EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2019.19183

Invited Review

Linear Scleroderma of the Head - Updates in management of Parry Romberg Syndrome and En coup de sabre: A rapid scoping review across subspecialties

Daniel H. Glaser[1], Christina Schutt[1], Helena M. VonVille[2], Kaila Schollaert-Fitch[3], Kathryn Torok[1,3]

Abstract

To provide an update on the current management, including evaluation and treatment, and the available diagnostic tools for linear scleroderma of the head, i.e., Parry-Romberg Syndrome and *en coup de sabre* (PRS/ECDS). A rapid scoping review of the literature was conducted to include manuscripts published in English between 2010 and 2019. Literature searches were performed in PubMed and EMBASE databases. The were analyzed for descriptive statistic reporting. This study reviewed 215 manuscripts reporting these 1430 patients. Surgical reports comprised the majority of the reviewed literature. Most PRS/ECDS did not appear to receive comprehensive multisubspecialty evaluation for extracutaneous manifestations; 21% of cases noted neurological screening, 4% noted dental screening, and 3% noted ophthalmologic screening. Methotrexate and glucocorticoids remain the most frequent choice for immunosuppressive treatment, though fewer than 7% of patients reported receiving systemic medical therapies. Surgical procedures for cosmetic or functional improvement were common (59%) among the reported patients. Autologous fat grafting was the most frequently utilized cosmetic treatment (50% of procedures) followed by free flap transfers (24% of procedures). There is ongoing need for standardized evaluation, monitoring, and treatment to prevent morbidity in PRS/ECDS, especially in children. When these patients are managed by rheumatologists, methotrexate, and steroids remain the first-line treatment, but a review of the published literature reflects that this may be a minority. Most PRS/ECDS patients are not evaluated in a multidisciplinary fashion. We propose comprehensive evaluations across subspecialties at the baseline and follow-up levels to monitor disease activity and record extracutaneous manifestations, treatment algorithms, and surgical intervention considerations.

Keywords: Parry Romberg, facial hemiatrophy, *en coupe de sabre*, evaluation, treatment, localized scleroderma

ORCID IDs of the authors:
D.H.G. 0000-0002-2934-5366;
C.S. 0000-0002-6863-5366;
H.M.V. 0000-0001-5193-2391;
K.S.F. 0000-0001-9062-1772;
K.T. 0000-0002-1662-143X.

Cite this article as: Glaser DH, Schutt C, VonVille HM, Schollaert-Fitch K, Torok K. Linear Scleroderma of the Head - Updates in management of Parry Romberg Syndrome and En coup de sabre: A rapid scoping review across subspecialties. Eur J Rheumatol 2020; 7(Suppl 1): S48-S57.

[1] UPMC Children's Hospital of Pittsburgh, Pittsburgh, PA, USA
[2] University of Pittsburgh Health Sciences Library System, Pittsburgh, PA, USA
[3] University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Address for Correspondence: Kathryn Torok; University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

E-mail: kathryn.torok@chp.edu

Submitted: November 4, 2019
Accepted: November 24, 2019

Introduction

Localized scleroderma (LS), also known as morphea, is an autoimmune condition defined by sclerosis and the resulting atrophy of the skin and subcutaneous tissues after an initial inflammatory phase. LS typically presents in childhood with an annual incidence of 1-3 per 100,000 individuals, and has a prevalence of 2 per 1000 children (1). LS can present as isolated lesions or spread more diffusely and has been subtyped via the Padua criteria according to the extent and depth of the associated lesions (2), which are as follows: circumscribed (superficial and deep), linear (trunk/extremity and face), generalized, and pansclerotic. Certain LS subtypes and deep tissue lesions have been associated with significant morbidity, and may especially affect the musculoskeletal and neurological systems (3). The clinical manifestations of LS differ significantly from a related disorder, systemic sclerosis (SSc), which histologically mirrors LS from a cutaneous standpoint, but has differing internal organ manifestations, especially in the gastrointestinal and cardiopulmonary systems (4). Linear scleroderma is the most common subtype of LS and typically presents as a line of dyspigmented, fibrotic, or atrophic skin on the limbs, forehead, or scalp (2).

Linear LS lesions located on the scalp and forehead are commonly termed *en coup de sabre* (ECDS) for their resemblance to scars caused by a sword strike to the head. Lesions generally occur unilaterally in the form of a Blashkoid distribution, potentially involving deeper neurologic, ocular or oro-dental tissues (5). This condition is closely associated with and is frequently found in concurrence with idiopathic progressive hemifacial atrophy, also termed Parry-Romberg Syndrome (PRS) (6). PRS is characterized by progressive unilateral atrophy of the skin and soft tissues of the face and underlying muscle and os-

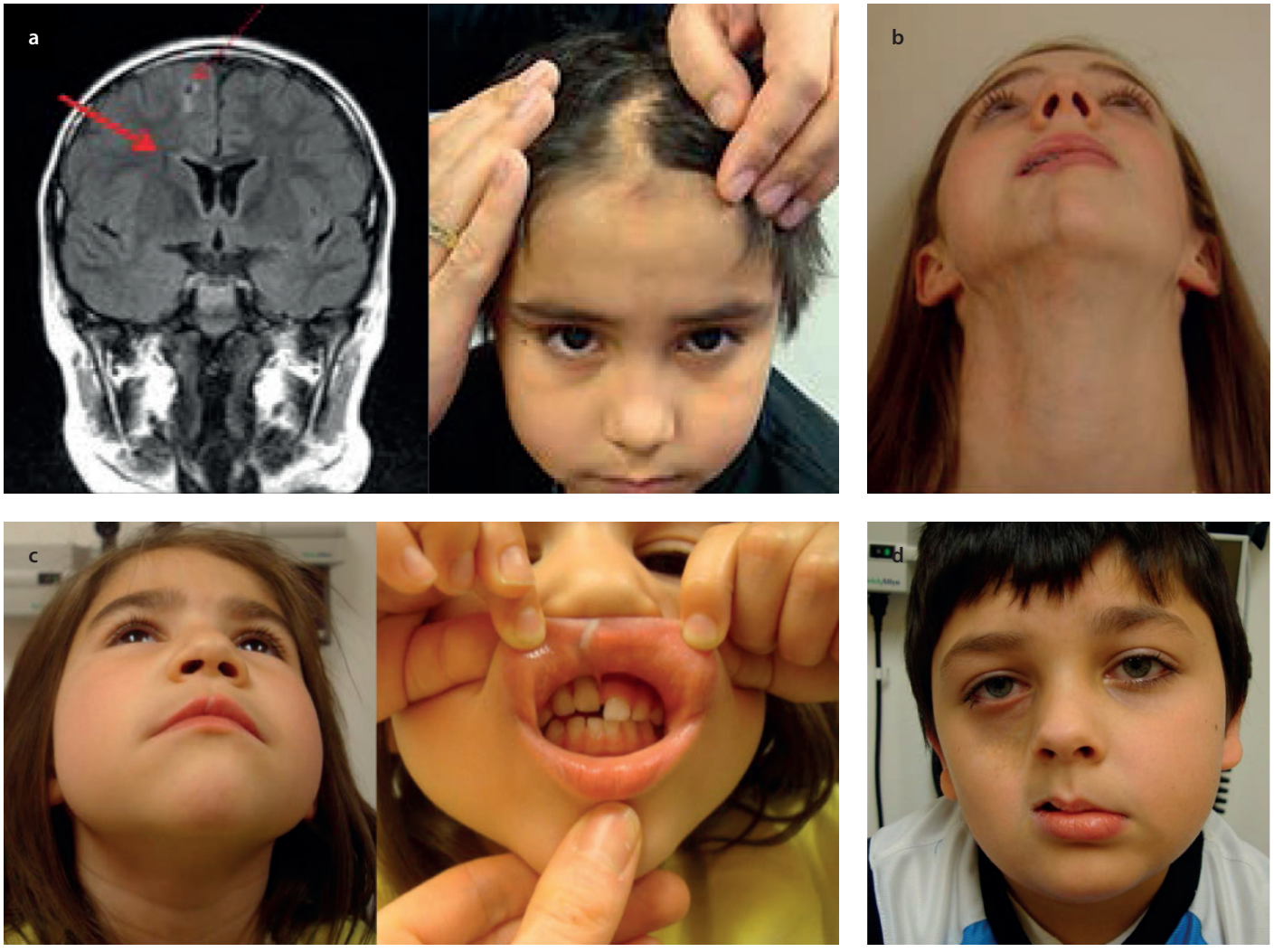

Figure 1. a-d. Spectrum of Parry-Romberg syndrome (PRS)/ en coup de sabre (ECDS) patient findings. (a) ECDS lesion of scalp with ipsilateral abnormal T2 signal on brain magnetic resonance imaging (MRI) in a similar plane as the cutaneous findings. (b) PRS/ECDS overlap with skin, soft-tissue, and bone atrophy. (c) PRS/ECDS overlap with single cutaneous band accompanied by significant intraoral manifestations in the same anatomical plane. (d) PRS/ECDS overlap with predominant soft tissue and bone atrophy.

"Written publication consent was obtained from the parents of the patients who participated in this study."

teo-cartilagenous structures (7). Classification by severity or type has been reported in surgical contexts, but these have not been generally utilized by dermatologic or rheumatologic disciplines. Surgical classification schemes include the level of trigeminal nerve branch involvement and the depth or level of tissue layer involvement (7-9).

There remains significant controversy in the literature as to the relationship between ECDS and PRS (10). Currently, both are considered subtypes of linear LS of the head, whose distinguishing clinical features lie along a continuum that is unique to each patient (Figure 1). Both PRS and ECDS were traditionally considered self-limiting, with the active disease phase lasting 2-10 years prior to "burnout", although more recent longitudinal cohort studies have shown that its recurrence is similar to other autoimmune conditions (11, 12). When compared, both ECDS and PRS have similar frequency and severity of extracutaneous clinical manifestations (ECMs) (13). In some cases, ECMs can precede apparent cutaneous development of classical ECDS or PRS symptoms, posing a significant challenge to clinicians (14). Retrospective cohort studies in pediatric and adult populations have reported the presence of neurological, musculoskeletal, vascular, ocular, and oromaxillofacial ECMs in 20%-40% of ECDS/PRS patients (15).

The underlying etiology for ECDS/PRS remains unclear (6, 13). There is a clear role of autoimmune-based inflammation in other forms of LS, as well as a strong suggestion of a similar role in ECDS/PRS based on CSF findings, histology, response to treatment, and the fact that a proportion of these patients have concurrent LS lesions in other areas of the body (1). Biopsy results of ECDS lesions classically show atrophy of the epidermal, dermal, and subcutaneous layers along with

Main Points

- Coordinated subspecialty evaluation of PRS/ECDs patients is important to fully address the multisystem impact of the disease.
- Systemic immunosuppression remains the gold standard of treatment, though prospective studies are lacking to verify its effectiveness.
- Autologous fat grafting and free flap transfers are the most frequently utilized aesthetic corrective procedures, though validated outcome measures are generally absent.
- Continued development of prospective disease assessment and monitoring metrics is important for improving clinical care.

thickened and disorganized collagen fibrosis (16). Lymphocytic inflammatory infiltrates may be present around adnexal, vascular, or neural structures. Similar histopathological findings have been noted in biopsy of regions of hemiatrophy without clinically apparent sclerosis in the skin in PRS patients (13, 17).

A neurogenic component is suggested by the presence of facial atrophy patterns that are commonly limited by the sensory dermatomes of the trigeminal nerve (7). This has been experimentally demonstrated in rat and mouse models undergoing sympathectomy of the superior cervical ganglion that have been observed to develop similar appearances (18). Trauma and infection have been implicated in case reports but are not clearly linked to ECDS/PRS development (19).

A delayed diagnosis is common due to the gradual onset of symptoms and the multitude of specialties that may initially be involved in the evaluation process. Furthermore, ECDS and PRS have historically been recognized by a variety of names across medical disciplines, further frustrating collaborative clinical diagnostics. Recognizing the need for an up-to-date understanding of the practice of each of the specialties treating PRS/ECDS, a scoping review of original-research literature in the past 10 years was performed to identify updates to diagnostic and monitoring modalities and treatment options, with the development of a proposal of minimum standards for the evaluation, treatment, and monitoring of PRS/ECDS.

Methods

Protocol and registration

This rapid scoping review follows the reporting guidelines set forth by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and has been assessed for quality using the AMSTAR checklist (https://amstar.ca/Amstar_Checklist.php) (20). This review was not registered with PROSPERO.

Eligibility criteria

The patient eligibility criteria and methods of analysis were determined *a priori*. The included studies were required to focus on patients or participants with LS, specifically the subset of linear scleroderma affecting the head: *en coup de sabre* and/or Parry-Romberg syndrome of any age. Only articles published in English from 2010 to 2019 were included in the final review. Research articles from indexed journals were included, whereas comments, editorials, dissertations, conference proceedings, etc. were excluded. Case reports and case series, as well as cross-sectional, case-control, and cohort studies were included in this review.

Information sources for literature search

The PubMed (NLM) and EMBASE (Elsevier) databases were searched and a health sciences librarian (HVV) with systematic review experience developed all the search parameters. The date of the final search was July 26, 2019. Concepts that comprised the search were: linear scleroderma and Parry-Romberg syndrome. A combination of MeSH terms along with title, abstract, and keywords were used to develop the initial PubMed search criteria (Table 1). The search was then adapted to search EMBASE. Information on strategies and date searched in each database is available from the corresponding author.

Bibliographies of relevant articles were examined by the first author (DG) for studies not found through previous database searches. A final author search was also performed on authors with four or more articles that were included in the systematic review. Relevant articles were searched in Scopus (Elsevier) by the health sciences librarian (HVV) to determine if they were cited by studies not found through previous searches. Next, each article was searched in Retraction Watch (http://www.retractionwatch.com). An additional search was completed for each study in PubMed using a retraction/correction database search filter (http://bit.ly/pubmed-filters) to ensure that the study was included and the correct data was used for analysis.

EndNote (Clarivate) was used to store and manage all citations found in the search process and to check for duplicates. Search strategies and results were tracked using an Excel 2016 (version 1803, build 9126.2295, Microsoft Inc, Redmond, WA) workbook designed specifically for this purpose (https://showcase.dropbox.com/s/Kf4pYVTvFqSJdZR2Spzlu). A list of excluded citations from each step may be requested from the corresponding author.

Study selection

To determine the agreement of the results between search engines, an inter-rater reliability test was conducted using a Cohen's kappa reliability test. Prior to screening all titles and abstracts, an online random number generator (https://www.random.org/integers/) was used to create a random sample of 31 numbers that were input into a spreadsheet (Excel 2016, Microsoft, Redmond, WA, USA) workbook designed specifically for the this test. If there were any duplicate numbers, a replacement was assigned by choosing a number between the pair and the adjacent number below or above. The numbers corresponded to line numbers within the Excel workbook, resulting in a random sample of titles and abstracts; authors and journal titles were not included in the sample. Two authors (DG and CS) independently screened the sample. The test was considered successful if Cohen's κ was >0.70. The authors then independently screened all titles and abstracts while being blinded to the authors and journal titles, using an Excel workbook developed for this purpose. The data were compiled and a consensus was

Table 1. Example of an electronic search strategy.

PubMed Search Strategy	
#1	Scleroderma, Localized[mesh:noexp]
#2	"en coup de sabre"[tiab] OR morphea[tiab] OR morphoea[tiab] OR scleroderma[tiab]
#3	Facial Hemiatrophy[mesh:noexp]
#4	"en coup de sabre"[tiab] OR facial hemiatrophy*[tiab] OR hemifacial atrophy*[tiab] OR HFA[tiab] OR Parry Romberg*[tiab]
#5	(#1 OR #2 OR #3 OR #4)
#6	head[mesh:noexp] OR face[mesh:noexp] OR cheek[mesh:noexp] OR chin[mesh:noexp] OR eye[mesh:noexp] OR forehead[mesh:noexp] OR mouth[mesh:noexp] OR lip[mesh:noexp] OR nose[mesh:noexp] OR scalp[mesh:noexp]
#7	head[tiab] OR face[tiab] OR cheek[tiab] OR chin[tiab] OR eye[tiab] OR forehead[tiab] OR mouth[tiab] OR lip[tiab] OR nose[tiab] OR scalp[tiab]
#8	(#6 OR #7)
#9	#5 AND #8
#10	((#9 AND English[la] AND 2010:2020[dp]))

reached on disputed items via arbitration by an expert in the field (KT). Articles considered for inclusion were independently reviewed by two authors (DG, CS) and consensus was reached by facilitating discussions on any disagreements. Additional articles were excluded during the data extraction process if the reviewer was unable to identify sufficient congruent data points for extraction based on the predefined data extraction forms. Both reviewers (CS and DG) agreed on the exclusion of these articles.

Data collection process

Data extraction was performed using electronic Excel 2016 workbooks developed by the primary author (DG), with variables guided by an expert in the field (KT). Forms were piloted by independent extraction by two authors (DG, CS) of two random studies of each study type (case report, case series, or cohort). The final data extraction from all the included studies was performed by a single reviewer (DG). After this final extraction, 5% of the included studies were randomly selected and re-extracted by a single reviewer (CS) to ensure consistent inter-rater data variable extraction. The missing data were not interpolated and authors were not contacted for additional details.

Data items

Data variables sought included bibliographic information, geographic location, patient demographics, clinical and diagnostic evaluations, pharmacological treatments, nonpharmacological treatments, and surgical treatments. Outcomes were assessed descriptively as no consensus outcome measures exist for ECDS/PRS treatment.

Risk of bias in individual studies

Bias was not systematically assessed in this review at the individual study level.

Summary measures

Descriptive statistics were calculated for multiple clinical variables in Excel 2016. No formal measures of difference were calculated due to the significant heterogeneity among studies and lack of standardized outcome measures.

Synthesis of results

Data extracted from the included manuscripts was tabulated and combined using simple arithmetic methods. The case series data was tabulated on the individual patient level wherever available, while the cohort study data was extracted for analysis via tabulation of reported instances of each variable and combined additively with summed data from individual patients to produce overall descriptive and summative statistics (DG, CS, KS). Excel 2016 and Word 2016 (Microsoft, Redmond, WA, USA) were used for data visualization.

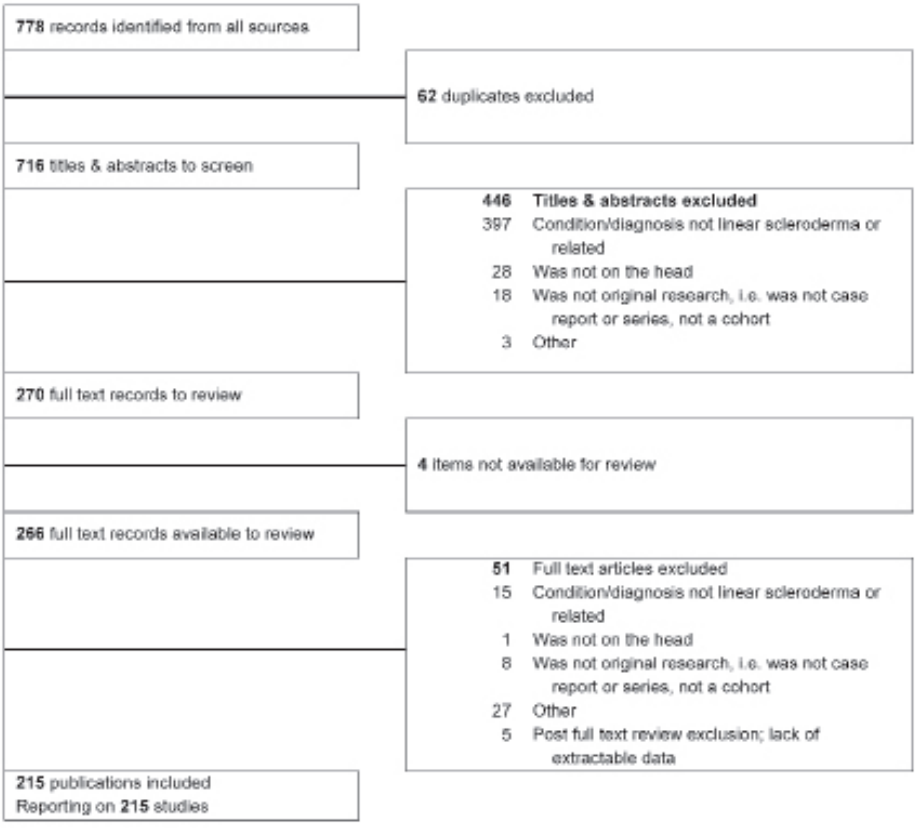

Figure 2. PRISMA flowchart for rapid scoping review process.

Results

Literature and demographics

The systematic review and manual search identified a total of 778 records, of which 215 met the final inclusion criteria for evaluation (Figure 2). Six countries were described, with the majority of patients being in the United States of America, and China and Brazil accounting for 60% of the total (Table 2). Surgical and dermatological subject journals were the source for approximately half of included articles (111/215, 51%) (Figure 3). Only a minority of articles were published in rheumatology or pediatric subject journals.

Table 2. Demographics (N=1430).

	n	(%n)	(%N)
Age	-	-	-
Authorship (Mean = 25 years)	357	-	(25.0)
Under 18	128	(36.0)	(9.0)
Onset (Mean = 15 years)	195		(13.7)
Under 18	140	(71.9)	(9.8)
Sex	**1019**	-	**(71.3)**
Female	662	(65)	(46.3)
Male	357	(35)	(25.0)
Lesion Location	**516**	-	**(36.1)**
Right	248	(48.1)	(17.3)
Left	248	(48.1)	(17.3)
Bilateral	13	(2.5)	(0.9)
Midline	7	(1.4)	(0.5)
Diagnosis	**1427**	-	**(99.8)**
Parry-Romberg Syndrome (PRS)	863	(60.5)	(60.3)
En coup de sabre (ECDS)	433	(30.3)	(30.3)
PRS + ECDS	131	(9.2)	(9.2)
Country of Origin	-	-	-
United States			(28)
Other (combined)			(19)
China			(17)
Brazil			(15)
United Kingdom			(8)
Germany			(7)
India			(6)

ECDS: *en coup de sabre*; PRS: Parry-Romberg Syndrome.

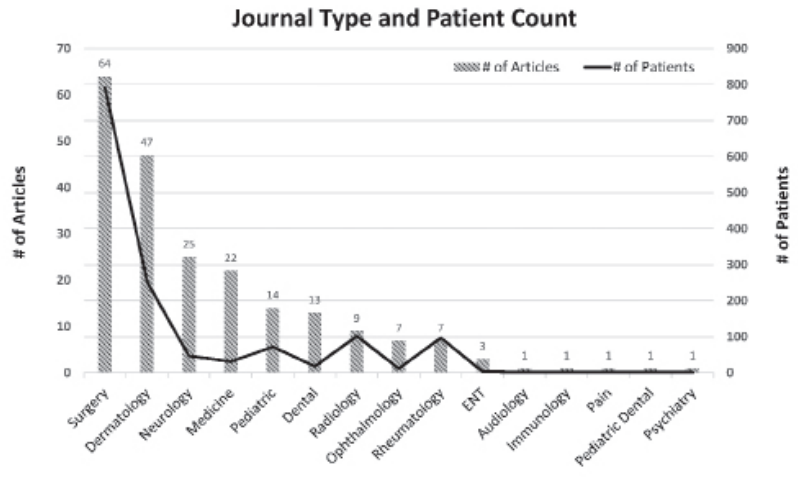

Figure 3. Journal topic-category and relative contribution of patient cases. There is apparent over-representation of surgical journals in terms of both publication number and patient cases. Note that journal topic-category may not reflect the medical specialty of the primary authors.

Table 3. Clinical evaluations (n=patients who received at least one exam, N=1430).

	n	(%n)	(%N)
Neurological	**300**	**-**	**(20.9)**
MRI Brain	272	(65.5)	(19.0)
CT Head	84	(20.2)	(5.9)
MRA/CTA	24	(5.8)	(1.7)
EEG	21	(5.1)	(1.5)
Advanced*	14	(3.4)	(1.0)
Ophthalmological	**39**	**-**	**(2.7)**
Dilated Exam	28	(62.2)	(2.0)
Tonometry	4	(8.9)	(0.3)
Ex-ophthalmometry	9	(20.0)	(0.6)
OCT/US	10	(19.6)	(0.7)
Osteological	**168**	**-**	**(11.7)**
CT Face	34	(17.9)	(2.4)
3D-CT	78	(41.1)	(5.5)
Cone Beam CT	43	(22.6)	(3.0)
Cephalogram	35	(18.4)	(2.4)
Dental	**61**	**-**	**(4.3)**
Panorex	50	(75.8)	(3.5)
Advanced^	16	(24.2)	(1.1)
Dermatological	52	-	(3.6)
Biopsy	52	(100)	(3.6)
Photographical	**63**	**-**	**(4.4)**
3D stereophotogrammetry	44	(60.3)	(3.1)
Laser	29	(39.7)	(2.0)

*MR spectroscopy, fiber tractography, SPECT, FDG-EPT.
^3D or 2D intraoral photography, gingival biopsy.

Table 4. Surgical Intervention (n=patients who received at least one treatment, N=1430).

	n	(%n)	(%N)
Surgical Intervention	**844**	**-**	**(59.0)**
Autologous Fat Graft	713	(84.5)	(49.9)
Flap	346	(41.0)	(24.2)
Autologous Fat Graft with Supplement	58	(6.9)	(4.1)
Dermal Fat Graft	56	(6.6)	(3.9)
Other (combined)	48	(5.7)	(3.4)
Medpor Implant	18	(2.1)	(1.3)
Eye Repair	16	(1.9)	(1.1)
Osteotomy	13	(1.5)	(0.9)
Vermillion Flap	11	(1.3)	(0.8)
Rhinoplasty	8	(0.9)	(0.6)
Hyaluronic Filler	7	(0.8)	(0.5)

The included articles described a total of 1430 cases of PRS and ECDS. Over half of the cases were described in surgical journals while rheumatology and pediatric journals were in a significant minority in terms of case reports.

The overall average age of onset reported was 15 years, while the average age at the time of case authorship was 25 years (Table 2). Raw data for both the age at onset and the age at time of authorship was not available from cohort studies, therefore, was not included in the final analysis. Most of the described cases received a diagnosis of PRS and only a minority of cases were noted to have a PRS/ECDS overlap. When reported, the lesion location was evenly distributed between either the right or left side of the face, with a minority of cases showing lesions at the midline or with bilateral presentation (Table 2).

Clinical evaluation for extracutaneous manifestations (ECMs)

The percentage of patients receiving clinical evaluation for ECMs varied according to the ECM type (Table 3). Many of the reviewed cases did not report screening for ECMs. For neurologic manifestations, magnetic resonance imaging (MRI) of the brain was the most common test performed, followed by CT of the head, MRA/CTA, and EEG. Abnormalities were reported in 40% (108/272) of MRI studies. Advanced evaluations including MR spectroscopy, fiber tractography, SPECT, and/or FDG-EPT were performed in a minority of patients. At least one neuroimaging evaluation was reported in 20% (300/1430) of patients.

Ophthalmologic evaluations, including dilatation examination, tonometry, exophthalmometry, and/or optical computed tomography/ultrasound were reported in only 3% of cases. The findings were broad, but most commonly included enophthalmos, lagophthalmos, iritis, and anterior uveitis.

Osteological investigations, including CT Face, 3D-CT, cone beam CT, and/or cephalogram were reported in 12% of cases, both for diagnostic aid and surgical planning. Formal dental evaluation beyond clinical inspection was performed in 4% of cases. Abnormal findings included shortened roots, missing secondary teeth, and alveolar resorption. This does not include indirect dental evaluation from osteological studies. Dermatologic biopsy was infrequently utilized in the reported cases. Quantitative photographical evaluations including 3D stereophotogrammetry and/or laser photogrammetry (not including 2D clinical photographs) were present for 4% of cases.

Treatment

Surgical treatments were noted in over half of patients with many patients receiving concurrent multiple interventions (Table 4). Autologous fat grafting was the most frequently reported intervention followed by various flap-based procedures. Fat graft procedures generally utilized the Coleman technique, also known as structural fat grafting. A variety of additional reconstructive procedures were also utilized, depending on the severity of the patient, encompassing both soft-tissue and bony structural interventions.

Medications were infrequently utilized in the cases reviewed. Topical therapies were identified in 4% of cases, most frequently done by glucocorticoids and calcipotriol. Systemic

Table 5. Pharmacological Treatments (n=patients who received at least one treatment, N=1430).

	n	(%n)	(%N)
Topical	**57**	**-**	**(4.0)**
Glucocorticoid	53	(44.5)	(3.7)
Calcitriol	31	(26.1)	(2.2)
Tacrolimus	18	(15.1)	(1.3)
Phototherapy	10	(8.4)	(0.7)
Other	7	(5.9)	(0.5)
Steroids	**76**	**-**	**(5.3)**
PO	33	(43.4)	(2.3)
IV	16	(21.1)	(1.1)
Unknown	16	(21.1)	(1.1)
Intralesional	11	(14.5)	(0.8)
DMARDs	**96**	**-**	**(6.7)**
Methotrexate	90	(81.1)	(6.3)
Mycophenolate mofetil	14	(12.6)	(1.0)
Azathioprine	3	(2.7)	(0.2)
Cyclophosphamide	3	(2.7)	(0.2)
Cyclosporine A	1	(0.9)	(0.1)
Biologics	**5**	**-**	**(0.3)**
Tocilizumab	4	(80.0)	(0.1)
Abatacept	1	(20.0)	(0.3)

PO: oral; IV: intravenous.

treatment with DMARDs and corticosteroids were noted, though not all DMARD-treated patients received systemic steroids (Table 5). The use of a new targeted monoclonal antibody therapy, including tocilizumab or abatacept, was rare. Adjunctive treatment with cutaneous phototherapy (UVA or UVB) was utilized in less than 1% of patients.

Discussion

Demographics

Consistent with the known epidemiology of PRS/ECDS, more than two-thirds of patients with available data had the onset of disease with the first 2 decades of life. There was an approximately a 2:1 female-male ratio noted in this review, which is in agreement with established literature (2). There was also equal distribution of the side of the lesions, as was expected. Interestingly, more patients received a diagnosis of Parry-Romberg Syndrome (PRS) as compared to linear scleroderma *ECDS*, though this may be an artifact related to the over-representation of surgical literature in this review. It is notable that despite the pediatric-onset predominance of PRS/ECDS, there is a relative paucity of papers published in pediatric literature. This may be due to the traditional focus of allowing PRS/ECDS to "burnout" and only intervening later in life with cosmetic procedures (21). As the recognition of the autoimmune nature of PRS/ECDS and the role of disease-modifying treatments increases, there will hopefully be more prospective analysis on the same published in the coming years (22).

Labs

No universal diagnostic labs exist for PRS/ECDS and exhaustive laboratory investigation is not needed for diagnosis. Previous summaries of the literature have failed to identify any reliable correlation between standard laboratory evaluations (such as CBC and sedimentation rate) and disease status. The same has been suggested for antibody testing, such as Antinuclear antibody (ANA) (23). However, there is potential for risk stratifying LS patients as a whole (PRS/ECDS patients included in prior analyses) with antibody positivity, such as ANA, anti-histone, and anti-single stranded antibody, with these autoantibodies demonstrating the ability to predict disease relapse and correlate their status with disease burden/severity (22, 24, 25). However, evaluation of these autoantibodies has not been performed in larger subsets of PRS/ECDS subjects specifically.

Recent prospective investigations of serum cytokines in LS patients have identified potential blood markers of disease activity including CXCL9 (1, 26). However, the application of these markers to PRS/ECDS patients is unclear and they are not yet widely available in clinical practice.

CNS manifestations

Neurological findings are increasingly being recognized as a common ECM of PRS/ECDS. Previous cohorts have identified CNS manifestations in up to 44% of patients with ECDS/PRS (27). Patients may present with clinically apparent CNS disturbances, such as seizures, hemiparesis, stroke, or cognitive decline, however, a significant number of patients are found to have asymptomatic lesions that are identified only through prospective screening or have lesions that may silently progress (28). As was found in this review, a wide variety of CNS findings have been associated with PRS/ECDS across multiple recent cohorts (29, 30). The incidence of asymptomatic lesions, possibility for progression, and the long-term clinical significance are largely unknown due to the small size of most cohort studies and lack of standardized neuroimaging evaluations.

Multiple cohort studies have identified MRI as a safe and effective means of determining CNS involvement, especially in patients that are symptomatic (27-29). Contrast-enhanced imaging should be considered as part of the initial neurologic evaluation, especially given the putative inflammatory nature of ECDS/PRS (27, 31). The wide spectrum of MRI findings and poor correlation to dermatologic and neurologic symptoms, however, argue strongly that screening brain MRIs should be considered the gold standard of care (23). There are few prospective studies to suggest appropriate intervals for neuroimaging despite the recognition that a minority (up to 20%) of CNS lesions can progress with time even in the absence of clear cutaneous changes (27).

The role of dedicated vascular imaging for screening purposes is currently unclear. In the majority of cases noted in this review, dedicated MRA or CTA appeared to be relatively low in yield except in cases where there was a high suspicion for vascular involvement, such as the presence of stroke-like symptoms (32). This may be due to the involvement of the blood vessels below the resolution of these modalities.

Osteological evaluation and 3D imaging

In addition to soft-tissue changes, atrophy or abnormality of the facial bones is commonly observed in PRS/ECDS, especially in more severe or earlier-onset cases when the bone is still developing (9, 21). These abnormalities lead to both aesthetic and functional concerns that may be progressive and may require significant surgical interventions in combination with soft-tissue augmentation (33, 34). Therefore, detecting and monitoring bone-level changes are critical. The role for advanced 3D imaging was noted in several studies, with surgical groups utilizing both conventional multidetector computed tomography (MDCT) reconstruction and low-dose cone beam CT for perioperative planning (35). Conventional 3D-MDCT reconstruction provides excellent resolution of bone and soft-tissue structures, but machines are expensive and require exposure to ionizing radiation. Cone beam CT has been proposed as lower cost method of disease assessment, but it has significant limitations in its ability to track lesions involving the forehead and requires a high amount of radiation exposure on the part of the patient (36, 37).

Three-dimensional stereophotogrammetry (3D photography) is a radiation-free method to generate high quality volumetric models of soft-tissue

surfaces using three calibrated camera images and associated software (38). It has been utilized for postoperative monitoring to track fat graft retention and reliably assess the volume change of soft tissues, though it may not capture accurate osteological changes (21, 39, 40). Images can also be integrated with other DICOM (CT or MRI) data to create interactive 3D models of patients (41). The increasing portability, ease of use, low cost of these imaging techniques, and the absence of radiation exposure are supportive of continued integration of stereophotogrammetry into clinical practice. Additionally, the advanced algorithmic analysis of captured images can provide information about pigmentation and vascularity that may be useful in monitoring disease activity, especially in combination with cutaneous outcome assessments and adjunctive noninvasive disease monitoring (42-45).

Dental evaluation

Dental investigations were not well-documented in most patients, despite potentially significant morbidity. It is possible that more patients are receiving comprehensive screening during annual dental visits, but this is not clearly reported in the cases studied in this review. Basic screening with panoramic dental images were infrequently obtained in this review, despite their low cost and high clinical accessibility. Lack of screening is worrisome because root atrophy, tooth crowding, gingival recession, and bite abnormalities are well-reported in PRS/ECDS (36, 46). A recent international consensus conference acknowledged the need for dental screening in ECDS/PRS and recommended baseline and follow-up dental assessment for all children with this condition, including baseline panoramic radiographs (23).

Ophthalmologic evaluations

A wide range of periocular, ocular, and neuro-ophthalmic manifestations have been reported in association with PRS/ECDS; a full review of observed manifestations can be found in Bucher et al. (47). Although many periocular disorders such as enophthalmos or lagophthalmos can be readily visualized on inspection, sight-threatening ocular manifestations, such as uveitis, may be clinically silent. In line with other ECMs, the onset may occur at any time during the ECDS/PRS course and may occur/flare discordant with cutaneous change (48). A significant risk of permanent visual abnormalities posed by silent ECMs again reinforces the need for multidisciplinary evaluations. A recent international effort to reach consensus among pediatric rheumatologists and dermatologists regarding baseline screening and monitoring of PRS/EDCS determined that twice yearly eye examinations are recommended (23).

Surgical treatments

Autologous fat grafting utilizing the Coleman technique and microsurgical flaps are currently the two most frequently used aesthetic interventions. Autologous fat grafting has been noted to have lower perioperative morbidity and shorter surgical times as compared to flap procedures, however, more severe defects require an increased number of surgical procedures as compared to flap-based reconstructions (49-51). In addition, the resorption of grafted fat may be difficult to predict and exaggerated fat growth of the graft with total body weight gain has been noted in cases (49). Efforts to increase the retention rate through the use of cell-assisted adipose, including adipose-derived stem cells, has yielded generally positive results (35, 52). However, significant work remains to understand the optimal cell-transfer techniques and the basic biology of these enhanced fat products (53). Synthetic tissue fillers, such as hyaluronic acid polymer, represent a potentially attractive alternative to fat grafting as there is no donor site and minimal surgical recovery (54). Although fillers have been used successfully for other pediatric conditions, there is no clear role of the same in the management of pediatric facial correction at this time (55).

Free flaps

For large or severe ECDS/PRS manifestations, the use of free flap grafts is a common approach (5). A variety of autograft donor sites were identified in this review, including anterolateral thigh and the scapula-thoracic area, which is concurrent with previous reviews of the topic (56-58). The advantages and limitations of various flap procedures and the details of surgical techniques are beyond the scope of this review, but can be found elsewhere (50). New and interesting approaches include the use of 3D modeling to better fit grafts in individual patients to minimize donor site scarring and maximize the aesthetic outcome (59).

Additionally, a standing debate remains regarding the optimal timing to initiate surgical correction, with authors more recently advocating for early intervention during the active phase of the disease (51, 60). Preliminary data suggests that early intervention with free flaps may alter the gene expression of diseased areas to better resemble healthy skin, however, at the same time, it is during the active and inflammatory phase during which the timing is most appropriate for systemic immunosuppressive medications to bring about an effect in halting the disease process (1, 3, 60).

Bony reconstruction

Adjunctive reconstruction techniques to repair bony defects are well-recognized as important for achieving good cosmetic and functional outcomes. Patients in this review underwent a variety of procedures, including osteotomies and on-lay bone grafting with novel integration of 3D preoperative modeling, to improve their aesthetic outcomes (51, 61, 62). Moldable and 3D-printable porous synthetic or engineered tissue implants can also be utilized and may prove attractive due to their high customizability (33, 34). The specific applications and surgical techniques of each treatment option is beyond the scope of this review, but is available for review in other publications (7).

Medical treatments

The combination of steroids and conventional DMARDs, specifically methotrexate (MTX), remain the first-line therapy for LS and its subtypes (23, 31, 63). A recent Cochrane review affirmed the probable utility of early immunosuppressive therapy in LS, though was not able to identify data for PRS/ECDS specifically (64). The influence of treatment on morbidity from ECMs in PRS/ECDS has yet to be prospectively determined, though waxing and waning of the symptoms being coincident with immunosuppressive treatment was frequently reported (14, 65-67). Mycophenolate mofetil is gaining popularity as a second-line and potential first-line agent in treating LS, in combination with corticosteroids (63, 68). Newer monoclonal antibodies, including tocilizumab (anti-IL6) and abatacept (CTLA4), do not yet have a clear role in treatments, though they are an option for treatment-resistant patients (69). There is an established role for phototherapy with UVA1 or narrowband UVB in LS, though it has been scarcely studied in pediatric patients or the PRS/ECDS subtype (64).

Nevertheless, there remains substantial subspecialty-specific variation with regards to the treatment. Pediatric rheumatologists in the UK and North America overwhelmingly chose systemic immunosuppression as first-line therapy in a recent study, while a survey of pediatric dermatologists in the USA reported that 37% considered topical agents as primary or solo therapy for LS of the head or neck (63, 70, 71). The low number of patients receiving systemic medical treatment in this review likely stem from the high percentage of surgical and dermatological studies that were analyzed (Figure 3) and may not reflect the true global practice patterns of clinicians caring for PRS/ECDS patients in the active phase of the disease. Additionally, the Cochrane review noted the overall low quality of available clinical studies for treatment of LS (64). There is a clear need for well-designed, prospective, and randomized-controlled trials with strong validated out-

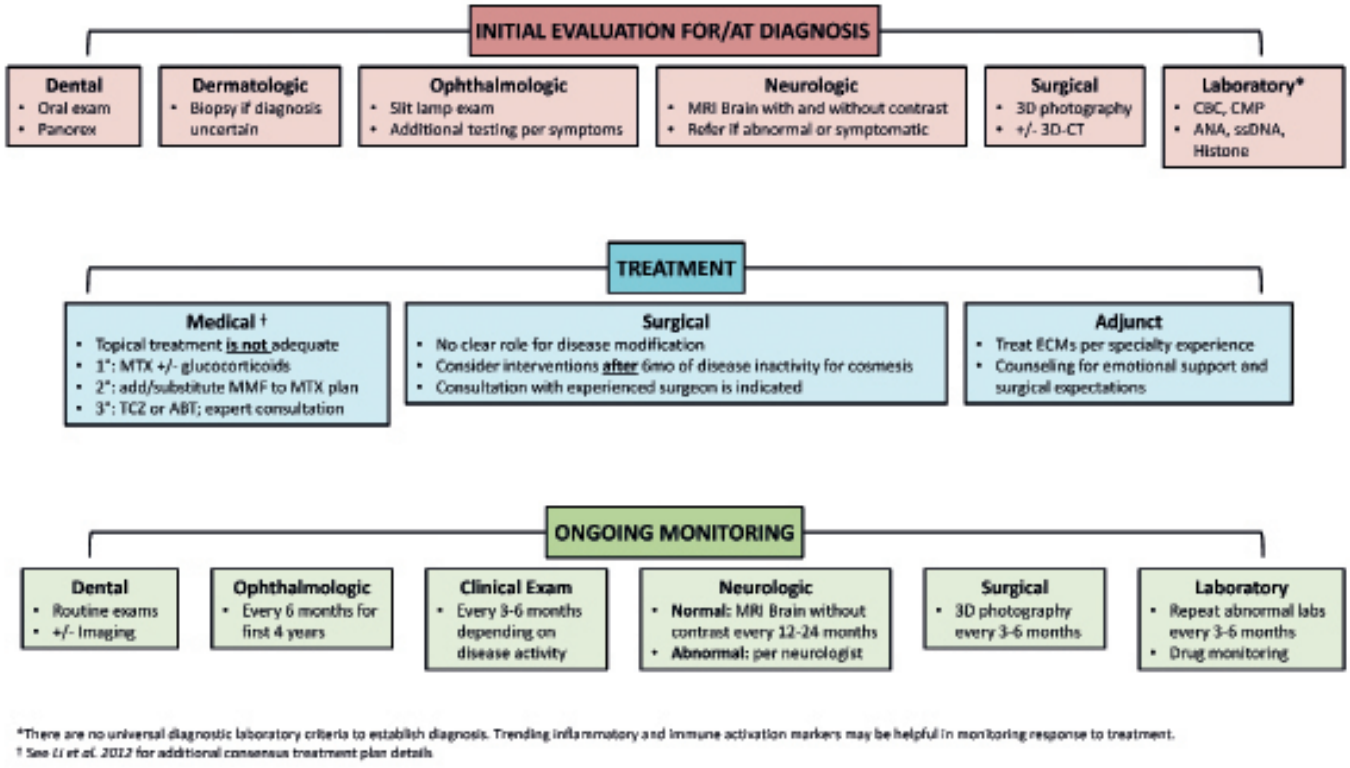

Figure 4. Proposed clinical evaluation, treatment, and monitoring algorithm.

comes and assessment measures to move the field forward in optimizing treatment selection for individual patients.

Assessment

To aid clinicians in assessing cutaneous disease activity, a variety of scoring systems and instrument techniques are available (72). The Localized Scleroderma Cutaneous Assessment Tool is a validated clinical scoring system for tracking lesions over time (73, 74). A number of different cutaneous monitoring techniques including ultrasound, infrared thermography, and optical coherence tomography have been proposed to aid detection and monitoring of cutaneous lesions but have not been validated in larger scale studies (44, 45, 75). At this time, there is no clear standardized role for these assessment modalities, and further research is needed before they can be broadly applied.

Conclusion

Based on the findings of this review and in accordance with recommendations of other expert groups, a flowchart of screening evaluations, treatments, and monitoring intervals is proposed to serve as a reference for any provider caring for a patient with PRS/ECDS (Figure 4). Developing a consistent approach to systemic screening and monitoring is critical for improving the outcome of patients with ECDS/PRS. Despite published recommendations for multidisciplinary evaluations of LS, there remains significant shortfall in screening for ECMs (23, 31). A recent national assessment of patient care by pediatric rheumatologists in the UK noted 71% of PRS/ECDS patients receiving MRI screening for CNS involvement but only 2% receiving regular uveitis screening (71). Potential reasons for this are likely complex and may include low provider awareness of the need for comprehensive screening, lack of access to pediatric subspecialty care, and limited validated assessment and outcome measures.

In conclusion, this study identifies the ongoing lack of interdisciplinary care and evaluation received by PRS/ECDS patients, despite the clear evidence of multisystem involvement in these diseases. It reaffirms the importance of both baseline and ongoing screening for ECMs, the important role of early recognition and referral for medical therapy, and the variety of cosmetic surgical procedures available to patients. Lastly, it suggests specific methods for ensuring holistic clinical assessments to improve the clinical outcomes for patients.

Informed Consent: Written publication consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.G., K.T.; Design - D.G., K.T., H.M.V.; Supervision - D.G., K.T.; Resources - K.T.; Data Collection and/or Processing - D.G., C.S., K.T., H.M.V.; Analysis and/or Interpretation - D.G., C.S., K.S.F., H.M.V.; Literature Search - D.G.; Writing Manuscript - D.G., K.T.; Critical Review - D.G., K.S.F., K.T.

Acknowledgments: HVV, MLS, MPH (University of Pittsburgh, Pittsburgh, PA) for guiding search strategy and data extraction.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Torok KS, Li SC, Jacobe HM, Taber SF, Stevens AM, Zulian F, et al. Immunopathogenesis of Pediatric Localized Scleroderma. Front Immunol 2019; 10: 908. [CrossRef]
2. Laxer RM, Zulian F. Localized scleroderma. Curr Opin Rheumatol 2006; 18: 606-13. [CrossRef]
3. Li SC. Scleroderma in Children and Adolesecent: Localized Scleroderma and Systemic Sclerosis. Pediatr Clin North Am 2018; 65: 757-81. [CrossRef]
4. Torok KS. Pediatric scleroderma: systemic or localized forms. Pediatr Clin North Am 2012; 59: 381-405. [CrossRef]
5. Taub P, Torok KS, Schuster L. Hemifacial Atrophy. In: Losee J editor. Plastic Surgery: Pediatric Plastic Surgery. Elsevier; 2018. p.801-14.
6. Tollefson MMaW, Patricia M. En coup de sabre morphe and Parry Romberg Syndrome: a retro-

spective review J Am Acad Dermatol 2007; 56: 257-63. [CrossRef]
7. Schultz KP, Dong E, Truong TA, Maricevich RS. Parry Romberg Syndrome. Clin Plast Surg 2019; 46: 231-7. [CrossRef]
8. Li A, Buck A, Lee J, Meals C, Dipple K, Sedano H, et al. The Kawamoto Classification Scheme for Parry Romberg Syndrome. Plast Recons Surg 2013; 132: 12. [CrossRef]
9. Guerrerosantos J, Guerrerosantos F, Orozco J. Classification and Treatment of Facial Tissue Atrophy in Parry-Romberg Disease. Aesthetic Plast Surg 2007; 31: 424-34. [CrossRef]
10. Khamaganova I. Progressive Hemifacial Atrophy and Linear Scleroderma En Coup de Sabre: A Spectrum of the Same Disease? Front Med 2017; 4: 258. [CrossRef]
11. Ardalan K, Zigler CK, Torok KS. Predictors of Longitudinal Quality of Life in Juvenile Localized Scleroderma. Arthritis Care Res 2017; 69: 1082-7. [CrossRef]
12. Martini G, Fadanelli G, Agazzi A, Vittadello F, Meneghel A, Zulian F. Disease course and long-term outcome of juvenile localized scleroderm: Experience from a single pediatric rheumatology centre and literature review. Autoimmun Rev 2018; 17: 727-34. [CrossRef]
13. De Somer L, Morren M-A, Muller PCEH, Despontin K, Jansen K, Lagae L, et al. Overlap between linear scleroderma, progressive facial hemiatrophy and immune-inflammatory encephalitis in a paediatric cohort. Eur J Pediatr 2015; 174: 1247-54. [CrossRef]
14. Anderson LE, Treat JR, Licht DJ, Kreiger PA, Knight AM. Remission of seizures with immunosuppressive therapy in Parry-Romberg syndrome and en coup de sabre linear scleroderma: Case report and brief review of the literature. Pediatr Dermatol 2018; 35: e363-e5. [CrossRef]
15. Tolkachjov SN, Patel NG, Tollefson MM. Progressive hemifacial atrophy: a review. Orphanet J Rare Dis 2015; 10: 39. [CrossRef]
16. Walker D, Susa JS, Currimbhoy S, Jacobe H. Histopathological changes in morphea and their clinical correlates: Results from the Morphea in Adults and Children Cohort V. J Am Acad Dermatol 2017; 76: 1124-30. [CrossRef]
17. Orozco-Covarrubias L, Guzmán-Meza A, Ridaura-Sanz C, Daza DC, Sosa-De-Martinez C, Ruiz-Maldonado R. Scleroderma 'en coup de sabre' and progressive facial hemiatrophy. Is it possible to differentiate them? J Eur Acad Dermatol Venereol 2002; 16: 361-6. [CrossRef]
18. Resende LA, Dal Pai V, Alves A. [Experimental study of progressive facial hemiatrophy: effects of cervical sympathectomy in animals]. Revue neurologique 1991; 147: 609-11.
19. El-Kehdy J, Abbas O, Rubeiz N. A review of Parry-Romberg syndrome. J Am Acad Dermatol 2012; 67: 769-84. [CrossRef]
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339: b2535-b. [CrossRef]
21. Slack GC, Tabit CJ, Allam KA, Kawamoto HK, Bradley JP. Parry-Romberg reconstruction: beneficial results despite poorer fat take. Ann Plast Surg 2014; 73: 307-10. [CrossRef]
22. Kurzinski KL, Zigler CK, Torok KS. Prediction of disease relapse in a cohort of paediatric patients with localized scleroderma. Br J Dermatol 2019; 180: 1183-9. [CrossRef]
23. Constantin T, Foeldvari I, Pain CE, Pálinkás A, Höger P, Moll M, et al. Development of minimum standards of care for juvenile localized scleroderma. Eur J Pediatr 2018; 177: 961-77. [CrossRef]
24. Arkachaisri T, Fertig N, Pino S, Medsger TA. Serum Autoantibodies and Their Clinical Associations in Patients with Childhood- and Adult-Onset Linear Scleroderma. A Single-Center Study. J Rheumatol 2008; 35: 2439. [CrossRef]
25. Takehara K, Sato S. Localized scleroderma is an autoimmune disorder. Rheumatology 2004; 44: 274-9. [CrossRef]
26. O'Brien JC, Rainwater YB, Malviya N, Cyrus N, Auer-Hackenberg L, Hynan LS, et al. Transcriptional and Cytokine Profiles Identify CXCL9 as a Biomarker of Disease Activity in Morphea. J Invest Dermatol 2017; 137: 1663-70. [CrossRef]
27. Doolittle DA, Lehman VT, Schwartz KM, Wong-Kisiel LC, Lehman JS, Tollefson MM. CNS imaging findings associated with Parry-Romberg syndrome and en coup de sabre: correlation to dermatologic and neurologic abnormalities. Neuroradiology 2015; 57: 21-34. [CrossRef]
28. Maloney E, Menashe SJ, Iyer RS, Ringold S, Chakraborty AK, Ishak GE. The central nervous system manifestations of localized craniofacial scleroderma: a study of 10 cases and literature review. Pediatr Radiol 2018; 48: 1642-54. [CrossRef]
29. Chiu YE, Vora S, Kwon E-KM, Maheshwari M. A Significant Proportion of Children with Morphea En Coup De Sabre and Parry-Romberg Syndrome Have Neuroimaging Findings. Pediatr Dermatol 2012; 29: 738-48. [CrossRef]
30. Lis-Święty A, Brzezińska-Wcisło L, Arasiewicz H. Neurological abnormalities in localized scleroderma of the face and head: a case series study for evaluation of imaging findings and clinical course. Int J Neurosci 2017; 127: 835-9. [CrossRef]
31. Zulian F, Culpo R, Sperotto F, Anton J, Avcin T, Baildam EM, et al. Consensus-based recommendations for the management of juvenile localised scleroderma. Ann Rheum Dis 2019; 78: 1019-24. [CrossRef]
32. Polcari I, Moon A, Mathes EF, Gilmore ES, Paller AS. Headaches as a Presenting Symptom of Linear Morphea en Coup de Sabre. Pediatrics 2014; 134: e1715-e9. [CrossRef]
33. Palmero MLH, Uziel Y, Laxer RM, Forrest CR, Pope E. En Coup de Sabre Scleroderma and Parry-Romberg Syndrome in Adolescents: Surgical Options and Patient-related Outcomes. J Rheumatol 2010; 37: 2174-9. [CrossRef]
34. Hu J, Yin L, Tang X, Gui L, Zhang Z. Combined Skeletal and Soft Tissue Reconstruction for Severe Parry-Romberg Syndrome. J Craniofac Surg 2011; 22: 937-41. [CrossRef]
35. Chang Q, Li J, Dong Z, Liu L, Lu F. Quantitative Volumetric Analysis of Progressive Hemifacial Atrophy Corrected Using Stromal Vascular Fraction-Supplemented Autologous Fat Grafts. Dermatol Surg 2013; 39: 1465.
36. Trainito S, Favero L, Martini G, Pedersen TK, Favero V, Herlin T, et al. Odontostomatologic involvement in juvenile localised scleroderma of the face. J Paediatr Child Health 2012; 48: 572-6. [CrossRef]
37. Di Giovanni C, Puggina S, Meneghel A, Vittadello F, Martini G, Zulian F. Cone beam computed tomography for the assessment of linear scleroderma of the face. Pediatr Rheumatol Online J 2018; 16: 1. [CrossRef]
38. Plooij JM, Swennen GRJ, Rangel FA, Maal TJJ, Schutyser FAC, Bronkhorst EM, et al. Evaluation of reproducibility and reliability of 3D soft tissue analysis using 3D stereophotogrammetry. Int J Oral Maxillofac Surg 2009; 38: 267-73. [CrossRef]
39. Jiang T, Xie Y, Zhu M, Zhao P, Chen Z, Cheng C, et al. The second fat graft has significantly better outcome than the first fat graft for Romberg syndrome: A study of three-dimensional volumetric analysis. J Plast Recons Aesthetic Surg 2016; 69: 1621-6. [CrossRef]
40. Van der Cruyssen F, Meeus J, Schoenaers J, Politis C. Parry Romberg syndrome: A long-term retrospective cohort study of 10 patients. Oral Maxillofac Surg Cases 2018; 4: 73-83. [CrossRef]
41. Abdullaev KF, Orlova EV, Yadav MK, Vasilyev EA, Mokhirev MAe, Gileva KS. Preoperative planning for advanced modelling of anterolateral thigh flaps in the treatment of severe haemifacial atrophy in Parry-Romberg and Goldenhar syndrome. JPRAS Open 2018; 16: 36-49. [CrossRef]
42. Segna E, Pucciarelli V, Beltramini GA, Sforza C, Silvestre FJ, Giannì AB, et al. Parry Romberg Syndrome and linear facial scleroderma: management in pediatric population. J Biol Regul Homeost Agents 2017; 31: 131-8.
43. Kelsey CE, Torok KS. The Localized Scleroderma Cutaneous Assessment Tool: Responsiveness to change in a pediatric clinical population. J Am Acad Dermatol 2013; 69: 214-20. [CrossRef]
44. Wortsman X, Wortsman J, Sazunic I, Carreño L. Activity assessment in morphea using color Doppler ultrasound. J Am Acad Dermatol 2011; 65: 942-8. [CrossRef]
45. Li SC, Liebling MS, Dempsey-Robertson M, Doria AS, Edgerton S, Hamer C, et al. Reliability of using an ultrasound scoring measure for juvenile localized scleroderma (jLS). Pediatr Rheumatol Online J 2012; 10: A69-A. [CrossRef]
46. Al-Aizari NA, Azzeghaiby SN, Al-Shamiri HM, Darwish S, Tarakji B. Oral manifestations of Parry-Romberg syndrome: A review of literature. Avicenna J Med 2015; 5: 25-8. [CrossRef]
47. Bucher F, Fricke J, Neugebauer A, Cursiefen C, Heindl LM. Ophthalmological manifestations of Parry-Romberg syndrome. Surv Ophthalmol 2016; 61: 693-701. [CrossRef]
48. Lenassi E, Vassallo G, Kehdi E, Chieng AS, Ashworth JL. Craniofacial linear scleroderma associated with retinal telangiectasia and exudative retinal detachment. J AAPOS 2017; 21: 251-4. [CrossRef]
49. Rodby KA, Kaptein YE, Roring J, Jacobs RJ, Kang V, Quinn KP, et al. Evaluating Autologous Lipofilling for Parry-Romberg Syndrome-Associated

Defects: A Systematic Literature Review and Case Report. Cleft Palate Craniofac J 2016; 53: 339-50. [CrossRef]
50. Agostini T, Spinelli G, Marino G, Perello R. Esthetic Restoration in Progressive Hemifacial Atrophy (Romberg Disease): Structural Fat Grafting Versus Local/Free Flaps. J Craniofac Surg 2014; 25: 783. [CrossRef]
51. Slack GC, Tabit CJ, Allam KA, Kawamoto HK, Bradley JP. Parry-Romberg reconstruction: optimal timing for hard and soft tissue procedures. J Craniofac Surg 2012; 23: 1969-73. [CrossRef]
52. Koh KS, Oh TS, Kim H, Chung IW, Lee KW, Lee HB, et al. Clinical application of human adipose tissue-derived mesenchymal stem cells in progressive hemifacial atrophy (Parry-Romberg disease) with microfat grafting techniques using 3-dimensional computed tomography and 3-dimensional camera. Ann Plast Surg 2012; 69: 331-7. [CrossRef]
53. Moustaki M, Papadopoulos O, Verikokos C, Karypidis D, Masud D, Kostakis A, et al. Application of adipose-derived stromal cells in fat grafting: Basic science and literature review. Exp Ther Med 2017; 14: 2415-23. [CrossRef]
54. Sivek R, Emer J. Use of a Blunt-Tipped Microcannula for Soft Tissue Filler Injection in the Treatment of Linear Scleroderma (En Coup De Sabre). Dermatol Surg 2014; 40. [CrossRef]
55. Dinulos JGH. Cosmetic procedures in children. Curr Opin Pediatr 2011; 23. [CrossRef]
56. Oyama T, Ohjimi H, Makino T, Nishihira T, Eto A, Takagi S. Bilayer Reconstruction for Parry-Romberg Syndrome: Using a Free Circumflex Scapular Artery-Based Adipofascial Flap for Both the Buccal Fat Pad and Subcutaneous Fat. Ann Plast Surg 2011; 67: 372. [CrossRef]
57. Si L, Zeng A, Qiao Q, Liu Z, Zhao R, Wang Y, et al. Microsurgical Correction of Progressive Facial Hemiatrophy Using Free Anterolateral Thigh Adipofascial Flap. J Craniofac Surg 2012; 23: S109-S14. [CrossRef]
58. Chen JT, Schmid DB, Israel JS, Siebert JW. A 26-Year Experience with Microsurgical Reconstruction of Hemifacial Atrophy and Linear Scleroderma. Plast Reconstr Surg 2018; 142: 1275-83. [CrossRef]
59. Shimizu F, Uehara M, Oatari M, Kusatsu M. Three-dimensional visualization of the human face using DICOM data and its application to facial contouring surgery using free anterolateral thigh flap transfer. J Plast Reconstr Aesthetic Surg 2016; 69: e1-e4. [CrossRef]
60. Chen JT, Eisinger B, Esquibel C, Poore SO, Eliceiri K, Siebert JW. Changes in Cutaneous Gene Expression after Microvascular Free Tissue Transfer in Parry-Romberg Syndrome. Plast Reconstr Surg 2018; 142: 303e. [CrossRef]
61. Qiao J, Gui L, Fu X, Niu F, Liu J, Chen Y, et al. A Novel Method of Mild to Moderate Parry-Romberg Syndrome Reconstruction: Computer-Assisted Surgery With Mandibular Outer Cortex and Fat Grafting. J Craniofac Surg 2017; 28: 359-65. [CrossRef]
62. Wang C, Zeng R-s, Wang J-n, Huang H-z, Liu X, Wang A. Simultaneous maxillomandibular distraction osteogenesis in severe progressive hemifacial atrophy with two distractors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011; 111: 292-7. [CrossRef]
63. Li SC, Torok KS, Pope E, Dedeoglu F, Hong S, Jacobe HT, et al. Development of consensus treatment plans for juvenile localized scleroderma: a roadmap toward comparative effectiveness studies in juvenile localized scleroderma. Arthritis Care Res 2012; 64: 1175-85.
64. Albuquerque JVd, Andriolo BN, Vasconcellos MR, Civile VT, Lyddiatt A, Trevisani VF. Interventions for morphea. Cochrane Database of Systematic Rev 2019. [CrossRef]
65. Fain ET, Mannion M, Pope E, Young DW, Laxer RM, Cron RQ. Brain cavernomas associated with en coup de sabre linear scleroderma: Two case reports. Pediatr Rheumatol Online J 2011; 9: 18. [CrossRef]
66. Chokar G, Cerase A, Gough A, Hasan S, Scullion D, El-Sayeh H, et al. A case of Parry-Romberg syndrome and alien hand. Journal of the Neurological Sciences 2014; 341: 153-7. [CrossRef]
67. Khan MA, Shaw L, Eleftheriou D, Prabhakar P, Chong WK, Glover M. Radiologic Improvement After Early Medical Intervention in Localised Facial Morphea. Pediatric Dermatology 2016; 33: e95-e8. [CrossRef]
68. Zulian F. Scleroderma in children. Best Practice & Research Clinical Rheumatology 2017; 31: 576-95. [CrossRef]
69. Magro CM, Halteh P, Olson LC, Kister I, Shapiro L. Linear scleroderma "en coup de sabre" with extensive brain involvement-Clinicopathologic correlations and response to anti-Interleukin-6 therapy. Orphanet Journal of Rare Diseases 2019; 14: 110. [CrossRef]
70. Tollefson MM, Chiu YE, Brandling-Bennett HA, Pope E. Discordance of pediatric morphea treatment by pediatric dermatologists. Pediatr Dermatol 2018; 35: 47-54. [CrossRef]
71. Lythgoe H, Almeida B, Bennett J, Bhat C, Bilkhu A, Brennan M, et al. Multi-centre national audit of juvenile localised scleroderma: describing current UK practice in disease assessment and management. Pediatr Rheumatol 2018; 16: 80. [CrossRef]
72. Lis-Święty A, Janicka I, Skrzypek-Salamon A, Brzezińska-Wcisło L. A systematic review of tools for determining activity of localized scleroderma in paediatric and adult patients. J Eur Acad Dermatol Venereol 2017; 31: 30-7. [CrossRef]
73. Arkachaisri T, Vilaiyuk S, Li S, O'Neil KM, Pope E, Higgins GC, et al. The localized scleroderma skin severity index and physician global assessment of disease activity: a work in progress toward development of localized scleroderma outcome measures. J Rheumatol 2009; 36: 2819-29. [CrossRef]
74. Agazzi A, Fadanelli G, Vittadello F, Zulian F, Martini G. Reliability of LoSCAT score for activity and tissue damage assessment in a large cohort of patients with Juvenile Localized Scleroderma. Pediatr Rheumatol 2018; 16: 37. [CrossRef]
75. Abignano G, Aydin SZ, Castillo-Gallego C, Liakouli V, Woods D, Meekings A, et al. Virtual skin biopsy by optical coherence tomography: the first quantitative imaging biomarker for scleroderma. Ann Rheum Dis 2013; 72: 1845. [CrossRef]