**CLINICAL VIGNETTE**

# Late Onset Parry-Romberg Syndrome (PRS) in a 35-Year-Old Female

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***Case Presentation***

A 35-year-old female with hypothyroidism noticed hair loss in the left temporal region months after orolabial HSV. This was followed by progressive left facial atrophy, hyperpigmentation, and pain with subsequent neck tension, double vision and cognitive deficits (including difficult facial recognition). The patient was living in China and presented to a local clinic. She was prescribed herbal medications and acyclovir with unclear benefit. Over the ensuing seven years while living in China, the patient had numerous medical opinions without clear diagnosis, until 10 years after initial symptoms when she was evaluated by a neuroophthalmologist. She was diagnosed with Parry-Romberg Syndrome (morphea en coup de sabre) vs localized scleroderma. The patient never received immunosuppressants because her disease had "burnt out" and become stable by the time of her diagnosis. The most recent MRI showed stable "extensive patchy FLAIR hyperintensity in the left cerebral white matter and splenium of the corpus callosum".

The patient developed hyperpigmentation involving the lateral eyebrow and temple and was treated with tretinoin with some success. Her facial atrophy was initially treated with rhytidectomy, followed by injection of hyaluronic acid fillers several times a year. Unfortunately, after several treatments, she developed excessive bruising and nodule formation. She subsequently responded to Sculptra treatment, a synthetic polymer used to stimulate collagen deposition.

The patient's alopecia included the left temple and vertex, partial loss of her left eyebrow, and madarosis in the left lower lid. Her scalp and eyebrow alopecia was treated with triamcinolone injections and topical minoxidil with some improvement.

She developed several recalcitrant ophthalmologic complications. These included eyelid retraction and atrophy which required blepharoplasty. She also lost orbital fat with enophthalmos, and vertical diplopia. On exam, she exhibited atrophy of the periorbital fat, limited abduction and adduction of the left eye, left hypertropia, and exotropia. Strabismus surgery temporarily corrected temporal tenotomy of right inferior rectus tendon. Symptoms recurred intermittently several months after surgery, generally when fatigued in the late day. Acetylcholine antibody tests were negative. Her diplopia was thought to be due to asymmetric left ocular motility limitations that were increasingly difficult to overcome with fatigue, and somewhat improved with prism lenses.

The patient also developed hemifacial atrophy with enhanced subcutaneous vasculature, and an alopetic scalp patch on the same side. A trial of hyaluronic acid fillers was complicated by excessive bruising and nodule formation. She had a better response to treatment with Sculptra, a synthetic polymer used cosmetically to improve wrinkles by stimulating collagen deposition.

***Discussion***

Parry-Romberg syndrome (PRS), otherwise known as progressive hemifacial atrophy, was first described in the early 1800s by doctors Parry and Romberg. It is a self-limited but slowly progressive condition including hemi facial atrophy with or without neurological involvement. The condition usually starts in childhood or early adulthood, unlike our patient, It predominantly affects females, and can involve skin, muscle, cartilage, vascular structures, soft tissue, brain, connective tissue and even bone. It is slowly progressive, over years to decades, and often reaches a "burned out" phase where with stabilization for 2-20 years. The underlying etiology is still widely debated, with possible autoimmune, vascular, infectious, and neurological causes.[1]

Diagnosis of PRS relies on history, physical exam, imaging, and exclusion of other causes. It is often misdiagnosed as scleroderma, morphea, Lyme disease, lipodystrophy among others.[2] Debate persists whether PRS is a separate entity from linear scleroderma en coupe de sabre, a subset of morphea named for the linear scar like appearance as if from a sword. Generally, PRS involves deeper structures of the head and neck, as in our patient, compared to localized scleroderma. There is some suggestion that later age of onset is correlated with a better prognosis. Initial physical exam findings include periorbital or maxillary skin/soft tissue/muscle atrophy, which can progress to involve jaw and neck, forehead and teeth. Limb and bilateral involvement are extremely rare. Approximately 15% of patients have neurological involvement, including cranial nerve deficits, epilepsy, migraines, and cognitive deficits. Intracranial involvement ranges from vascular abnormalities to cerebral atrophy. Symptoms include hemi facial spasm, facial pain or headaches, and seizures which can be difficult to treat. Neurological symptoms also include trigeminal nerve, facial nerve, and other cranial nerve dysfunction.[1] Ophthalmologic involvement is reported in 10 to 35% of cases, and includes uveitis, retinal nerve optic nerve abnormalities, and enophthal-

mos due to atrophy of the retrobulbar fat. Vascular complications include aneurysms, vascular malformations, infarcts, microhemorrhages and stenosis.[2]

Laboratory abnormalities can include positive ANA, anti–DNA, RF, and increased IgG levels. Biopsy often shows chronic inflammation and hair follicle atrophy associated with cicatricial alopecia.

CT and MRI findings include frontal lobe calcifications, white matter hypoattenuation on CT and hyperintensities in the T2 signal on RI, ipsilateral cerebral atrophy, and less commonly loss of cortical gyrations. The presence or severity of intracranial involvement does not necessarily correlate with extracranial findings, so additional imaging is recommended for accurate diagnosis and treatment.[1,3,4]

To date, no standard of care or disease course altering treatment has been established, due to disease rarity. Treatments have been given in hopes of altering the disease course and intracranial involvement. These include immunosuppressants such as oral and topical steroids, antimalarials, tetracycline, cyclophosphamide, methotrexate, plasmapheresis, calcipotriol, and cream psoralen with UVA with varying levels of success. There is also limited evidence for antibiotics, penicillamine, antimalarials and vitamin D3 analogues. Once symptom stabilize, treatments for extracranial pathologies include Botox injections (for pain, spasms, and appearance), pulse dye lasers, fat grafts, muscle flap grafts, silicone injections and bone augmenttations.[1,5] Treatment success is difficult to quantify, but generally volumetric improvements can be seen in 3-D CT reconstructions. Some success has been reported with adipose arrived stem cell fat grafting.[6] Sculptra is a commercial synthetic biodegradable polymer (Polyl-L-Lactic Acid or PLLA) which stimulates a subclinical inflammatory response involving collagen deposition into the local extracellular matrix, theoretically with a lasting, controlled treatment response. A small single arm study suggested small improvements in collagen deposition with minimal side effects.[7]

Ophthalmologic complications can be extensive, and involve the eyelid (retraction, lagophthalmos, atrophy, pseudoptosis), orbit (enophthalmos due to retroorbital fat atrophy or bone atrophy, or even orbital tumors), ocular manifestations(corneal keratophathies/deposits, scleral melting, uveitis, iris atrophy or deposits, vitritis, retinal vasculitis/edema/detachment).[8] Neuro-ophthalmological manifestations can involve the optic nerve, extraocular muscles (thinning, fibrosis, restrictive strabismus, CN III paresis), amblyopia, anisocoria, and Horner syndrome, etc. Prism lenses can improve diplopia by decreasing the workload on extra ocular muscles needed to overcome modality limitations.

Systemic manifestations include congenital heart disease, hypertrophic cardiomyopathy, rheumatological involvement, hyper or hypothyroidism, and sympathetic dysfunction. Early diagnosis may hopefully halt disease progression - especially with ophthalmologic, intra-cranial, or other soft tissue complications. Appreciation of the wide variety of possible complications may help primary care practitioners to identify and refer patients earlier in the disease course.

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