

## Acrocyanosis as a side effect of tricyclic antidepressants: A case report

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Acrocyanosis is probably the most unusual side effect of tricyclic antidepressant drugs. In this paper, we report a 10-year-old boy with primary enuresis nocturna and attention deficit hyperactivity disorder who developed two episodes of acrocyanosis, the first of which was after imipramine treatment and the second after desipramine usage. We also review the possible pathogenesis of acrocyanosis. We suggest that physicians should be aware of this rare side effect of tricyclic antidepressants.

Tricyclic antidepressant (TCA) agents are widely used in children and adolescents. The many adverse effects of these drugs are well known in addition to their therapeutic activities for disorders such as enuresis, attention deficit hyperactivity disorder, depression and anxiety disorder. The most common side effects are anticholinergic, antihistaminic and cardiovascular.

We describe acrocyanosis as the most unusual side effect of imipramine, which is widely used in childhood and adolescents, and we review the pathogenesis of this phenomenon. There are seven cases of digital vasospasm due to imipramine in the literature. Ayyelbaum and Kapoor<sup>2</sup> reported coldness of the hands and feet in two of 52 hyperkinetic and in two psychotic children treated with imipramine. They had also described digital vasospasm in an adult patient treated with 150 mg/day of imipramine for depression<sup>2</sup>. They suggested that this patient might have developed a reaction against imipramine. According to the authors, underlying eosinophilic granuloma (which had remained in complete remission) may have been a possible factor in the vasospasm. It was shown that tricyclic antidepressants increase the plasma norepinephrine levels and this may induce vasoconstriction by affecting  $\alpha$ -1 adrenergic activity<sup>3,4</sup>. Anderson et al.<sup>5</sup> reported acrocyanosis which developed in an 11-year old girl who received imipramine for

enuresis and they suggested that neurohormonal activities of imipramine may cause this reaction. Imipramine inhibits reuptake of monoamine neurotransmitters at the central and peripheral receptors. It also has an anticholinergic effect which is useful in treating enuresis. Imipramine also antagonizes both H<sub>1</sub> and H<sub>2</sub> histaminergic receptors<sup>3,4</sup>. The reporters proposed that antihistaminic and proadrenergic properties may be responsible for the digital vasospasm in susceptible patients<sup>5</sup>.

### Case Report

A 10-year-old boy was treated with imipramine, 30 mg/day, for attention deficit hyperactivity disorder and primary nocturnal enuresis by the Department of Child and Adolescent Psychiatry. His medical history was normal except for an episode of a febrile convulsion when he was six months old. There were no physical or psychological disorders in his family history and his motor and mental development were entirely normal.

A bluish discoloration and coldness of the fingers of his hands and feet developed at the 3<sup>rd</sup> week of the imipramine treatment. As the dose of the imipramine increased to 40 mg/day, his parents observed that the discoloration and the coldness extended from the tip of the fingers to the wrists.

On physical examination, his body temperature

was 36.5°C, blood pressure 100/70 mmHg, pulse 92 beats/minute and respiratory rate 18/minute. He was not found to be dyspneic and the capillary filling time was shorter than 2 minutes. His hands and feet were symmetrically and strikingly cold, blue and sweaty from the fingers and toes to the wrists and ankles (Fig. 1). A peripheral cyanosis was present. On admission, his hemoglobin concentration was 13.3 g/dl, white blood cell count 6,440/mm<sup>3</sup>, platelets 274,000/mm<sup>3</sup> and erythrocyte sedimentation rate 5 mm/hr. Rheumatoid factor, antinuclear cold agglutinins and IgM antibodies against Epstein-Barr virus were absent. The urinalysis and coagulation screen gave normal results. Arterial blood gas revealed a pH of 7.52 PaO<sub>2</sub> 105.5 mmHg and PaCO<sub>2</sub> 25.5 mmHg. His chest X-ray and anti-double stranded DNA antibody, (anti-ds-

DNA), echocardiogram (ECG) were normal. A minimal mitral valve prolapsus was determined by echocardiography.

Imipramine was discontinued in the 5<sup>th</sup> week of the treatment due to this side effect. Cyanosis in his hands and feet decreased within the first week of imipramine withdrawal and disappeared within the second week.

Two years later, the patient admitted to the Department of Child and Adolescent Psychiatry again, suffering from a similar clinical picture as experienced previously. We learned that the patient had used desipramine (20 mg/day), which was recommended by a relative, and again he had cyanosis in his hands and feet within the first week of this treatment. He had not experienced any cyanotic episodes when exposed to cold within the two years until the

Fig. 1. Acrocyanosis after desipramine usage.

desipramine administration. Physical examination and laboratory findings were again within normal limits and the type of the acrocyanosis on his second admission was exactly as seen before. Acrocyanosis disappeared entirely within 10 days of discontinuation of the drug.

### Discussion

The diagnosis of this case was acrocyanosis characterized by persistent dusky discoloration of the hands and feet, which were sometimes cold and sweaty as well. Acrocyanosis is an unusual side effect of TCA agents. Childhood Raynaud's phenomenon and erythromelalgia are in the differential diagnosis<sup>1</sup>. Childhood Raynaud's phenomenon is rare and usually associated with collagen vascular disease. Our patient had no associated findings suggesting vasculitis or Raynaud's phenomenon but the presence of a strong association between onset of acrocyanosis and use of imipramine confirmed the adverse effect of the TCA.

We suggest that our patient had acrocyanosis due to the sympathomimetic effects of imipramine. As the patient developed the same symptoms with

two drugs-desipramine (an active metabolite of imipramine) and imipramine itself- we considered an idiosyncratic reaction.

Finally, we suggest that physicians should be aware of this possible side effect of tricyclic antidepressants.

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