Pediatric Raynaud phenomenon workup and treatment: A case report

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Abstract: Raynaud phenomenon (RP) occurring in the pediatric population can be of particular concern due to the possibility of underlying disease as well as permanent tissue damage. This case investigates the efficacy of specific therapies used to reduce the incidence of Raynaud attacks in a 14-year-old female who had previously had a negative work up for systemic disease. Treatment was predominantly sought due to the pain and loss of fine motor movement associated with frequent attacks, which affected fingers, toes, nose, ears, and nipples. Effectively treating pediatric patients with Raynaud phenomenon can be challenging due to the side effects associated with first-line treatments. In this case, greatest success and tolerability was accomplished with sildenafil 20 mg daily and as needed prior to exposure to triggers.

Case Presentation:

A 14-year-old female with no significant past medical history presented to the rheumatology clinic, referred from pediatrics, for evaluation of RP. The patient's RP first presented during the winter at approximately age 10 years and lasted for about 3-5 minutes once weekly in the toes and fingers. The attacks progressed in severity and frequency, and around age 13 they began occurring 6 times daily for 10-20 minutes. Even the smaller attacks were followed by a tingling pain in the affected parts for as much as one hour after the attack. Approximately twice monthly the attacks lasted 45-60 minutes. The fingers [Fig. 1, Fig. 2] and toes were mostly affected, but some attacks also included her nose, ears, and nipples. The attacks occurring in the nipples were noted to be remarkably painful in comparison to other regions. RP symptoms were interfering with her ability to write at school and to participate in sports such as swimming. The patient admitted to a couple of instances of flares resulting in scabs on the fingertips. She denied any history of joint pain or swelling, muscle pain or weakness, dysphagia, regurgitation of food or liquids, heartburn, persistent cough, shortness of breath, weight loss, rashes, oral ulcers, alopecia, xerostomia, or dry eye. Nevertheless the severity of her RP, as well as involvement of areas outside of the extremities, led to evaluation.

Of note her mother’s medical history was significant for RP and hypothyroidism which presented, simultaneously, around age 35. The mother’s evaluation was negative for rheumatic disease.
Fig. 1: Active Raynaud attack: The digits show pallor beginning at the 2nd-5th PIP joints and the 1st MCP joint.

Fig. 2: Recovery from Raynaud attack: Reactive hyperemia is prominent in the 2nd and 5th digits.
At the initial rheumatology clinic visit, her blood pressure was 112/78, heart rate was 72, and BMI was 17.6. Bluish discoloration of the fingers and toes was noted on initial physical exam, as well as several pitting scars at the tips of the fingers. No other physical exam findings were remarkable, including no evidence of cutaneous calcinosis. Initial workup included anti-centromere, anti-Th/To, anti-RNA polymerase II, anti-topoisomerase 1, anti-Ro, anti-La, anti-RNP, anti-Sm, C3/C4, aldolase, serum protein electrophoresis, total IgG, Rheumatoid factor, anti-dsDNA, anti-CCP, hepatitis C antibody, HIV antibody & antigen, CBC, CMP, EGFR, ESR, CRP and urinalysis. All values were within normal limits, except for ANA, which was 1:320 with a homogenous pattern. The ESR was 2 mm/hr, CRP was 0.28 mg/dL, and C3/C4 levels were 102 and 14.4 mg/dL respectively. Chest x-ray and pulmonary function tests were normal and failed to demonstrate any pattern of interstitial lung disease or pulmonary hypertension. Nailfold capillaroscopy showed tortuous, dilated capillaries and dropout [Fig. 3].

A diagnosis of RP was reached, with close follow-up for early detection of potential underlying connective tissue conditions. Since the patient already attempted lifestyle modifications, pharmacologic therapy was initiated. Amlodipine 5 mg daily was trialed for 3 months, which resulted in self-reported mild improvement in duration of attacks, but not the frequency of attacks, during the last month of treatment. The patient, however, was not satisfied with the results, and the dose was increased to 10 mg daily. After two weeks at the higher dose, the patient discontinued the regimen due to fatigue and dizziness. Losartan 25 mg was trialed for 3 weeks, which was also discontinued due to orthostatic hypotension that failed to improve with time. Unlike the amlodipine, no improvement was seen in either frequency or duration of attacks. After two failed medications, sildenafil 20 mg twice daily was initiated.

At two months follow-up, the patient reported drastic improvement in both frequency and duration of symptoms. She reported no side effects from the medication. At one year follow-up, she self-reported improvement in quality of life and satisfaction with the medication's ability to prevent attacks, particularly when taken about 45 minutes prior to cold exposures. While taking sildenafil therapy, attacks occurred only during exposure to rapid temperature changes, lasting less than 10 minutes, and only involved the fingers and toes. When medication was forgotten, attacks occurred frequently and

Fig. 3: Nailfold capillaroscopy: Capillary tortuosity and enlargement are present. There is capillary dropout (arrow).
occurred for over 10 minutes like they had previously. She currently follows up in clinic every 6 months, and reports fewer than 10 attacks per month, which each last about 5 minutes, while taking sildenafil. Overall, she has had significant symptomatic relief using sildenafil. No additional manifestations of connective tissue disease have emerged to date.

Discussion:

In cases of Raynaud phenomenon (RP), it is important to distinguish primary from secondary RP. The primary type occurs by itself, while the secondary type is attributed to an underlying condition, most commonly connective tissue diseases including SLE and systemic scleroderma. Although this can seem quite concerning, RP is relatively common and most cases represent the primary type. In a study of 728 children aged 12-15 in England, 12% of boys and 18% of girls reported experiencing RP. Of note, pharmaceutical agents including beta-blockers, cisplatin, and bleomycin can also cause RP.

Symptoms concerning for secondary RP that warrant further workup include sclerodactyly, telangiectasia, puffy fingers, history of digital ulcers, digital pitting scars, and involvement of the thumb. Although primary RP can be a strictly clinical diagnosis based on history alone, nailfold capillaroscopy is the preferred means of distinguishing primary from secondary RP. In addition to capillaroscopy, workup may also include autoantibody testing, specifically anti-centromere, anti-Th/To, anti-topoisomerase I, and anti-RNA polymerase III.

Treatment begins with patient education and lifestyle modification. Avoidance of triggers, such as avoiding the refrigerated section of grocery stores, and keeping hand warmers and extra layers of clothing readily available in the event of an attack prove to be sufficient for many patients. In pediatric patients with significant RP, avoidance of ADHD drugs including methylphenidate and dextroamphetamine is recommended.

Pharmacologic therapy is necessary in patients with significant attacks refractory to lifestyle modifications. First-line drugs include the dihydropyridine calcium channel blockers (CCBs) nifedipine (30-180 mg daily) and amlodipine (5-20 mg daily). Response to the highest tolerated dose various amongst patients, and current literature fails to account for pediatric patients. Second-line agents include losartan, fluoxetine, topical nitrates, sildenafil, and local injection of type A botulinum toxin. Sildenafil in particular has been shown to increase mean capillary blood flow velocity and fingertip temperature. Alternative therapies including therapeutic gloves, acupuncture, and laser therapy may be of benefit to some patients, but current consensus remains inconclusive. Although endoscopic thoracic sympathectomy may be offered to severe treatment-resistant RP patients, current evidence is concerning for high rates of recurrence at one year post-op.

The challenge of this case was the patient’s age and lack of efficacy of first line medications, with dose-limiting hypotension. With evidence of pitting scars and worsening RP since age 10, adequate therapy was necessary to prevent permanent tissue damage. It was also necessary to give the young patient the ability to perform in school and extracurricular settings. Although uneventful to date, the presence of typical scleroderma-like nailfold capillary changes, history of digital ischemic sores, and ANA+ status remain concerning for the possibility of a systemic rheumatic disease. Although follow-up guidelines have not been established for this specific scenario, indefinite follow-up every 6 months will ensure efficacy of treatment as well as recognition of new signs and symptoms.
Guidelines for treating pediatric RP patients have not been well-established. In this case, the standard first-line pharmacologic agents in adult patients were tried when lifestyle interventions proved insufficient. When this patient did not get good results with amlodipine or losartan, a (more costly) PDE5 inhibitor with less impact of blood pressure was tried. Sildenafil alone proved to be successful in treating the patient’s RP to a satisfactory degree. One notable feature of this medication choice is the patient’s ability to take additional doses prior to exposure to known triggers. Although she suffered no adverse effects, the most common side effects (revealed in clinical trials for sildenafil as treatment for pediatric pulmonary hypertension) may include diarrhea, hyperactivity, headache, pyrexia, URI, vomiting, diarrhea, and increased erections.\textsuperscript{17-19}

Conclusion:

Pediatric patients presenting with RP first require workup and, at times, ongoing scrutiny to rule out underlying connective tissue disease. When lifestyle modifications fail to provide satisfactory reduction in ischemic injury, attack frequency, and/or attack duration pharmacologic agents should be considered. If first line agents are unsatisfactory, due to inefficacy or intolerability, daily doses of sildenafil as well as dosing prior to trigger exposures should be considered. It is possible that pediatric patients may have lower blood pressure and more potential for hypotension with the usual first line agents used in adults. It may be appropriate to consider whether agents that have less effects on blood pressure should be used sooner in the therapeutic algorithm in pediatric RP patients.

Bibliography


