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NEUROLOGY OF SYSTEMIC DISEASES (J BILLER, SECTION EDITOR)

Protean Neurologic Manifestations of Two Rare Dermatologic Disorders: Sweet Disease and Localized Craniofacial Scleroderma

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Abstract

Purpose of Review To describe diverse neurologic and neuroradiologic presentations of two rare, immunologically mediated skin conditions: Sweet disease and localized scleroderma (morphea).

Recent Findings Core syndromes of neuro-Sweet disease (NSD) are steroid responsiveness, recurrent meningitis, and encephalitis. Focal neurologic, neuro-vascular, and neuro-ophthalmologic syndromes have been reported recently in NSD. A variety of steroid-sparing treatments and biologics have been used for relapsing NSD. Localized craniofacial scleroderma is associated with seizures, headaches, and less commonly, focal deficits and cognitive decline. Immunosuppressive therapy may be required in patients with disease progression; some refractory cases have responded to IL-6 inhibition.

Summary Our review provides an up-to-date reference for neurologists faced with a patient with a history or skin findings consistent with Sweet disease or localized scleroderma. We hope that it will stimulate collaborative studies aimed at unraveling the pathogenesis of these disorders, better characterization of their neurologic manifestations, and discovery of optimal therapeutic solutions.

Keywords Sweet syndrome · Neuro-Sweet disease · Localized scleroderma · Progressive hemifacial atrophy · Anti-Il 6 therapy · Neurologic complications

Introduction

Examination of the skin may provide critical clues to the neurological diagnosis. In a young patient with a stroke, angiokeratomas point to a diagnosis of Fabry's disease, while livedo reticularis brings to mind Sneddon's vasculopathy and anti-phospholipid syndrome. In cases of meningitis, a purpuric rash could be indicative of meningococcal infection; while erythema chronicum migrans is pathognomonic for Lyme disease; with optic neuritis, skin stigmata of sarcoidosis or systemic lupus erythematosus raise the possibility of the respective systemic autoimmune disease. Such examples can be

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readily multiplied. A review by Hurko and Provost mentions over 300 disorders with cutaneous and neurologic manifestations [1].

Our article focuses on two immune-mediated, dermatologic disorders that are relatively less known to the neurologic community due to their rarity—Sweet syndrome and localized scleroderma (morphea)—but which are associated with a very wide variety of neurologic manifestations, including neuroinflammatory brain lesions. Our goal is to provide an up-to-date review of the rapidly expanding spectrum of neurologic syndromes and neuroradiologic findings associated with these two diseases that could serve as a useful reference for neurologists faced with a patient with a history or skin findings consistent with Sweet disease or localized scleroderma.

Neurologic Complications of Sweet Disease (Neuro-Sweet's Disease)

Sweet disease is characterized by fever, peripheral neutrophilia, and painful erythematous skin lesions with a predilection for the face, neck, trunk, and extensor surfaces. Skin lesions may be single or multiple, of variable size, and may present as nodules, plaques or blisters, often with a central clearing (Fig. 1a, b) [2]. Skin biopsy shows a striking neutrophilic infiltrate that assumes an interstitial pattern concentrated in the superficial half of the dermis with concomitant papillary dermal edema and a mononuclear cell dominant vascular reaction (Fig. 1c). While there is prominent leukocytoclasia and focal red cell extravasation, frank vasculitic changes are uncommon except in an acral variant, designated pustular vasculitis of the dorsum of the hand [3]. The eyes, lungs, liver, kidneys, gastrointestinal tract, bone marrow, and muscle may be affected in Sweet syndrome, where the same pattern of extracutaneous neutrophilic infiltration prevails [4••]. The central nervous system, and very rarely, the peripheral nervous system may be involved as well, as will be discussed below.

Sweet syndrome may be seen following an infection (e.g., gastrointestinal tract, respiratory tract, tonsillitis) or drug exposure (e.g., colony stimulating factor, chemotherapies, antimicrobials, oral tretinoin, oral contraceptives, non-steroidal anti-inflammatory drugs, anti-hypertensives, anti-psychotics, and anti-epileptics [5–7]). Likewise, Sweet syndrome may be seen in the context of autoimmune conditions (e.g., inflammatory bowel disease, systemic lupus erythematosus), pregnancy, and malignancy, most commonly with hematologic malignancies or hematopoietic disorders and, less commonly, with solid neoplasms. Sweet syndrome may be the presenting manifestation of a cancer or herald cancer recurrence, especially hematologic dyscrasias. Thus, cancer screening is warranted in a patient with Sweet syndrome of unknown etiology [8].

The term "neuro-Sweet disease" (NSD), coined by Hisanaga et al. in 1999 refers to the neurological

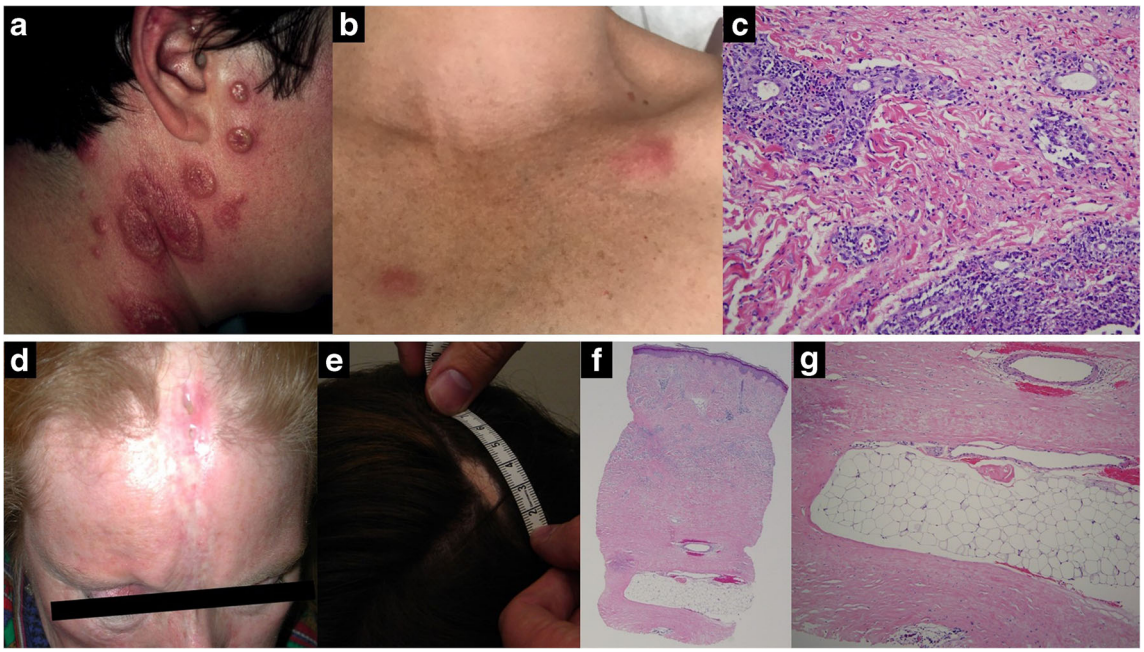

Fig. 1 Clinical and pathological examples of Sweet disease (top row) and craniofacial scleroderma (bottom row). Top row: Sweet disease. **a** and **b** show examples of Sweet disease lesions on the face and chest; **c** demonstrates skin biopsy with an angiocentric mononuclear cell infiltrate accompanied by interstitial neutrophilia with debris and hemorrhage. The mononuclear cells (lymphocytes and monocytes) are the source of cytokines that lead to the influx of neutrophils in the dermis. Bottom row: craniofacial scleroderma. **d** and **e** show examples of craniofacial scleroderma en coup de sabre (ECDS) on the forehead and scalp; **f** and **g** are lower and higher power images, respectively, of a skin biopsy that shows a hyalinizing fibrosing reaction in the deeper dermis and subcutaneous fat

complications of Sweet syndrome [9]; they later proposed diagnostic criteria based on their experience with forty-two cases of presumed NSD [10]. The core neurologic manifestations of NSD are meningitis or meningoencephalitis, which are highly responsive to systemic glucocorticoids. Meningoencephalitis may be recurrent and may be preceded or followed by cutaneous lesions of Sweet syndrome [10]. Thus, the diagnosis of NSD requires not only a search for characteristic skin lesions at the time of neurologic symptoms, but an inquiry into prior dermatologic history as well.

NSD may be difficult to differentiate from neuro-Behcet's. In the original cohort of forty-two patients with NSD, 13 patients (31%) fulfilled criteria for neuro-Behcet's as well [10]. Cutaneous vasculitis, thrombosis, uveitis, and HLA-B51 haplotype favored neuro-Behcet's, while episcleritis, conjunctivitis, and HLA-B54 or HLA-Cw1 haplotype—in Japanese patients—favored NSD. Compared to neuro-Behcet's, NSD had a more equal representation of men and women (male:female ratio of 1.4:1 in NSD vs. 3–4:1 in neuro-Behcet's); was more common in patients of Japanese ancestry (though publication bias may in part explain this finding); and had a wider age distribution at onset (peak age at onset of 30–70 years for NSD vs. 20–40 years for neuro-Behcet's [4••, 10]).

Since the publication of the NSD criteria, a number of reports have appeared which have considerably expanded the spectrum of NSD. Most of the reported manifestations of NSD have been described in neuro-Behcet's as well [11, 12]. In almost all cases of NSD, only the central nervous system (CNS) is affected, but there are also reports of sensorineural hearing loss and polyneuropathy with or without CNS involvement [13, 14]. Interestingly, NSD does not appear to be associated with malignancy—only 11% of cases in our review had a previous or concurrent diagnosis of cancer. This is in contrast to other extracutaneous manifestations of Sweet syndrome that are strongly indicative of an underlying myeloproliferative disorder [15].

Broadly, CNS syndromes associated with Sweet syndrome fall under the following categories:

1. Encephalitis, usually recurrent: much more common in NSD than neuro-Behcet's [10].
2. Meningitis, usually recurrent: cranial neuropathies are rarely seen [16, 17]; meningeal enhancement may be present on MRI even without clinical signs of meningitis [10, 18].
3. Focal neurologic syndromes with parenchymal, inflammatory brain lesions can manifest as aphasia [19], hemisensory loss [20], hemiparesis [21], ataxia [21], movement disorder [22], and focal seizures [23, 24]. NSD does not appear to have a predilection for the basal ganglia and brainstem which is seen in neuro-Behcet's.
4. Neurovascular complications: case reports of embolic stroke, possibly due to cerebral vasculopathy [25]; multiple strokes in a patient with neutrophilic meningitis and history of Sweet's [26]; we found no cases of cerebral sinus thrombosis in NSD, but one case of ophthalmic vein thrombosis [27]. In contrast, sinus thrombosis is a well-described manifestation of neuro-Behcet's [12].
5. Myelitis: a single case of progressive, necrotizing vasculitis of the spinal cord with a longitudinally extensive cord lesion involving both gray and white matter has been reported in a patient with a history of Sweet disease [28].
6. Neuro-ophthalmologic: optic disc edema may be present alongside uveitis [17, 29, 30]. Uveitis is a more common feature of Behcet's, while conjunctivitis and episcleritis are more common in NSD [10, 13].

An important caveat to the above discussion is that the total number of presumed NSD cases is small—66 cases are reviewed here—which makes it difficult to ascertain whether a particular neurologic syndrome, such as stroke, should be considered a form of NSD or is merely comorbid with it.

NSD does not show a predilection for specific brain areas on MRI. T2/FLAIR hyperintense lesions may be found in the cortex, juxtacortical and subcortical white matter, basal ganglia, and brainstem; extensive white matter abnormalities have also been reported [20, 22, 23, 31•, 32]. Brain lesions may be contrast enhancing, sometimes mimicking a brain tumor [33] or neuroinflammatory disease. Lesion appearance on MRI may lag behind clinical symptoms [30]. Conversely, "silent" MRI lesions may be seen in the absence of symptoms [10, 27]. Parenchymal lesions may resolve spontaneously or after administration of systemic glucocorticoids. Meningeal enhancement and dural thickening in the absence of parenchymal disease have been reported [18].

Cerebrospinal fluid (CSF) profile in NSD may be normal [30] or show a wide range of abnormalities: mild elevation in protein [33]; mild lymphocytic pleocytosis with normal protein, normal glucose and no oligoclonal bands [22]; mild elevation in protein with unique oligoclonal bands [20]; pleocytosis with monocyte predominance and elevated protein without elevation in IgG index or oligoclonal bands [24, 28]; viscous xanthochromia with high protein and high immunoglobulin levels [23]. Opening pressure may sometimes be elevated [29]. Longitudinal analysis of the cytokine composition of CSF in a single patient with NSD revealed that levels of several pro-inflammatory cytokines (IL-6, IFN-gamma, IL-8 and CXCL-10) were markedly elevated relative to neurologic controls and correlated with CSF leukocyte counts, while IL-8 levels in CSF correlated with neutrophil counts in CSF and serum [24].

There are few neuropathology reports of NSD. Brain biopsy of a woman with a history of acute myeloid leukemia and Sweet syndrome who presented with new headaches, fever, malaise, and an avidly enhancing brain lesion demonstrated a striking neutrophilic vasculitis [31•]. Similar pathologic

findings were seen in a Japanese patient with NSD [34]. Spinal cord biopsy of a man with a 3-month progressive longitudinally extensive myelitis indicated polyclonal lymphoid cell infiltration (B cells and T cells) with necrotizing vasculitis with a mild neutrophil infiltration [28]. The presence of frank injurious vascular alterations along with a predominance of neutrophils within the vessel wall in CNS specimens of presumed NSD is in contrast to skin biopsy findings in classic Sweet syndrome. In cutaneous Sweet syndrome, vessels are surrounded and infiltrated by mononuclear cells (lymphocytes and monocytes) without significant luminal or fibrin deposition, while the interstitium shows significant neutrophilia (Fig. 1c). An autopsy of a patient with history of NSD and multiple recurrences of encephalitis demonstrated perivascular cuffing of inflammatory cells preferentially surrounding small veins associated with microscopic hemorrhage and loss of myelin. Infiltrating cells were primarily macrophages (anti-CD68) with little destruction of neurons by phagocytic cells, perhaps, drawing a morphologic parallel with histiocytoid Sweet syndrome [35]. The findings in the autopsied case may represent an inactive stage of NSD, while the biopsied cases represent the active phase.

Systemic glucocorticoids are the mainstay of treatment, and responsiveness to steroids is part of the proposed diagnostic criteria of NSD [10]. Typically, intravenous corticosteroids are administered for 3–7 days, with doses ranging from prednisolone 1 mg/kg/day to methylprednisolone 1000 mg/day, followed by a prednisone taper for up to 6 weeks [8, 23, 30]. Fever generally responds within a day of steroid initiation, while cutaneous and neurological manifestations take longer to resolve. Rebound after steroid taper is treated with restarting steroids. Other agents that have been tried in individual cases include colchicine, dapsone, cyclosporine, methotrexate, azathioprine, interferon alpha, plasmapheresis and tumor necrosis factor antagonists (infliximab, adalimumab) [4••, 16, 39, 40•]. In some cases of refractory Sweet syndrome, anakinra (IL-1 receptor antagonist) [36, 37, 40•], or rituximab (anti-CD20 antibody) [38] have been used, but, to our knowledge, not specifically in NSD. In malignancy-associated Sweet syndrome, treatment of the underlying cancer may treat the dermatosis as well [40•] and in medication-induced Sweet disease, the treatment may consist of stopping the inciting agent.

Neurologic Complications of Localized Craniofacial Scleroderma (Neuro-Morphea)

Localized scleroderma, also known as morphea, is characterized by sclerotic lesions of the skin and underlying tissue (Fig. 1d, e). The cutaneous findings in this localized form of scleroderma are temporally heterogeneous; incipient presclerotic lesions are characterized by significant lymphocytic and plasmacytic infiltration showing perieccrine, perineural, and perivascular accentuation accompanied by dermal mucin deposition. With temporal evolution, the inflammation and mucin recede and there is ensuing fibrosis which commences in the deeper dermis and subcutaneous fat (Fig. 1f, g). The fibrosis exhibits proximal extension to involve the more superficial components of the dermis in end-stage lesions. As well, in end-stage lesions, there is significant adnexal atrophy and at times lipoatrophy can be observed as well. The fibroblasts, while not increased in number, have a potent procollagen forming phenotype characterized by the expression of smooth muscle actin and loss of CD34 expression. While there is a brisk lymphocytic vascular reaction, frank vasculitic changes are uncommon [41•, 42]. Given the extent of deep-seated skin involvement and the fact that the initial inflammation and sclerosis affects the deeper dermis, it is not surprising that this pathologic process can extend into bone, joints, and deeper tissues, but significant internal organ involvement or progression to systemic scleroderma is exceptional [43–45]. Predisposing and triggering factors of localized scleroderma include genetic factors (X chromosome mosaicism in scleroderma following Blaschko's lines; HLA DRB1*04:04 haplotype in Caucasians) [46–48]; endocrine changes associated with pregnancy, menopause, and menarche [49, 50]; physical trauma; infections/vaccinations; medications (e.g., valproate); malignancies; and treatments for malignancies (including radiation) [51, 52]. The high prevalence of coexisting autoimmune diseases, such as psoriasis, celiac disease, and polyarthritis, in patients with localized scleroderma suggests an autoimmune basis for this disorder [47, 53, 54]. Furthermore, skin morphology in morphea is oftentimes indistinguishable from systemic scleroderma and patients with systemic scleroderma can develop lesions of morphea. Thus, a role for autoimmune-based endothelial cell injury in the pathogenesis of morphea likely exists, similar to that proposed for systemic scleroderma. Presumably, the antibodies in localized scleroderma are skin specific and are not directed at the endothelium of other organ systems; hence, the disease process is confined to the cutaneous system in the vast majority of cases [55, 56].

Localized scleroderma has been classified into several subtypes [57]. Central nervous system manifestations are seen almost exclusively with two craniofacial variants: linear scleroderma "en coup de sabre" and progressive hemifacial atrophy, also known as Parry-Romberg Syndrome. En coup de sabre (ECDS), French for "cut of the sabre," represents a linear patch of thickened hyperpigmented skin, usually over unilateral frontoparietal bone, sometimes extending to the cheek, orbit, and scalp. When the lesions are present only on the scalp, they may not be evident on cursory examination. Progressive hemifacial atrophy is a self-limited, but often severe syndrome in which there is loss of dermis and deeper tissue on one side of the face, but minimal damage to the overlying skin [58•, 59]. Both ECDS and progressive hemifacial atrophy usually present in childhood and

adolescence, but may also develop in adulthood. The two variants can coexist and the distinction between them is not always clear cut either clinically or pathologically, leading some authors to speculate that they lie on a continuum of craniofacial scleroderma [54, 59–62].

The frequency of CNS involvement in craniofacial scleroderma is estimated to be 28–38% in pediatric series [63, 64], and even higher—62%—among patients with rare congenital morphea [65•]. The literature on CNS complications of craniofacial scleroderma has been summarized in two review articles published in 2008 (a total of 54 cases reviewed) [60] and 2013 (a total of 224 cases) [66]. Table 1 compares the major findings of the two reviews. Epilepsy was reported in 42–58% of published cases [60, 66], and 17% (7 of 54 patients) of consecutive cases with craniofacial scleroderma seen in Mayo Clinic [62]. The most common seizure type is focal in onset, including epilepsia partialis continua and Rasmussen's encephalitis [60, 67]. One affected child with craniofacial scleroderma and Rasmussen's encephalitis was found to have CSF-specific oligoclonal bands and NMDA-R antibodies, raising the question of whether seizures were due to craniofacial scleroderma or comorbid NMDA encephalitis [53].

In patients with craniofacial scleroderma and seizures, brain MRI is usually abnormal. Multiple or diffuse T2/FLAIR hyperintense lesions are usually seen ipsilateral to the skin lesion, but singular, bilateral, and, rarely, contralateral lesions have been observed as well [60, 63]. The frontal lobes are the most common lesion location, followed by other lobes of the cerebrum, deep gray matter nuclei [68, 69•], and least likely, brainstem. In addition, cranial MRI in patients with craniofacial scleroderma and seizures may show a variety of other findings: calcifications or microhemorrhage, cysts, cortical lesions (raising the question of focal cortical dysplasia), cavernomas [70], leptomeningeal, and parenchymal enhancement [41•, 71, 72]. MR imaging findings may be much more extensive than expected relative to the patient's clinical status [69•]. There is limited data on other imaging modalities; a single case of PET/CT in a patient with intractable epilepsy demonstrated diminished FDG avidity of the dominant MRI focus of signal abnormality, possibly representing sequelae of prior inflammation [69•].

Table 1 Frequency of neurologic and neuroradiologic findings in craniofacial scleroderma in two recent reviews

	Kister et al. [60]	Amaral et al. [66]
Clinical features		
Epilepsy	73%	42%
Headache	29%	19%
Focal symptoms	34%	28%
Neuropsychiatric	14%	4%
Radiographic features		
Normal brain MRI	11%	15%
Calcification on CT or MRI	37%	26% (CT); 4% (MRI)
MRI T2 lesions	94%	34%

Headaches in craniofacial scleroderma with neurological symptoms are reported by 19–27% of patients [60, 66], likely an underestimate as headache prevalence and characteristics have not been systematically assessed. Recent reports have identified some unusual headache and facial pain syndromes. One patient developed a nummular headache followed 10 days later by a characteristic groove on his forehead, determined to be ECDS on skin biopsy [71]. Nummular headache could be secondary to local nerve ischemia due to endoneurial vascular inflammation in ECDS. In another patient with ECDS, atypical hemifacial pain was responsive to low-dose botulinum toxin injection [73]. In a patient with a history of ECDS and seizures as a teenager who developed intractable migraines in her 40s, MRI showed leptomeningeal enhancement; headache and leptomeningeal enhancement resolved following a course of intravenous steroids [74]. The case of headache with leptomeningeal enhancement is atypical in that brain MRI obtained in the setting of headache as the only neurological symptom does not usually show overt abnormalities, though focal calvarial thinning, blurring of the gray-white junction, sulcal effacement, and calcifications ipsilateral to the skin lesion may be seen on close inspection [41•, 60, 63, 66, 73, 75–77].

Focal neurologic symptoms—cranial neuropathies, hemiparesis, hemisensory disturbance, movement disorders, cognitive, and neuropsychiatric symptoms—are rare [60, 66, 78] and highly variable, as the following examples will illustrate. A 2-year-old with craniofacial morphea initially presented with seizures, cortical asymmetry and a subtle subdural collection on MRI. He developed bilateral oculomotor and unilateral facial palsy two years later with a corresponding T2 hyperintense lesion at the right pons and midbrain, worsening hemiatrophy and ex vacuo dilation. The patient continued to decline neurologically and ultimately succumbed to his illness [79]. A 5-year-old with bilateral craniofacial scleroderma, sensory deficits, and dysmetria had focal right scalp atrophy, multiple T2 hyperintensities at the bilateral cerebellum and right thalamus on MRI [63]. A 6-year-old with left hemiparesis and hemisensory loss following an infection had contralateral T2 hyperintensity and meningeal enhancement on MRI. She improved clinically after steroids, but there was enlargement of the T2 hyperintensity and midline shift [42]. A 23-year-old with a non-progressive mild cognitive impairment in the setting of ECDS and progressive hemifacial atrophy had right temporal lobe atrophy and MR spectroscopic evidence of "demyelination" [80]. In some cases, neurological symptoms did not have an MRI correlate, such as a 39-year-old with morphea of the face and limbs who developed a mixed movement disorder (focal spasms, dystonia, bradykinesia, and tremor) and possible seizures, but had normal brain MRI and EEG [78]. The inverse scenario is also possible and

probably more likely; in one series, only half of the children with craniofacial scleroderma and brain MRI lesions had clinical symptoms [63]. The spinal cord does not appear to be involved in craniofacial scleroderma, though we found a single report of recurrent longitudinally extensive transverse myelitis in an aquaporin-4-seronegative patient with ECDS [81].

The clinical course of neuro-morphea is usually monophasic, but may be relapsing remitting as well. A young woman with long-standing ECDS developed contralateral hand weakness and epilepsy. Subsequent workup was significant for intrathecal oligoclonal IgG synthesis and MRI brain with bilateral progressive T2 hyperintensities of the gray and white matter, and contrast-enhancing lesions with spontaneous improvement and reemergence of symptoms. Additional suspicious lesions necessitated biopsy to elucidate the nature of the pathologic process, which revealed a perivascular lymphocytic infiltrate [71]. This is consistent with most other brain biopsies in craniofacial scleroderma, which show inflammatory changes that are largely vasocentric. Smaller caliber vessels can show evidence of active vasculitis characterized by angiocentric cuffs of lymphocytes accompanied by luminal and mural fibrin deposition. As well, vessels may show basement membrane zone thickening reflective of antecedent episodes of vascular injury [42, 60, 71, 82, 83]. However, inflammatory changes are not uniformly noted in craniofacial scleroderma. The failure to demonstrate inflammation may signify an inactive phase of the disease. This is exemplified by a patient with long-standing ECDS and intractable seizures, whose epileptogenic focus was resected and demonstrated mild-to-moderate gliosis of the parenchyma with dystrophic calcifications and thickened parenchymal and leptomeningeal vessels unaccompanied by significant inflammation [84].

Angiograms may demonstrate abnormally diminutive and ectatic vessels and aneurysms which may be the sequelae of vasculitis or vasculopathy [60, 69•], but clinical neurovascular syndromes are very rare. In a review of 224 patients with craniofacial scleroderma, only 3 ischemic stokes were recorded [66]; hemorrhagic stroke is rare as well [85]. It is unclear whether strokes in these cases are pathologically related to craniofacial scleroderma. For example, a Japanese woman with craniofacial scleroderma and watershed infarct attributed to stenosis of the M2 branch of the middle cerebral artery (MCA) underwent skin biopsy which showed thickening of the vessel walls with a thinning of the arteriolar lumen and mild mononuclear cell infiltration; it is conceivable that a similar process affected the ipsilateral MCA as well [82].

Ophthalmologic complications of craniofacial scleroderma occur ipsilateral to the cutaneous lesion and manifest as enophthalmos in 10–35% of cases [58•]. Other findings include uveitis, papillitis, episcleritis, orbital myositis, refractive error, and dry eye, and, even more rarely, retinal atrophy with choroidal excavation, retinal vasculopathy with resultant retinal detachment [77], and retinal telangiectasia with stellate neuroretinitis [86, 87]. Patients with eye involvement are more likely to have neurological involvement; it would be prudent to screen these patients for the known neurologic complications of craniofacial scleroderma (seizures, headaches, cognitive, and focal neurologic deficits) and refer them to a neurologist when appropriate. Neuro-ophthalmic complications include ptosis, hemianopsia, oculomotor palsy, abducens palsy, diplopia, pseudopapilledema, mydriasis, and Adie's tonic pupil [42, 66, 88, 89]. In a series of 31 patients, neuro-ophthalmologic complications included 2 cases of ipsilateral optic neuritis and 3 ocular motility abnormalities (2 with diplopia) [90]. MRI of the brain in patients with neuro-ophthalmologic symptoms may demonstrate non-specific subcortical T2 hyperintensities [88], radiographic stigmata of pseudotumor cerebri [87], or an infiltrative orbital mass [42]. Given that ophthalmologic and neuro-ophthalmologic complications are not infrequent in craniofacial scleroderma, a routine eye examination is advisable even in patients who do not have visual complaints.

No guidelines exist for the treatment of neuro-morphea. The decision to treat must be made on a case-by-case basis taking into account the severity of the symptoms and pace of progression. Treatment may not be necessary in all cases. For example, a patient who developed ECDS at age 6, presented to a neurologist at the age of 30 with subacute sensory disturbance that progressed proximally from his hand to his arm, then to his face and leg. Brain MRI was normal and the decision was made to observe him. He remained free of clinical or radiographic disease progression during 2-year follow-up [41•]. Other cases with profound neurological deficits and worrisome neuroradiological findings may warrant an attempt at treatment with the caveat that no high-level evidence-based data are available to guide physicians [83]. Steroids and methotrexate—either individually or in combination—are the most commonly used first-line agents. One strategy is to implement a 6-month course of pulse high-dose methylprednisolone, and long-term weekly oral methotrexate [42]. Mycophenolate mofetil, azathioprine, cyclosporine A, intravenous immunoglobulins, antimalarials, abatacept, infliximab, rituximab, and imatinib have all been tried with variable success [41•, 54, 91–93].

An interesting and promising new therapeutic approach to severe, refractory neurologic disease associated with craniofacial scleroderma is tocilizumab, an IL-6 inhibitor approved for the treatment of rheumatoid arthritis, giant cell arteritis, and juvenile idiopathic arthritis. A young girl with craniofacial scleroderma, intractable epilepsy, uveitis, and an enlarging periventricular white matter lesion, who was not responsive to escalating doses of prednisone and methotrexate was started on tocilizumab as an add-on therapy and experienced a remarkable decrease in both skin and brain lesion size, as well as resolution of seizures and uveitis [94]. We have had a

similar experience with a dramatic response to tocilizumab in a young woman with craniofacial scleroderma and intractable epilepsy, cognitive decline, and enumerable, persistently enhancing brain lesions, who failed to respond to high-dose methylprednisolone, intravenous immunoglobulins, plasmapheresis, a 6-month course of intravenous cyclophosphamide, rituximab, oral methotrexate, and azathioprine over the course of 7 years. Following the initiation of tocilizumab, the patient showed a remarkable improvement of cognitive deficits and seizure control, and had resolution of most of the enhancing lesions, as described in detail [95]. These two reports, alongside with others that document positive response of skin lesions of localized scleroderma to tocilizumab [69•, 96•] suggest that anti-IL-6 therapy should be considered when neurologic symptoms due to craniofacial scleroderma continue to progress despite first-line therapies.

Conclusion

Neurologic symptoms in a patient with a history or skin findings consistent with Sweet disease or craniofacial scleroderma should prompt the question of whether these symptoms are manifestations of the underlying dermatologic disorder. Neurologists should be aware that both Sweet disease and craniofacial scleroderma are associated with a wide variety of neurologic presentations and MRI findings. Neurologic complications of Sweet disease should be included on the differential diagnosis of meningitis and encephalitis—especially if recurrent, focal neurological syndromes with parenchymal brain lesions, and clinically silent multifocal T2/FLAIR hyperintense lesions with or without contrast enhancement are present. Neurologic and neuroradiologic findings in craniofacial scleroderma include new-onset focal seizures, rarely as epilepsia partialis continua and Rasmussen's encephalitis; headaches and atypical facial pain; focal neurological deficits; clinically silent T2/FLAIR hyperintensities, calcifications, and cortical dysplasia. Although neuro-imaging findings of craniofacial scleroderma are often non-specific, findings of focal thinning of the calvarium and subcutaneous tissue, blurring of the gray-white junction, and enophthalmos could alert the astute physician to the possibility of craniofacial scleroderma.

Much remains to be learned about the pathophysiology of these two rare immune-mediated disorders associated with a wide spectrum of neurologic manifestations including inflammatory brain lesions. We hope that our overview of the recent developments will stimulate collaborative studies that will advance our understanding of these conditions, and lead to a fuller characterization of their neurologic manifestations and development of effective therapeutic solutions.

Compliance with Ethical Standards

Conflict of Interest Asya Wallach reports educational grants from the National MS Society and Biogen. Lee Shapiro reports he served on advisory board for Genentech. Ilya Kister reports he served on advisory boards for Biogen and Genentech and received research support for investigator-initiated grants from Sanofi Genzyme, Biogen, EMD Serono, National MS Society, and Guthy Jackson Charitable Foundation. Cynthia Magro and Andrew Franks each declare no potential conflicts of interest.

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- • Of importance
- •• Of major importance

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