

Case reports

Iloprost treatment for refractory Raynaud's phenomenon in two infants

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ABSTRACT

Raynaud's phenomenon (RP) is rare in young children. We describe two infants with severe RP, manifesting as fingertip necrosis, who were resistant to conventional vasodilators and were treated successfully with iloprost, a prostacyclin analogue. The application of iloprost is safe and should be considered in children with threatening ischemic digits.

Introduction

Raynaud's phenomenon (RP) is an exaggerated vascular response to various stimuli, such as cold and stress, presenting as changes in color of the distal extremities. This disorder can be classified as primary or idiopathic, without an underlying disease, and secondary, in which it is associated with a medical problem such as a connective tissue disorder. While RP is relatively common in adults, with a prevalence of up to 20% in some populations (1), the rate in children is less clear.

The initial treatment of RP consists of conservative measures, such as avoiding cold weather and minimizing emotional stress, followed by calcium channel blockers, considered the cornerstone of pharmacological treatment. In the presence of severe digital ischemia, intravenous infusion of a prostaglandin analogues such as iloprost (a prostacyclin analogue) can be beneficial (2).

The published data on RP in young children is very limited, and there is almost no information on the therapeutic use of prostaglandin analogues in early childhood for this condition. We describe two infants with severe RP who were successfully treated with iloprost. The literature on young pediatric patients with RP and on prostaglandin analogue treatment in children suffering from RP is also reviewed.

Case histories

Case 1

A 19-month-old girl was referred for evaluation of sudden onset of pallor of the distal fingers followed by non-painful episodes of cyanosis, several times a day, during the spring of 2006. Her medical history was unremarkable, she was fully vaccinated according to age (without recent vaccinations) and had not received any medication in the past. Family history revealed a grandmother with hypothyroidism and hearing loss of unknown cause at the age of 55.

On physical examination the patient was afebrile and well appearing. Her fingers were cold and pale, with episodic cyanosis of the distal phalanges of 3 fingers of both hands. Each episode lasted 30 minutes and subsided gradually. Nail-fold capillaroscopic findings were normal. The rest of the physical examination revealed no abnormalities.

Laboratory findings including complete blood count, liver and kidney function tests, muscle enzyme measurements and urinalysis were all within normal limits. Erythrocyte sedimentation rate was 35 mm/hour and C-reactive protein level was 0.7 mg/dL (normal ≤ 0.5). Serologic studies for cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae* and parvovirus B19 were negative. Anti-nuclear antibody (ANA) titer was positive at 1:80. Anti-double-stranded-DNA, anti-Smith, anti-RO, anti-LA, anti-scl70, anti-RNP, anti-cardiolipin and anti- $\beta 2$ -glycoprotein antibodies, as well as lupus anticoagulant, were negative. Complement levels were normal and rheumatoid factor was negative. A thorough coagulopathy work-up did not reveal any abnormalities except for heterozygosity for 677 C \rightarrow T mutation of methylenetetrahydrofolate reductase (MTHFR).

Competing interests: none declared.

Conservative measures, including warming of the hands, proved ineffective, and after one week blisters appeared on the distal phalanges of three fingers. Therefore, treatment with nifedipine (calcium channel blocker), low-molecular-weight heparin and nitroglycerin patches was started. Nevertheless, the process progressed with appearance of black dots suggesting fingertip necrosis and incipient digital gangrene. At that point iloprost infusion was added at a rate of 0.5 ng/kg/minute for two days followed by 1 ng/kg/minute for three more days, without side effects. Thereafter, gradual improvement was noticed: the blisters healed, black areas were replaced by new skin and the episodes of pallor and cyanosis became much less frequent. The other medications were gradually tapered down over a period of three months and finally discontinued, without exacerbation of symptoms. Two months after cessation of treatment, and six months after onset of symptoms, the child looked well, fingers appeared normal and repeated ANA titer was negative. Almost two years later, the child is still asymptomatic except for mild episodic pallor of the distal fingers during stress (mainly during crying), without cyanosis.

Case 2

A 14-month-old boy was referred for evaluation of pallor of the distal part of two fingers of both hands, with episodes of cyanosis and blanching, during the spring of 2002. One week prior to admission, black spots had appeared at the tips of the two fingers. Past medical record was unremarkable, he was fully vaccinated according to age (without recent vaccinations) and there was no family history of connective tissue disease. On physical examination, the patient was afebrile and well appearing. His fingers were cold and white, and two of them were necrotic at the tip. Laboratory findings, including complete blood count, liver and kidney function tests, muscle enzyme measurements and urinalysis were all within normal limits. Erythrocyte sedimentation rate on admission was 70 mm/hour. Anti-nuclear antibody titer was 1:160; anti-double-stranded-DNA antibody

titer was 35% (normal $\leq 20\%$) and lupus anticoagulant was positive according to two tests (LAC-KCT and LAC-RVVT). Titers of anti-Smith, anti-RNP, anti-RO, anti-LA, anti-cardiolipin and anti- $\beta 2$ -glycoprotein antibodies were negative. Complement levels were normal, and rheumatoid factor was negative. Thorough coagulopathy panel revealed that the patient was homozygote for the 677 C \rightarrow T mutation of MTHFR. Homocysteine level was 5.1 $\mu\text{mol/L}$ (normal range 5 to 15 $\mu\text{mol/L}$). Infectious disease serology work-up yielded negative findings against cytomegalovirus, Epstein-Barr virus and parvovirus B19. Doppler study performed on admission failed to show blood flow to distal part of two fingers in both hands.

No improvement was noted with conservative measures, and treatment with nifedipine, nitroglycerin patches, low-molecular-weight heparin and aspirin was initiated. When the patient failed to respond, continuous infusion of iloprost was started at a rate of 0.5-1 ng/kg/minute for six hours each day, for five days. Thereafter, symptoms gradually subsided, and the appearance of the fingers returned to normal. Medications were gradually tapered down and discontinued three months after onset of symptoms. At that time, ANA, anti-double-stranded-DNA antibodies and lupus anticoagulant were negative, and erythrocyte sedimentation rate was 27 mm/hour. Doppler study showed normal flow to all digits. At the five-year follow-up the child was asymptomatic.

Discussion

We present the clinical course of two infants with severe RP, who were successfully treated with iloprost, a prostacyclin analogue. Raynaud's phenomenon is well studied in adults, but only few reports in children have been published. In teenagers the prevalence was reported to be 15%, with a female predominance (3, 4). The median age of onset is 12 years (4, 5), while onset of RP in infancy is rare. In a series of 123 children with RP, only 8 (6.5%) were younger than two years (4).

We suggest that in both our cases, RP occurred secondary to a viral illness. During illness both had positive ANA,

while the second patient also had high titers of anti-double-stranded-DNA antibodies, positive lupus anticoagulant and a high estimated sedimentation rate. After recovery of symptoms antibodies and lupus anti-coagulant were negative and estimated sedimentation rate turned normal. While it is well known that ANA are related to connective tissue disorders, some reports have also linked them to various infections such as human immunodeficiency virus and hepatitis C virus (6, 7). It is possible that a concomitant vasculitis process triggered by a viral illness was also present in our patients, as proved by the rapid development of fingertip necrosis. There are isolated reports of vasculitis in association with infectious mononucleosis, cytomegalovirus, Parvovirus B19 and human immunodeficiency virus (8-11). In these cases, the inflammatory process involves essentially the small vessels, and fingertip necrosis is not unusual. The resolution of the symptoms and pathological laboratory values in our patients within a few months suggests that RP was associated with an underlying condition. Rheumatic diseases are uncommon in this age group, and therefore we believe that an infectious cause, most probably a viral agent, led to development of RP with positive rheumatic markers. The second patient we presented was homozygote to an MTHFR mutation. Although such patients have an increased risk to develop ischemic events, we believe that this condition only had a minor contribution, if any, to development of symptoms in the second patient. Moreover, by the time we received the results of the MTHFR mutation and initiated treatment with folic acid, the patient already exhibited a dramatic improvement following iloprost treatment.

In both infants described here, RP manifested as small areas of gangrene. This is a severe and unusual manifestation of RP in children. In the largest study of children with RP reported to date, complications were reported in only 10% and included mainly blisters and ulcers (4). Higher complication rates were associated with secondary RP than with primary RP (18% vs. 7%),

possibly because the underlying vascular disease disrupts the mechanisms that normally control vessel reactivity. Several studies in adults found prostaglandin analogues to be effective for the treatment of severe refractory RP, especially in systemic sclerosis patients (12, 13). Only one study evaluated the efficacy of iloprost in children with digital ischemia and underlying connective tissue disorders, and included fourteen patients with RP (14). The mean age of the patients was 9.5 years, and only one was less than 2 years old. Administration led to a substantial improvement in the blood flow to involved fingers and healing of necrotic lesions. It also decreased the frequency of RP episodes and completely or significantly alleviated pain. Another case report demonstrated a rapid response of ischemic digits to infusion of iloprost in a 3-year-old girl with cutaneous polyarteritis nodosa (15). As in our two patients, iloprost treatment has proved safe, with no major adverse reactions (14, 15).

In conclusion, we present two unique cases of infants with severe refractory RP leading to fingertip necrosis, who

were successfully and safely treated with intravenous iloprost. Pediatricians should consider using this drug in patients with severe RP complicated by digital ischemia or necrosis, who are not responding to conventional vasodilators.

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