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Case Report

Primary raynaud's phenomenon in a newborn: A case report

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ABSTRACT

Raynaud's syndrome indicates reversible, intermittent pallor or cyanosis or both, frequently affect fingers or toes, less often can affect the nose, ears, lips, nipples, or knees in response to cold or stress and is rare in childhood. Raynaud's phenomenon (RP) is an extremely unusual finding in early newborn. In severe cases the ischemia may lead to areas of infarction in hands and feet. In this case we describe a one-day old male early newborn who presented with unilateral acrocyanosis over the tip of fingers of the right hand since birth. He was healthy otherwise. Although acrocyanosis in newborn is known to be a benign and self-limiting condition, typically. It is bilateral and symmetric with no other symptoms. The unilateral acrocyanosis was an atypical finding in this newborn. After the exclusion of all other diseases by investigations, he was diagnosed to have primary RD. Due to the rarity of RD in children, we have reviewed the pathophysiology, epidemiology and management of RD and also discuss the differential diagnosis of unilateral and bilateral acrocyanosis in newborn.

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1. Introduction

Raynaud's disease (RD) was first described by Maurice Raynaud in 1862, a French medical student.¹ Classically, the initial description of RP involved triphasic color changes in the digits, with blanching (white) called pallor as the flow of blood stops leading to cyanosis (blue) as the blood's oxygen level drops followed by reactive hyperemia (red) called rubor as the vessels reopen and blood flows.^{2,3} However, not every patient experiences all 3 phases of color change and the majority of patients present with uniphase color change involving an isolated bluish discoloration of digits commonly known as acrocyanosis.⁴⁻⁶ In contrast to RP, acrocyanosis is a common phenomenon in infants and young children.⁴⁻⁷ Acrocyanosis is generally bilateral, symmetric and involves hands and feet. Since infantile acrocyanosis is a benign and self-resolving condition, it does not require medical attention.^{7,8} Rarely, acrocyanosis in infants can be caused by RP and may require immediate

medical attention to prevent complications of RP.⁹⁻¹³

In this report, we describe an early newborn who presented at day one of life with unilateral acrocyanosis and was diagnosed to have primary RD based on his subsequent clinical course.

According to the Arthritis Foundation, 4 to 15 percent of the people in the United States have Raynaud's phenomenon. In that group, more than 80 percent have primary Raynaud's (largely benign), while the rest have secondary Raynaud's (sometimes serious). And just as the severity of the two types of Raynaud's is different, so are their risk factors.

1.1. Risk factors for Primary Raynaud's

1. Gender: About 80 percent of those with primary Raynaud's are female.
2. Body type: Raynaud's is most often seen in slender girls and women.
3. Age: Primary Raynaud's usually develops between the ages of 12 and 30 years.

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4. Family history: About 25 percent of those with primary Raynaud's have a family history of the condition.
5. Other factors: Certain foods and medications can exaggerate vasospasm, including caffeine and drugs often used for attention deficit hyperactivity disorder (ADHD), such as Ritalin.
6. Risk factors for Secondary Raynaud's
7. Age: Secondary Raynaud's is more likely to occur in people older than 30 years.
8. Disease: Secondary Raynaud's is often seen in connection with scleroderma, lupus and other illnesses that damage blood vessels or the nerves that control them.
9. Other factors: Trauma to the hands or feet, like frostbite.



Fig. 1:

In this report, we describe an early newborn who presented at day one of life with unilateral acrocyanosis and was diagnosed to have primary RD based on his subsequent clinical course.

2. Case Report

We describe the case of a male neonate, first child of a non-consanguineous couple, born at 38 weeks of gestational age by vacuum-assisted delivery, weighing 2800g. The Apgar scores were 8 and 9 at 1 and 5 min, respectively. The pregnancy was uneventful and there was no relevant family history, specifically no history of congenital heart disease or neonatal cyanosis or drug intake.

The infant had cyanosis over the tip of fingers of left hand since birth with clear demarcation at the wrist. His left palm was cooler than the rest of the extremities with sluggish capillary refill <3 sec. The peripheral and central pulses were equal and regular bilaterally. He was able to move all the extremities without any pain (cry). The elevated arm stress test was negative for worsening of cyanosis or weakening of the radial pulse, thereby lessening the possibility of thoracic outlet syndrome.

On clinical examination, there was no respiratory distress and neonatal pulse oximetry screening for congenital heart disease was negative.

2.1. Evaluation during hospitalization

Arterial blood gas-with in normal limit.I

Infection screening -negative, In chest radiography-no abnormality was detected.

Echocardiography to rule out CCHD and PPHN-normal.

Upper extremity duplex ultrasound- normal.

MRI/MRA/MRV of head, neck and left upper extremity -Normal.

A transthoracic echocardiogram confirmed normal cardiac anatomy and did not demonstrate any intracardiac

mass, thrombus, or vegetation to suggest an embolic source for a presumed thrombotic event.

These results excluded several conditions, including thromboembolism, thoracic outlet syndrome contributing to compression of subclavian vein, vascular anomalies, and the presence of a mass or tumors in the region of cervical plexus including the stellate ganglion.

He underwent blood tests to detect infection and other systemic causes of acrocyanosis such as methemoglobinemia, polycythemia, antiphospholipid antibodies, and other hypercoagulable conditions. The complete blood count and comprehensive metabolic panel were normal. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests were also normal. His newborn screen for inborn errors of metabolism and hemoglobinopathies was negative. His coagulation tests (PT and aPTT) were normal and antiphospholipid antibodies and antinuclear antibody (ANA) assays were negative. He also underwent testing for inherited thrombophilia such as factor V Leiden mutation, prothrombin gene mutation, and methylene tetrahydrofolate reductase (MTHFR) mutation. Results were positive for homozygosity for a MTHFR C677T mutation with normal homocysteine levels.

Due to the concerns about the transplacental transfer of maternal antibodies contributing to development of RD in this young infant, his mother was evaluated for other medical conditions associated with RD. Her blood work up showed no evidence for systemic lupus erythematosus (antiphospholipid antibodies, ANA, antidsDNA), scleroderma (antitopoisomerase 1 antibodies) or cryoglobulinemia (cryoglobulin levels).

2.2. Blood report

1. 1Basal complete blood count: Hb 19.3 g/dL, hematocrit 58.4 %, erythrocytes $5.92 \times 10^{12}/L$, MCV 98.6 fL, MCH 32.6 pg, normal peripheral blood smear . crp was negative.

2. Hb electrophoresis at day 8: normal (HbF 85%)
3. Arterial blood gas analysis at day 1 was within normal limit
4. Glucose-6-phosphate dehydrogenase and pyruvate kinase activity assays: 6.5 U/g Hb normal

2.3. Course during hospitalization and outpatient follow up

Oxygen therapy was started based on the peripheral oxygen saturation (SpO₂), with no significant increase in this parameter. Serial measurements of arterial blood gases without supplemental oxygen revealed saturations of >95% and so therapy was discontinued.

Based on his clinical course, he was diagnosed to have "primary Raynaud's phenomenon". His treatment included close clinical monitoring. Over the next few months, he continued to have occasional episodes of acrocyanosis without any medical consequences.

At discharge, the infant was referred to the haematology outpatient clinic and during the follow-up he was asymptomatic, without clinical evidence of cyanosis.

The family was referred to genetic outpatient clinic but being unable to follow.

3. Discussion

The infant described in this report presented with a unilateral acrocyanosis at one day of age. He was diagnosed to have primary RP. This diagnosis was based on his clinical course and exclusion of other causes of unilateral acrocyanosis including vascular anomalies, thromboembolism and thoracic outlet syndrome. Even though acrocyanosis is very common condition in newborn period, involvement of only one hand was an atypical finding for infantile acrocyanosis. This finding provided a clue to consider the possibility of RP in the differential diagnosis.

Raynaud's phenomenon is traditionally classified as 'primary' (previously known as Raynaud's disease) or 'secondary'. Primary RP is diagnosed when it occurs in the absence of associated diseases. In contrast, secondary RP is diagnosed in the presence of a well-defined disease such as SLE, polyarteritis nodosa (PAN) or scleroderma. Primary RP is generally a benign condition but secondary RP can lead to significant morbidity, i.e. digital gangrene and may be life-threatening. Of those patients with primary RP, ~13% of patients will eventually be diagnosed to have secondary RP. Although it is difficult to predict which patients will be eventually diagnosed to have secondary RP, children with secondary RP can show changes in their nailfold capillaries. The direct observation of the nailfold microvasculature with videocapillaroscopy is useful for suspecting secondary RP earlier during the clinical course. Generally, the presence of giant capillaries, avascular fields

and irregular architecture of nailfold capillaries is predictive of the development of SLE, PAN, or scleroderma in patients with RP. According to Allen and Brown's criteria of minimum diagnosis, a negative antinuclear antibody titer and negative findings on capillaroscopy are the most reliable way to distinguish between primary and secondary RP. Our pt was not evaluated for capillary nailfold abnormalities due to his clinical presentation and blood report consistent with primary RP.

Since RP is extremely rare in children, specifically in infants, the knowledge about its epidemiology, clinical spectrum and the natural evolution is quite limited. The first description of RP in children appeared in 1967, almost 100 years after the initial description of RP by Raynaud in 1862.¹ This report described a series of 6 children (ages, 2.5 to 5 years) with classic RP.¹³ Since 1967, there are only a handful of reports of RP in children.^{9,11} In general, female children are more predisposed to development of RP and the onset of RP generally occurs around menarche implying the influence of ovarian hormones in the pathogenesis of this entity.^{4,11} Primary RP is more common in children than secondary RP.¹¹ Earlier reports in children suggest the association of RP with rheumatic diseases in children. Similar to adult literature, pediatric studies suggest that positive ANA and abnormalities of nailfold capillaries may be associated with secondary RP.

RP is highly heterogeneous in children.¹¹ Although exposure to cold was the primary trigger in the majority, (~70% of children) ~10% did not have any known trigger. Primary RP followed a bimodal pattern of age of onset affecting young infants and teenage population. Half of these children experienced additional symptoms such as pain, tingling, and numbness.

Irrespective of the underlying etiology, RP is manifested via vasospasm of the small muscular arteries and arterioles of the digits. Similar to benign acrocyanosis of infancy, RP is also triggered by exposure to cold and emotional stress. It can be asymmetric and may last longer than benign acrocyanosis. According to the available data, an over-activity of the sympathetic nervous system along with an imbalance of vasodilator and vasoconstrictor substances may be the most likely etiology for RP. In patients with RP, digital cutaneous neurons show a deficient release of a potent vasodilator, the calcitonin-gene related peptide. This primary pathology may be exaggerated by other factors as well, some of which are influenced by cold or emotional triggers. Substances such as catecholamines, endothelin-1, and 5-hydroxytryptamine are playing some role in pathophysiology. These chemical mediators could cause digital artery vasospasm and could trigger a cascade of neutrophil and platelet activation, which through the release of inflammatory agents such as endothelin-1 and TNF-alpha, can cause the endothelial damage seen with more severe RP. Elevated levels of homocysteine, a sulfur

amino acid is proposed as an independent risk factor for atherosclerosis and may have an association with RP. RP appears to have a strong familial component suggesting a genetic link, though this link is yet to be proved. Constipation also can stimulate the imbalance of vasodilator and vasoconstrictor substances but again yet to prove.

Collagen disorders in childhood particularly mixed connective tissue disease also can present as RP but it is generally not an isolated symptom and serological evidence of the underlying disorder is usually found.

He was evaluated for genetic risk factors of thrombosis due to the concerns about unilateral thrombosis at his presentation. He was homozygous for MTHFR C677T mutation. MTHFR mutation can be associated with hyperhomocysteinemia. High homocysteine levels are shown to be associated with decreased vasodilation both in animal models and in humans. On the same note, patients with RP are shown to have elevated homocysteine levels compared to normal controls. In our case the patient's homocysteine levels were normal, making this a less likely etiology for his RP. However, whether MTHFR mutation in itself plays a direct role in vascular instability is yet to be clarified.

Our patient was also evaluated for systemic causes of central cyanosis such as methemoglobinemia and congenital cyanotic heart disease. Generally this evaluation is not required for children with unilateral acrocyanosis. However, maternal anxiety and inability to provide a long-term prognosis of this infant forced the medical team to perform the extensive evaluation.

Management of RP is generally supportive and relies upon its accurate diagnosis by excluding other differential diagnoses. The mild forms of primary RP can be controlled by non-pharmacologic approaches such as avoidance of exposure to cold or emotional stress. In moderate to severe cases, vasodilator therapy including calcium channel blockers, either systemic or topical, is required to relieve the vasospasm. Rarely prostacycline infusions antiplatelet agents and antithrombotic therapies have been used with variable success.

Surgery is reserved for extreme cases and generally involves digital sympathectomy. In the severe forms of the disorder, intravenous infusion of prostacyclin as well as endothelin-1 receptor antagonists and specific inhibitors of phosphodiesterase-5 are emerging as the treatment of choice. Investigational agents for the treatment of RP include selective alpha-2c adrenergic receptor blockers, inhibitors of protein tyrosine kinase and Rho-kinase, as well as calcitonin gene-related peptide. In patients with secondary RP, treatment of underlying disease is critical to control the episodes of RP.

4. Conclusion

This case report signifies that despite an improved understanding of the pathophysiology of RP, the diagnosis

of primary RP in infants is challenging and It can take long time of follow up to confirm the diagnosis. There are several factors which delayed the diagnosis which include the rarity of its occurrence in infants, the similarities in clinical presentation between primary RP and benign acrocyanosis of infancy, and the absence of diagnostic tests confirming the diagnosis of primary RP .Clinical clues that should alert the clinician to suspect RP in infancy include the presence of atypical features such as a prolonged acrocyanosis episode (> 72 hours) and/or a unilateral acrocyanosis. A high index of suspicion and close clinical monitoring is required to ensure an accurate diagnosis and appropriate clinical management.

5. Consent

Written informed consent was obtained from the patient for publication of this case report.

6. List of abbreviations

MTHFR: Methylene Tetrahydrofolate reductase; MRI: Magnetic Resonance Imaging; MRA: Magnetic Resonance Angiogram; MRV: Magnetic Resonance Venography; ANCA: Antineutrophil cytoplasmic antibodies; PAN: Polyarteritis nodosa; PT: Prothrombin time; aPTT: Activated Partial thromboplastin time; RP: Raynaud's phenomenon; TNF: Tumor necrosis factor. ANA: Antinuclear antibodies; ANCA: Antineutrophil cytoplasmic antibodies; APLA: Antiphospholipid antibodies; CRP: C-reactive proteins; ESR: Erythrocyte sedimentation rate; LMWH: Low Molecular Weight Heparin;

7. Conflict of Interest

The authors declare that they have no competing interests.

8. Source of Funding

None.

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