

## Localized Scleroderma of the Head and Face Area: A Retrospective Cross-sectional Study of 96 Patients from 5 German Tertiary Referral Centres

Alexander KREUTER<sup>1\*</sup>, Georg MITRAKOS<sup>1</sup>, Silke C. HOFMANN<sup>2</sup>, Percy LEHMANN<sup>2</sup>, Michael STICHERLING<sup>3</sup>, Thomas KRIEG<sup>4</sup>, Nina LAHNER<sup>5</sup>, Christian TIGGES<sup>1</sup>, Nicolas HUNZELMANN<sup>4</sup> and Pia MOINZADEH<sup>4</sup>

<sup>1</sup>Department of Dermatology, Venereology, and Allergology, HELIOS St Elisabeth Hospital Oberhausen, University Witten-Herdecke, <sup>2</sup>Department of Dermatology, Allergology, and Dermatotomy, HELIOS University Hospital Wuppertal, University of Witten/Herdecke, <sup>3</sup>Universitätsklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, <sup>4</sup>University of Cologne, Köln, and <sup>5</sup>Ruhr-University, Bochum, Germany. \*E-mail: alexander.kreuter@helios-gesundheit.de

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Localized scleroderma (LS) is a relatively rare sclerotic autoimmune disease that primarily affects the skin, but might also involve adjacent tissues, such as the fat tissue, fascia, muscle, and bone. A recently published European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin includes a classification based on the current German guidelines for LS (1, 2). This guideline distinguishes 5 main subtypes (limited, generalized, linear, deep, and mixed) and considers eosinophilic fasciitis as a separate type within the spectrum of LS (2).

LS “en coup de sabre” (LSECDS) and progressive facial hemiatrophy (PFH) are rare subtypes located on the head and face area, belonging to the group of linear LS. Although large studies already exist on the demographic characteristics and subtype distribution in both adult and juvenile LS, there are fewer data available on the clinical findings of LSECDS and PFH, especially in patients with adult-onset disease (3). As neurological involvement and abnormalities in the central nervous system (CNS) are frequent in LSECDS and PFH, current guidelines recommend magnetic resonance imaging (MRI), irrespective of the presence of clinical symptoms (1, 2). The purpose of this study was to evaluate clinical, radiological and laboratory characteristics in a large cohort of patients with LSECDS, PFH, or overlap of both diseases.

### MATERIALS, METHODS AND RESULTS

A retrospective review was performed using the digital databases of LS patients with linear subtypes, such as LSECDS, PFH, or a combination of both types. A detailed description of the methodology is shown in Appendix S1<sup>†</sup>.

A total of 96 patients with head and face LS was included in this retrospective analysis. Of these, 70 patients had LSECDS, 16 had PFH, and 10 overlapping LSECDS and PFH. The female to male ratio was 2.5:1, with 68 female patients (25 girls and 43 adult women) and 28 male patients (11 boys and 17 adult men). Mean  $\pm$  standard deviation age at first diagnosis was  $21.9 \pm 16.4$  years (range 1–68) (Table S1<sup>†</sup>).

Of the whole cohort, 24 (25%) patients presented extrafacial LS lesions at initial diagnosis. Extrafacial disease was more frequent in patients with PFH (37.5%) and LSECDS/PFH overlap (40%) compared with patients with LSECDS (20%). The most frequently affected site of extrafacial LS lesions was the trunk (8.3%), followed by the neck (4.2%) (Table SII<sup>†</sup>).

MRI and computed tomography (CT) evaluations were available in 52 (54.2%) of the 96 patients (Table SIII<sup>†</sup>). Overall, 27 (28.1%) of the cohort presented neurological symptoms and/or radiological CNS abnormalities. These abnormalities were most common in LSECDS/PFH overlap (80%), followed by PFH (37.5%) and LSECDS (18.6%). Headache (5.2%) was the most frequently presented symptom, followed by epilepsy (4.2%) and migraine (3.1%). Most frequent MRI and CT abnormalities were gliosis (7.3%) and white matter lesions (6.3%). Psychiatric symptoms were not observed in any of the patients.

Among the 96 patients, 14 (14.6%) had other rheumatic diseases (1 case of rheumatoid arthritis and 1 case of spondyloarthritis) or other autoimmune disorders (1 case each of lichen sclerosus, linear IgA-dermatosis, multiple sclerosis, primary biliary cholangitis, and systemic lupus erythematosus; 2 cases of alopecia areata; 5 cases of autoimmune thyroiditis). Overall, 73 (76.0%) of the patients revealed blood parameters of autoimmunity (Table SIV<sup>†</sup>). All 10 (100.0%) patients with LSECDS/PFH overlap had at least 1 positive parameter (total: 18 parameters). The percentage of positive autoimmune parameters was similar in patients with LSECDS (64.3%) and PFH (62.5%). In the whole cohort, ANA were found most frequently (27.1%), followed by anti-smooth muscle antibodies (11.5%), and extractable nuclear antigens (7.3%). Serological screening for antibodies to *Borrelia burgdorferi* was performed in 70 (72.9%) of the patients. Six (6.25%) of them had detectable IgM and IgG antibodies. However, there was no history of a tick bite or clinical symptoms of Lyme disease.

### DISCUSSION

The demographics and subtype distribution of LS have been well described in several large cohorts, including 4 studies of adult-onset and 6 studies of juvenile LS (for review see Lis-Święty et al. (3)). Linear LS is the most common subtype in children (28.6–65%), whereas it accounts for only approximately one-tenth of adult-onset cases (7.1–13.8%) (4–7). There are limited data available on linear LS of the head and face area. To our best knowledge, only 2 comparable cohorts, including a large number of patients with LSECDS and PFH, have been published so far (4, 8). Zulian et al. (4) evaluated 113 patients (99 with LSECDS, 8 with PFH and 6 with LSECDS/PFH overlap) by retrospectively collecting the data of 70 paediatric dermatology and rheumatology centres from all over the world. Doolittle et al. (8) performed a retrospective single centre analysis over a 16-year interval and reported the CNS imaging findings of 88 patients with head and face LS (43 with LSECDS, 30 with PFH and 15 with LSECDS/PFH overlap).

In this study, a substantial proportion (25.0%) of patients presented LS lesions outside of the head and face

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area, with plaque lesions at the trunk and linear lesions at the extremities as the most common findings. Such lesions were more frequent in PFH (37.5%) and LSECDS/PFH overlap (40.0%) compared with LSECDS (20.0%). In the literature, only limited data are available on extrafacial involvement in patients with LSECDS and PFH. For example, in the 2 large cohorts of Zulian et al. (4) and Doolittle et al. (8), extrafacial disease in patients with LS of the head and face is not specifically reported. Presumably, such patients are rather classified as mixed LS. Similar to our findings, a small series of 12 patients with PFH revealed trunk involvement in 3 of them, indicating that careful examination of the entire body is mandatory in all patients with LS of the head and face (9).

CNS findings and neurological involvement are frequent in head and face LS, with abnormalities reported in 19–75% of patients (8). Similar to our findings, most commonly reported clinical symptoms were headache, epilepsy/seizures, and migraine. In our cohort, patients with PFH or LSECDS/PFH overlap more frequently had CNS abnormalities and neurological symptoms (37.5% and 80.0%) than did patients with LSECDS (18.6%). This is in contrast to other studies, where CNS findings were equally present in LSECDS and PFH (4). Interestingly, CNS imaging findings in head and face LS are often present in patients who have no clinical symptoms, CNS lesions are frequently bilateral, and lesions do not necessarily progress in parallel with cutaneous disease activity (8). Approximately half of the patients included in the present analysis had no CNS imaging examinations, similar to previous investigations (8). Thus, the real proportion of CNS abnormalities in LS of the head and face area might be even higher.

Concomitant autoimmune diseases frequently occur in LS. Several studies have evaluated the prevalence of autoimmune disorders in both juvenile and adult-onset LS, but outcomes were divergent (4, 6, 10–13). For example, Zulian et al. (4) have found concomitant autoimmune diseases in 1.7% of juvenile LS, whereas Leitenberger et al. (10) reported such disorders in 29% of adult-onset LS. Our finding of 14.6% of concomitant autoimmune diseases in head and face LS is in line with 2 other studies that demonstrated autoimmune disorders in 10% and 17% of juvenile LS, respectively (12, 13). To our knowledge, this is the largest study that comprehensively evaluated blood parameters of autoimmunity in head and face LS. In our cohort, such blood parameters were present in 76.0% of cases, with the highest rates (100.0%) found in LSECDS/PFH overlap patients. Overall, ANAs tested positive in 27.1% of our patients, similar to Leitenberger et al. (10) who found 28.6% ANA-positivity in 21 juvenile and adult patients with linear LS. Interestingly, the percentage of ANA-positivity seems to be higher in juvenile LS. In line with this, Zulian et al. (4) detected elevated ANA levels in 47.3% of patients with juvenile linear LS. According to these observations, all patients with LS should be monitored for the presence of concomitant autoimmune diseases.

The results of this study should be interpreted in light of its limitations. This was a retrospective cross-sectional study including a relatively small number of patients, especially in the respective subtypes (LSECDS, PFH, and LSECDS/PFH overlap). Moreover, not all evaluated examinations were performed in all patients in our cohort, probably leading to underestimation of its true incidence. Finally, response to treatment regimes, clinical follow-up, and recurrences after therapy were available only to a varying degree.

In conclusion, patients with head and face LS frequently present concomitant extrafacial skin lesions, neurological symptoms and CNS abnormalities, as well as concomitant autoimmune diseases and serological parameters of autoimmunity. These observations argue for distinct clinical, radiological, and laboratory screenings of such patients, as recommended in the current EDF guideline for sclerotic skin diseases. Prospective studies are currently ongoing within the European Network for Localized Scleroderma of the EADV to validate these recommendations.

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