospectively reviewed. Demographic, clinical and laboratory findings, and treatment options of the patients were recorded.

Results: A total of 39 pediatric patients (8 boys, 31 girls, mean age 12.1 years) with LS were enrolled in the present study. The age at disease onset was 8.6 years. The mean duration of the disease was 3.6 years. The most common type was plaque type morphea. In two cases, there was movement restriction in the legs, and lichen sclerosus was concurrently present in another case. 12 patients had antinuclear antibody positivity, while 3 cases had positive Borrelia antibodies.

Conclusion: Morphea has lifelong complications for children. Early diagnosis and monitoring of morphea in the childhood period is important in order to avoid both physical and psychological sequelae that may occur in the future.

Key Words: Epidemiology, Localized scleroderma, Morphea, Pediatric patients
Localized scleroderma (LS), which is also known as morphea, is a rare inflammatory skin disease, that causes sclerosis in the dermis and subcutaneous tissue. Although the exact underlying mechanisms have not been fully understood yet, many factors have been implicated in the etiopathogenesis of morphea (1-3). Morphea is more frequent in females and the incidence has been reported to be 0.4 to 2.7 % (1,2,4-6). The prevalence of morphea is equal in adults and children (2,7). 90 % of children with morphea are aged between 2 and 14 years old. Morphea is well-known with the potential to cause functional and cosmetic problems. While the erythematous purple patches and plaques are observed in the inflammatory phase, they become white and sclerotic lesions and surrounded by a violet halo over time. These lesions generate post-inflammatory hyperpigmentation during improvement (1,4,5).

There have been many classifications related to morphea, while the most recent classification belongs to Laxer et al. (6). 20 % of morphea patients consist of children, and it is 10 times more common than systemic sclerosis (4,7,9,10). Although several studies are available worldwide on the epidemiological, clinical and laboratory data of patients with pediatric morphea, there is a shortage of these data in our country (11-13). The aim of the present study was to investigate the demographic, clinical, laboratory characteristics and treatment modalities of pediatric patients with morphea, also to compare our findings with the available literature.

This study was approved by the local ethics committee (IRB NO:17/10/2017-2017/08/09-2017/47). The files of 39 patients, who had been clinically and histopathologically diagnosed with morphea and followed up in our clinic between 2012-2018, have been retrospectively reviewed. Patients aged 18 and below have been included in the study. Demographic characteristics, physical examination and laboratory findings (hemogram, sedimentation rate, biochemistry analysis, Borellia antibody, antinuclear antibody (ANA), antids- DNA (double stranted DNA antibody) etc.) of the patients were recorded. Age of disease onset, its duration, clinical type, involved anatomic site, accompanying systemic signs and symptoms, triggering factors, laboratory findings, family history of rheumatic disease, and treatment options were recorded. The presence of accompanying diseases was also investigated.

The disease subtypes were classified as localized plaque, linear, generalized and mixed type according to the Laxer classification (8). One or several plaques that were placed in maximum 2 anatomic sites (head - neck, each extremity, trunk) in oval or rounded configuration were regarded as localized morphea and the type which involved at least 2 anatomical sites with 4 or more infiltrated plaques, each of which was larger than 3 cm, was considered as generalized morphea; sclerotic lesions with linear fibrotic banding (affecting extremities and head region - en coup de sabre (ECDS)) were accepted as linear type; the type containing linear and plaque types was considered as mixed type; the type with the involvement of skin and deep layers of the connective tissue was regarded as pansclerotic morphea (8).

Patients have been divided into 4 groups depending on their age: age 0-2 (baby), age 3-5 (preschool), age 6-11 (school child) and age 12-18 (adolescent). 0-2 years of age consisted of 2.6 % (n=1) of cases, ages between 3-5 consisted of 7.7 % (n=3), ages between 6-11 years consisted of 30.8 % (n=12), and ages between 12-18 years consisted of 59 % (n=23) cases of the patients. Statistical analysis was performed using SPSS software, Version 20 (SPSS Inc., Chicago IL, USA). Frequencies were calculated for variables related to demographic and clinical patient characteristics. Qualitative variables were expressed in percentage. Quantitative variables were expressed in mean values.

A total of 39 pediatric patients (8 boys 31 girls, mean age 12.1 years, range: 2-18 years) with morphea were enrolled. 79.5 % of the patients (n=31) were girls, the female/male ratio was 3.9:1. The majority of patients were in the age group of 12-18 years (n=23). The mean duration of disease before diagnosis was 3.6 years. The age of disease onset was 1-16 with an average of 8.6. The most common morphea type was plaque type with 56.5 % (n=22); followed by linear type with 25.6 % (n=10) and generalized type with 10.2 % (n=4), and mix type with 7.7 % (n=3). There were no deep and pansclerotic types. The most common site of anatomic involvement was the trunk. Only trunk involvement was 33.3 % (n=13), while the involvement of extremities alone was 28.2 % (n=11), the involvement of more than one site was 17.9 % (n=7), and also there was head-neck involvement in 20.5 % (n=8) of patients. The plaque types...
### Table I: Age, gender and clinical characteristics of the cases.

| Patient Groups | P.No | F/M | Mean age | The Age of Onset | Mean D.period | Patient numbers / Lesion Type | Patient numbers / Localization% |
|----------------|------|-----|----------|-----------------|---------------|------------------------------|--------------------------------|
| 0-2y (n=1 2.56%) | 1/- | 1/2 | 2 years | 1 year | 1 year | 1-Plaque | On the left leg |
| 3-5y (n=3 7.69%) | 2/1 | 10/2 | 4 years | 2.6 years | 1.3 years | 1-Linear 2-Plaque | 6-Linear 5-Plaque 1-Mix |
| 6-11y (n=12 30.76%) | 1/1 | 10/2 | 8.25 years | 6.8 years | 1.8 years | 14-Plaque 4-Generalized 3-Linear 2-Mix | 5-Face 1-Nose 2-forehead 2-Cheek 5-Legs 6-Trunk 5-More than one |
| 12-18y (n=23 58.9%) | 18/5 | 18/5 | 15.1 years | 11 years | 14.6 years | 22-Plaque (56.4%) 10-Linear (25.6%) 4-Generalized (10.2%) 3-Mix (7.69%) | 8-Face- 20.5% 13-Trunk-33.3% 11-Legs-28.2% 7-More than one-17.9% |
| TOTAL n=39 100 % | 31/8 | 3.9:1 | 12.1 | 7.0 | 3.56 years | 22-Plaque (56.4%) 10-Linear (25.6%) 4-Generalized (10.2%) 3-Mix (7.69%) | 8-Face- 20.5% 13-Trunk-33.3% 11-Legs-28.2% 7-More than one-17.9% |

### Table II: Comparison of laboratory findings, treatment and concomitant diseases by age groups.

| Patient Groups | Concomitant Diseases, Travma story Family story | ANA, AntiDsDNA Positivity The other lab findings P.No | Treatments P.No |
|----------------|-----------------------------------------------|-----------------------------------------------------|----------------|
| 0-2years (1)   | Restriction of left leg motion -              | -                                                   | Topical Steroid |
| 3-5years (3)   | 2-Vitamin D defiency 1-Anemia (iron defiency,) | 1-ANA +                                            | 1-Topical steroid |
|                | 1-Genital Lichen sclerosus                    |                                                    | 2-Methotrexate |
|                | 1-Deformities of leg                          |                                                    | 1-Hydroxychloroquine |
|                | 1-Diabetes Mellitus                           |                                                    | 2-Systemic Steroid |
|                | 1-Travma story +                              |                                                    | 1-Calsipotril |
| 6-11y (12)     | 6-Anemia (iron defiency) 5-VitaminB12 defiency | 5-ANA+ 1-Anti dsDNA + 1-CRP +                      | 2-Topical steroid+2-Calsipotriol |
|                | 1-Hashimoto tiroiditis                        |                                                    | 6- Calcineurin inhibitors |
|                | 3-Travma story +1-Arthritis story of his brother |                                                    | 2-Methotrexate |
|                |                                               |                                                    | 3-Colchichine |
|                |                                               |                                                    | 1-Systemic Steroid |
|                |                                               |                                                    | 2-UVA -1 |
| 12-18y (23)    | 7-Anemia (iron defiency), 17.9%              | 6-ANA+ 1-Anti dsDNA + 1-CRP + 3-Borrelia antibodies 2-RF + | 8-Topical steroid+Calsipotriol |
|                | 5-VitaminB12 defiency 12%                     |                                                    | 6-Calcineurin inhibitors |
|                | 2-Vitamin D defiency 5.1%                     |                                                    | 7-Colchichine |
|                | 1-Genital LS, 2.5 %                           |                                                    | 2-Methotrexate |
|                | 1-Hashimoto tiroiditis, 2.5%                  |                                                    | 1-Systemic Steroid |
|                | 1-Diabetes mellitus, 2.5%                     |                                                    | 1-Hydroxychloroquine |
|                | 4-Travma story +10.2%                         |                                                    | 2-Narrow bandUVB, |
|                | 2-Deformities of leg, 5.1%                    |                                                    | 1-Laser |
|                | 1-Arthritis story of his brother, 2.5%        |                                                    | 2-Depigmentation therapy |
|                |                                               |                                                    | 1-İsotretinoin |
| Total % (39)   | 12- ANA +, 30.7%                              | 12- ANA +, 30.7%                                   | 1-Topical steroid, 2.5 % |
|                | 2 Anti ds DNA, 5.1%                           |                                                    | 10-Topical steroid+Calsipotriol |
|                | 3- Borrelia antibodies, 7.7%                  |                                                    | 12-Calcineurin inhibitors |
|                | 2-RF +, 5.1%                                 |                                                    | 10-Colchichine, 25.6% |
|                | 2-CRP +, 5.1%                                |                                                    | 12-Calcineurin inhibitors, 30.7% |
|                |                                               |                                                    | 10-Colchichine, 25.6% |
|                |                                               |                                                    | 6-Methotrexate, 15.4% |
|                |                                               |                                                    | 2-Hydroxychloroquine, 5.1% |
|                |                                               |                                                    | 4-Systemic Steroid, 10.2 % |
|                |                                               |                                                    | 1-İsotretinoin, 2.5 % |
|                |                                               |                                                    | 2-Narrow band UVB, 5.1% |
|                |                                               |                                                    | 2-UVA-1, 5.1% |
|                |                                               |                                                    | 2-Depigmentation therapy, 5.1% |
|                |                                               |                                                    | 1-Laser, 2.5% |
Akbas A and Kılınc F

The incidence of linear morphea varies between 25%-70% (2,5,21). It is well-known that plaque type is seen more frequently in adults, and linear morphea is seen more frequently in children (2,5,6,14,19). Many researchers have made observations supporting this view (14-16,22,23). In a study from Turkey, Izol et al. (11) also stated that they encountered the linear type morphea more commonly. Marzano et al. (17) suggested that plaque type morphea is a more common subtype in children with a range of 48.4 %. Meanwhile according to results of our study, the incidence of plaque type was 56.4 %, while the linear type was 25.6 %. From this aspect, our study is similar to that of Marzano et al.'s (17). This rate was reported for plaque type by Christen Zaech (15) as 36 %, Mertens (16) as 28.6 %, Leitenberger (19) as 27.9 %, and Wu et al. (18) as 15 % . Mix type, which includes more than one type, is seen in 15 % of the children (2,21). Marzano et al. (17) reported that the rate of mix type was determined as 14.3 %, while Wu et al. (18) reported it as 20% and Zulian (14) as 23%. In our 39-case study, the rate of mix type was 7.7 %. In the generalized type morphea, there are four or more plaques in more than one anatomic site. It is observed in a range of 7-9 % (2,5). In our study, the rate of generalized type morphea was 10.2% (4 cases).

Some triggering factors such as vaccination, drugs, chemical substances, trauma, insect bites, sunburn, infections, radiation, autoimmunity and psychological stress may play a role in the etiopathogenesis of morphea (3,24). The presence of environmental factors was found in 13.3% (n=100) of the patients, 7.3% of which was traumatic (14). Only 4 of our...
patients (10.2%) had an history of trauma and were compatible with the literature. The role of Borrelia burgdorferi infection in the etiology of morphea has been questioned for many years. In recent years, the relationship with Borrelia Burgdorferi and morphea has been reported. Although there are reports describing clinical improvement of morphea with treatment of Borrelia Burgdorferi, some of the results are contradictory (25). In our study, we detected three cases, whom Borrelia IgG antibodies were positive. These patients had not previously received treatment for Borrelia infection.

In some studies, extracutaneous changes have been reported especially in the group of morphea starting in childhood (7,24). We, however, did not detect extracutaneous involvement in our patient group. This may be due to the inadequacy in the monitoring of the disease progression because of the retrospective nature of the study.

In juvenile morphea frequently autoimmune diseases can accompany the disease. This ratio can vary from 1% to 3% (20). In some studies, the association of autoimmune diseases with morphea has been reported as high as 17% (20). In a study conducted by Leitenberger et al. (19), 4.9% of morphea cases showed an accompanying autoimmune or rheumatologic disease such as vitiligo, psoriasis, celiac disease, alopecia areata, autoimmune thyroiditis, etc., similar to what Ceylan et al. (26) reported from our country. In our study, there were only one case of autoimmune thyroiditis, diabetes mellitus and lichen sclerosis. However, among our patients, there were 7 cases with (17.9%) iron deficiency anemia and 5 (12.8%) cases with vitamin B12 deficiency, which are frequently found in this age group. This may be related to inadequate intake of iron and vit B12 in the diet of children.

The presence of autoimmune disease in the family is 12%-25% higher in pediatric morphea than in adults (19,20). It has been reported that familial autoimmunity is more common in the generalized and mixed type (15). Zulian et al. (14) found this ratio to be 23.5% for generalized type, 12% for linear and plaque type, while Leitenberg determined it as 4.9% (19). One of our patients with plaque morphea had a sibling history with rheumatoid arthritis (2.6%).

Linear morphea is more frequent in the first two decades and causes deformation due to the fact that it may involve deep tissues affect the underlying tissue (4,6). Piram et al. (27) also stated that this type of morphea may be refractory to treatment, and that it needs long-term follow-up. Marzano et al. (17) reported that musculoskeletal anomalies such as limb contracture, limited range of motion and arthralgia etc. in children were normally 12%, while it was 45% children with linear morphea. In our study group, orthopedic complications were detected in only two patients with linear morphea, which were on the left side. This may support the view that orthopedic complications are more common in children with linear morphea.

Among the studies conducted, changes in various laboratory parameters were indicated in patients with morphea (5,28,29).

Patients with extracutaneous involvement were found to have increased levels of inflammatory parameters such as ESR and CRP (9). In those who have joint damage, the RF rate increases up to 25%-40% (9). In terms of the inflammation parameters, only 2 cases (5.12%) had elevated CRP and RF in our patient group.

Autoantibody positivity is also seen very commonly in morphea (30,31). However, the clinical and prognostic significance of these autoantibodies is still not understood (9). The presence of extensive morphea in a patient who had an ANA positivity of 1/1000 titer may indicate that serology may be important in terms of progression. Woo et al. noted that ANA and RF positivity should be considered as sign in terms of extracutaneous involvement (30). Many autoantibody positivity, such as ANA, anti-ds-DNA, anti-histone antibody, and anti-Scl 70 has been reported in morphea cases. Meanwhile, ANA positivity was found in 5.9%-73% of the cases on the literature (9,17,19). It has been reported that ANA positivity ratio is higher in generalized and mix types (19). These investigators reported that ANA positivity was 44%-53% in adults and 26%-53% in children, indicating a difference between the two groups. Parlak et al. (13) found in their study that ANA positivity was 26.1% for the generalized type and only 8.7% for the mixed type. Marzano et al. (17) detected a similar rate of ANA positivity (26%-53%), while other autoantibodies were detected in 7%, and it was higher in the generalized type. The rate of ANA positivity was 30.7% in our study (in 12 cases).

In addition to ANA; Scl-70, anti-centromere, anti-dsDNA, and anti-histone antibody positivity can be seen in patients. Zulian et al. (14) found antids-DNA at 4%. In a study performed by Sato et al. (29), anti-histone antibodies were found to be associated with the number of morphea lesions and it was suggested that it could be a serologic marker for generalized involvement. In our study, the antids-DNA antibodies were present in only 2 (5.1%) cases, whereas no anti-histone antibody was detected in any case.

Since the cause of morphea is not known exactly, there is no effective specific treatment. The goal of the treatment is to reduce the progression of the disease in the early period in order to prevent functional and cosmetic complications. Treatment options are assessed according to the type and severity of the disease, and the presence of complications (1,2,5). For localized plaque type morphea, first-line treatment has been reported as topical steroids, tacrolimus, imiquimod, combination of calcipotriol and betamethasone, and lesion limited phototherapy [UVA, UVA1, narrowband UVB (nbUVB)] (31,32). Phototherapy, combination of systemic steroids and methotrexate (MTX), hydroxychloroquine, D penicillamine, cyclosporine, sulfasalazine, photopheresis, mycophenolate mofetil (MMF) are the treatment options in the generalized morphea (5,32,33).

In our study, MTX (15.3%) was given to each of the patients with generalized, mixed and ECDS. Systemic steroids were
administered to 4 patients (10.2%). Although colchicine is not mentioned in the morphea treatment guideline, inhibitory effect of this drug on fibroblast proliferation, the effect on elastic fibers, and its anti-inflammatory features have been shown “in vitro”[34]. Colchicine is a preferred drug in our country, as well as in Korea[35]. Some researchers in our country have reported the effectiveness of colchicine treatment in their patients[12,13]. In this study, colchicine treatment was given to 10 patients (25.6%). Spontaneously regression within 3 to 5 years is a matter of fact for morphea, thus treatment for plaque type morphea is generally regarded as unnecessary (9,4,32). In one of our cases with widespread, plaque-like lesions on the back, the treatment was refused by the patient and parents. After 10 years, post inflammatory hyperpigmentation was present, but there was no progress in the disease.

In our study, 24 (61.5%) patients with limited plaque type lesions received topical corticosteroids, calcipotriol, calcipotriol+steroid combination, and tacrolimus and pimecrolimus. Preferred treatment modalities were systemic steroids in 4 cases (10.2%), narrowband UVB, UVA 1 and hydroxychloroquine in two cases (5.1%) and isotretinoin in one case (2.5%). One patient did not receive any treatment. Two patients (5.1%) received scar treatment. It has been shown in various trials that MTX and MMF may be good treatment options in resistant cases (16,32,36). Zulian treated 37% of their patients with MTX, 2% with cyclosporine, 49% with steroids (14% topical steroids, 35% systemic steroids), 26% with D penicillamine, 4% with PUVA, 10% with vitamin D and 17 % with nonsteroidal anti-inflammatory drugs (NSAIDs). In our study, 15.4% of the patients were administered MTX. Treatment results could not be evaluated because the study was retrospective.

CONCLUSION

Although linear morphea was reported as the most common form of pediatric morphea, plaque type morphea was more frequently observed in our study. Due to the cosmetic and functional deformities that can develop in the linear type, early diagnosis and treatment are important. Patients should be carefully examined for extracutaneous symptoms, and further investigations should be performed when necessary. ANA should be followed in terms of systemic and extracutaneous involvement.

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