

Ergotism and Vascular Insufficiency: A Case Report and Review of Literature

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Abstract

We report a case of ergot-induced peripheral vascular insufficiency of the lower limbs and review the vascular complications, angiographic findings and the different modalities of treatment. The following case report highlights the clinical features and course of ergot toxicity, and the difficulty in early diagnosis.

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Key words: Arterial spasm, Ergot, Peripheral vascular insufficiency

Introduction

Toxicity from ergot and its derivative is well known. Great epidemics occurred during the middle ages due to consumption of rye contaminated with the fungus, *Claviceps purpurea*, which elaborates the ergot alkaloids.¹ Epidemic ergotism has virtually disappeared since the identification of the fungus. However, with the introduction of ergotamine tartrate in the 1920s, most of the reported individual cases of toxicity are iatrogenic either as an acute overdose or chronic excessive intake for the treatment of migraine.

Case Report

A 25-year-old woman was admitted to our hospital with complaints of right foot numbness and coldness for 1½ months associated with pulling cramps of her right calf after walking for 5 minutes. She had no history of Raynaud's syndrome or any previous or family history of connective tissue disease. She also had no risk factors of cardiovascular disease. She had a significant history of migraine for 3 years, irregular menses for 3 months and asthma for 4 years. At presentation, she was on Primolut N (norethisterone) 2 tabs om for her irregular and excessive menses, Tramal (tramadol) 100 mg tds, Lexotan (bromazepam) 1.5 mg on and Cafergot (ergotamine tartrate 1 mg and caffeine 100 mg) 1 tab pm for her migraine. She had been taking one to two tablets of Cafergot daily for the past 2 months.

Physical examination revealed a well-looking young lady. She was afebrile with a blood pressure of 95/50 mmHg. She had no skin rash or arthritis. The main

findings were confined to her lower limbs. Both lower extremities were cold and pale. There was no cyanosis, digital gangrene or Raynaud's phenomenon. Both the femoral pulses were present and of normal volume. However, no pulses could be felt below the femorals. The pulses of the upper extremities and carotids were normal.

The working diagnosis was an occlusive arterial disease of the lower limbs: either arterial thrombosis/thromboembolism, arteritis/vasculitis, or Cafergot-induced peripheral vascular disease.

Laboratory studies, which included complete blood count, platelet count, coagulation profiles, erythrocyte sedimentation rate, renal and liver functions, serum electrolytes and lipids, urinalysis and thyroid function test, chest roentgenogram and electrocardiogram, were normal. Antibodies for antinuclear factor, double-stranded DNA, antinuclear cytoplasmic and anti-cardiolipin were negative. Her lupus anticoagulant was only weakly present, ratio 1:4. Both Venereal Disease Research Laboratory (VDRL) serology and D-dimer were negative. Fibrinogen and protein C and S levels were normal.

Angiogram of both lower limbs was done on the second day of admission. There were no abnormalities in the distal abdominal aorta, the iliac and the proximal femoral arteries. There was a diffuse narrowing of the distal half of the superficial femoral arteries and the popliteal arteries (Figs. 1 & 2). The tibia arteries were not well visualised and the legs were supplied mainly by the small vessels from the profunda and geniculate

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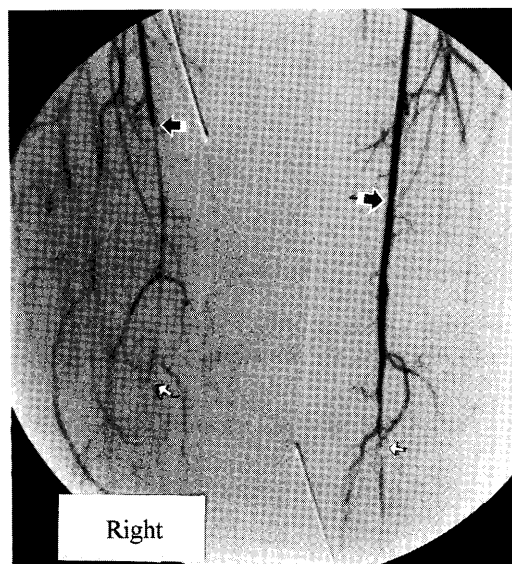


Fig. 1

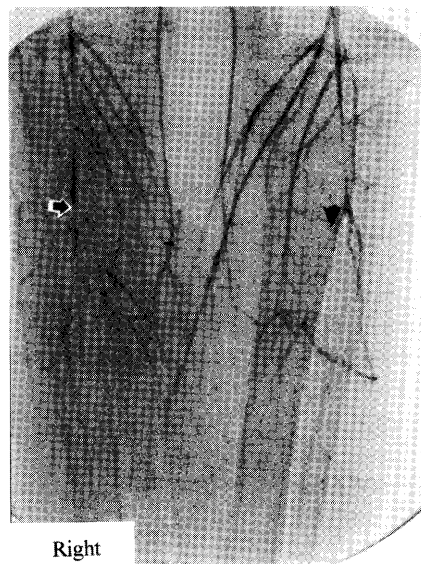


Fig. 2.

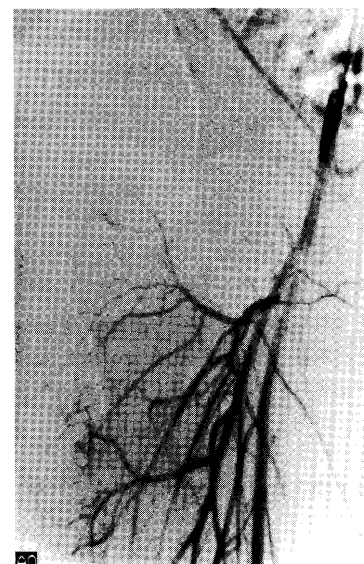


Fig. 3.

Fig. 1. Angiogram showing a long diffuse narrowing of the distal half of the right and left superficial femoral arteries, the right being more severely affected than the left. The black arrows indicate narrowings at the mid superficial femoral arteries and the white arrows indicate the stenoses at the adductor canals.

Fig. 2. Angiogram showing severely attenuated right and left popliteal arteries and their bifurcations. The arrow indicates an occlusion of the right popliteal artery bifurcation.

Fig. 3. Angiogram of the right main, superficial and deep femoral arteries after stopping Cafergot showing that the previous narrowings had disappeared.

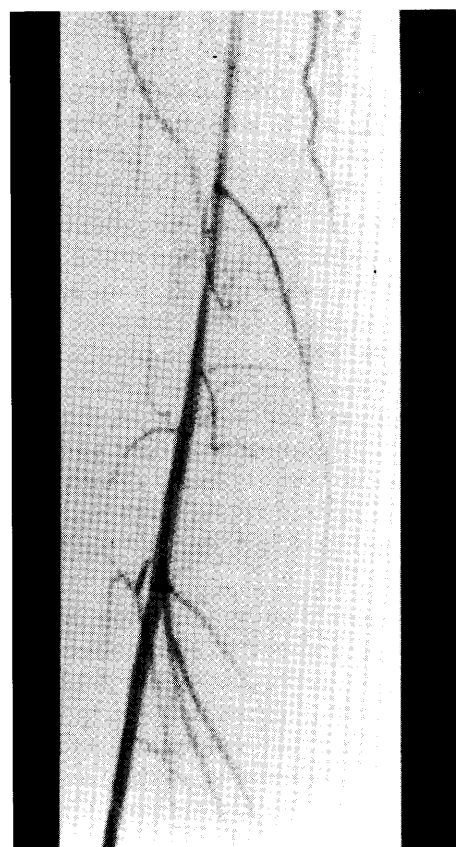


Fig. 4

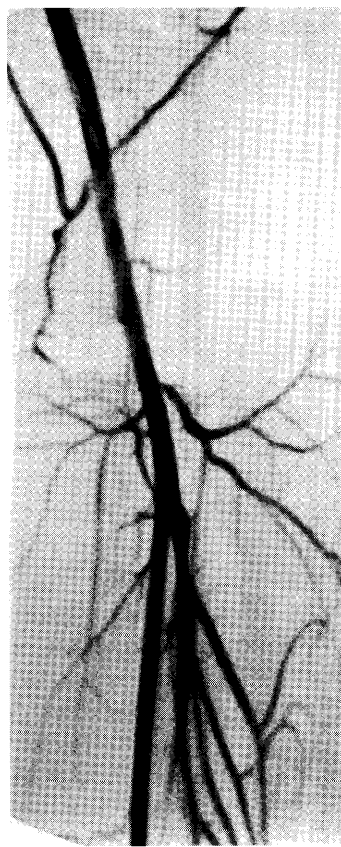


Fig. 5.

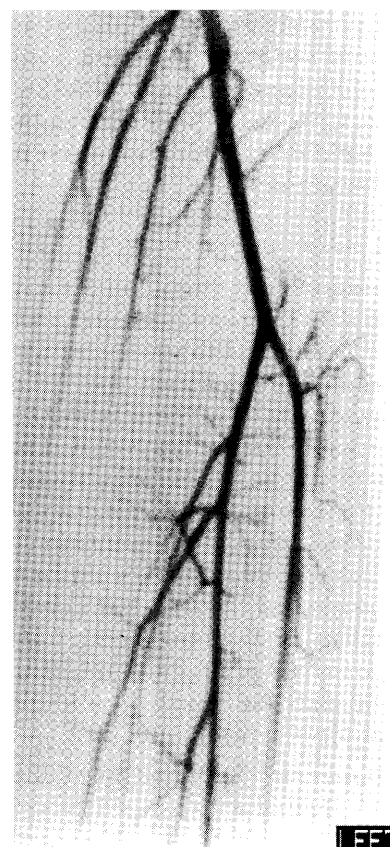


Fig. 6.

Fig. 4. Angiogram of the right popliteal artery after stopping Cafergot showing good vessel size and flow.

Fig. 5. Angiogram of the left main, superficial and deep femoral arteries after stopping Cafergot showing that the previous narrowings had disappeared.

Fig. 6. Angiogram of the left popliteal artery after stopping Cafergot showing good vessel size and flow.

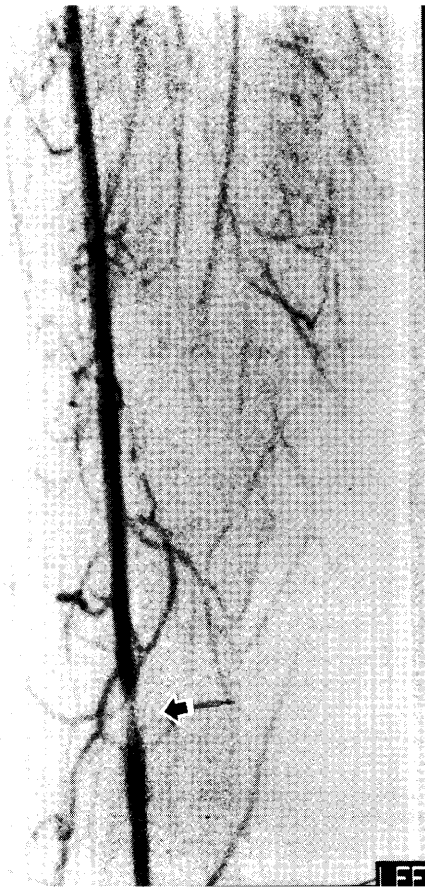


Fig. 7. Angiogram showing a residual stenosis of the left lower superficial femoral artery at about the level of the adductor canal. The arrow indicates the site of narrowing.

collaterals. The angiographic findings were compatible with arterial spasm or vasculitis. They were not suggestive of thrombosis.

Her medications, Cafergot and Primolut N, were stopped on admission. She was treated with subcutaneous Fraxiparine followed by oral warfarin. During the first 2 days her symptoms improved slightly despite no detectable changes in clinical findings. On the third day there was a remarkable return of her pulses including the dorsalis pedis and posterior tibial pulses. Her symptoms also improved significantly. She was discharged with warfarin.

On follow-up, her pulses remained strong and of good volume. A repeat angiogram 2 months later revealed that all her other previous narrowings had disappeared (Figs. 3 to 6) except a mild stenosis of the left lower superficial femoral artery (Fig. 7). Warfarin was thus discontinued and she was advised against using Cafergot.

Discussion

Although epidemic ergotism was documented in the West during the middle ages, it was not until 1920 that ergotamine tartrate was isolated and its pharmacology described.⁷ Ergotamine has a complex mode of action

mediated as partial agonist or antagonist on the 5-hydroxytryptamine, dopamine and noradrenaline receptors. The peripheral vasoconstrictory effect is probably due to its effect on both 5-HT₁ and 5-HT₂ receptors.^{1,2} The clinical signs of ergot toxicity do not correlate with the blood ergotamine level. After a single dose, the vasoconstrictive effect of ergotamine lasts more than 24 hours despite its short plasma half-life of about 2 hours.³ This prolonged vasoconstriction after a single dose has important clinical implications. Ergots are also toxic to the endothelium causing hyaline degeneration and necrosis.^{4,5}

Epidemic ergotism which is usually secondary to chronic massive ingestion of ergot and other contaminants is characterised by convulsion or gangrene of the limbs. In contrast, iatrogenic ergotism which is secondary to chronic overuse of pharmacologic doses of ergots is characterised by chronic vasospasm and tissue ischaemia. Toxicity is more common with the parenteral or suppositories than oral therapy.⁴ Symptoms may appear at any time during the course of treatment. Ergotism occurs more frequently in women (ratio of 5:1) and young patients (average age 38.4 years).⁵ Conditions associated with increased incidence of complications with ergotamine include: peripheral vascular disease, hypertension, coronary artery disease, pregnancy, thyrotoxicosis, sepsis, liver and renal dysfunctions, anaemia, malnutrition, smoking, oral contraceptives and concomitant use of methysergide and P-blockers for migraine.^{2,6}

The medium-sized muscular arteries, small arteries and arterioles are often involved but rarely the large arteries.⁷ The lower limbs are most often involved (60% to 70%), followed by the upper limbs and the visceral vessels. In the lower limbs, the femoral and the popliteal arteries are often involved. The proximal vessels, the iliac arteries and the distal aorta, are usually spared. In the upper limbs, the junction of the axillary and brachial arteries is often involved with marked narrowing.⁸ Involvement of the extremities is usually bilateral. Despite intense vasospasm, gangrene of the limbs is rare.⁹ This is often due to the intermittent dosing for the treatment of migraine resulting in intermittent vasospasm and thus allowing collaterals to form.

The angiographic finding of ergotism is quite unique and often diagnostic. The characteristic finding is a diffuse generalised smooth narrowing (spasm) and tapering of the arteries with little irregularity in the contour of the lumen.^{4,10,11} Less common findings are local constrictions which may be multiple mimicking atherosclerotic disease.¹² Collaterals are most prominent in chronic ischaemia, and are often around the vasospastic segment. Thrombosis may rarely be seen. The involved arteries usually return to normal with regression of collateral circulation with cessation of ergot.

Diagnosis is often suspected in young patients on ergotamine tartrate. Resolution of the clinical picture after stopping the drug is sufficient to make a presumptive diagnosis. Often the diagnosis can be missed if the drug history is not forthcoming or unusual sites are affected. Angiography is then recommended to establish the diagnosis and to rule out other causes of ischaemia.

Most reported cases usually recover by 48 hours after discontinuing ergotamine. Nevertheless numerous pharmacologic agents have been tried in the past e.g. ethyl alcohol, amyl nitrite, tolazolin, hydergine, phenolamine, sodium nicotinate, papaverine, phenoxybenzamine, hydralazine and reserpine and sodium nitroprusside.^{2,7,13,14} However, most treatments have no immediate clinical benefits and usually response is seen a few days later. Newer vasodilators such as calcium antagonists—nifedipine,¹⁵ prazosin and nitroglycerin are generally more effective, easier to use and have less side effects than earlier therapies. More recently treatment with prostacyclin and prostaglandin E₁¹⁶ have been advocated since they have both vasodilating and antiplatelet activity. Anticoagulation with heparin or the use of dextran may be of benefit since thrombosis may occur in the spastic vascular segments.

Direct sympathetic blockade (epidural or spinal anaesthetic)⁷ and regional sympathectomy^{7,9} are mostly ineffective. Surgery by mechanical intra-arterial dilatation (balloon angioplasty¹⁷ and periarterial stripping⁹) often produces immediate relief of symptoms. However, mechanical or surgical intervention is considered only if gangrene and necrosis are imminent as there is a risk of permanent anatomic damage to the otherwise normal arteries.

The case presented here is a migraine patient with ergotism. Like most reported cases, she had been taking daily doses of ergotamine tartrate resulting in the typical lower limbs ischaemia from arterial vasospasm. Her symptoms resolved within 72 hours after cessation of the drug. Although her angiogram showed the classical diffuse spasm of both superficial femoral arteries, there were localised constrictions of the popliteal arteries mimicking arteritis. The response of her symptoms and the return of her pulses to the cessation of ergotamine and the lack of inflammation and collagen markers make the diagnosis of arteritis unlikely. She developed residual stenosis of her left popliteal artery and this could be related to the damaged endothelium resulting in irreversible narrowing.

Conclusion

Nowadays clinical ergotism is usually iatrogenic. Although rare, clinical ergotism can be serious and

devastating. Ergotism should be suspected in young patients presenting with peripheral vascular insufficiency but without risk factors of vascular disease. Early diagnosis is important as simple discontinuation of the drug is often effective in reversing the process. Since a persistent vasoconstrictor effect occurs after a single dose of ergotamine, the drug should not be given daily as this will lead to chronic vasoconstriction. Ergotamine should never be used for migraine prophylaxis! All patients on ergot treatment should be informed of the potential complications and should be carefully monitored especially the peripheral pulses.

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REFERENCES

1. Gilman A G, Rall T W, Nies A S, Taylor I'. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press, 1990:933-53.
2. Olesen J, Tfelt-Hansen I', Welch K M A. The headaches. New York: Raven Press, 1993:313-22.
3. Tfelt-Hansen P. The effect of ergotamine on arterial system in man. *Acta Pharmacol Toxicol* 1986; 59(S3):1-30.
4. Glazer G, Myers K A, Davies E R. Ergot poisoning. *Postgrad Med J* 1966; 42:562-8.
5. Kempeziński R F, Buckley C J, Darling R C. Vascular insufficiency secondary to ergotism. *Surgery* 1976; 79:597-600.
6. Petersen H D, Lassen N A, Noer I, Tonnesen K H. Subclinical ergotism. *Lancet* 1977; 2:65-6.
7. Hudgson I', Hart J A L. Acute ergotism: report of a case and a review of the literature. *Med J Aust* 1964; 2:589-91.
8. Felix R H, Carroll J D. Upper limb ischaemia due to ergotamine tartrate. *Practitioner* 1970; 205:71-2.
9. Young J R, Humphries A W. Severe arteriospasm after use of ergotamine tartrate suppositories: report of a case. *JAMA* 1961; 175:1141-5.
10. Hirsch M, Eger M. Angiography in diagnosis of ergotism. *Radiology* 1972; 103:88-90.
11. Bagby R J, Cooper R D. Angiography in ergotism: report of two cases and review of the literature. *Am J Roentgenol Radium Ther Nucl Med* 1972; 116:179-86.
12. Doig S G, Fell G, French J. An unusual angiographic appearance of ergot poisoning. *Australas Radio* 1985; 29:265-7.
13. Greenberg D J, Hallett J W. Lower extremity ischaemia due to combined drug therapy for migraine. *Postgrad Med* 1982; 72:103-7.
14. Carliner N H, Denune D I', Finch C S, Goldberg L I. Sodium nitroprusside treatment of ergotamine induced peripheral ischaemia. *JAMA* 1974; 227:308-9.
15. Dagher E J, Pais S O, Richards W, Queral L A. Severe unilateral ischaemia of the lower extremity caused by ergotamine: treatment with nifedipine. *Surgery* 1985; 97:369-73.
16. Edwards R J, Fulde G W O, McGrath M A. Successful limb salvage with prostaglandin infusion: a review of ergotamine toxicity. *Med J Aust* 1991; 155:825-7.
17. Shifrin E, Perel A, Olschwang D, Diamant Y, Cotev S. Reversal of ergotamine-induced arteriospasm by mechanical intra-arterial dilatation. *Lancet* 1980; 2:1278-9.