Epidemic dropsy in India

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Summary

Epidemic dropsy is a clinical state resulting from use of edible oils adulterated with *Argemone mexicana* oil. Sanguinarine and dehydrosanguinarine are two major toxic alkaloids of *Argemone* oil, which cause widespread capillary dilatation, proliferation and increased capillary permeability. Leakage of the protein-rich plasma component into the extracellular compartment leads to the formation of oedema. The haemodynamic consequences of this vascular dilatation and permeability lead to a state of relative hypovolemia with a constant stimulus for fluid and salt conservation by the kidneys. Illness begins with gastroenteric symptoms followed by cutaneous erythema and pigmentation. Respiratory symptoms such as cough, shortness of breath and orthopnoea progressing to frank right-sided congestive cardiac failure are seen. Mild to moderate anaemia, hypoproteinaemia, mild to moderate renal azotemia, retinal haemorrhages, and glaucoma are common manifestations. There is no specific therapy. Removal of the adulterated oil and symptomatic treatment of congestive cardiac failure and respiratory symptoms, along with administration of antioxidants and multivitamins, remain the mainstay of treatment. Selective cultivation of yellow mustard, strict enforcement of the Indian Food Adulteration Act, and exemplary punishment to unscrupulous traders are the main preventive measures.

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Epidemic dropsy results from ingestion of edible oil adulterated with *Argemone mexicana* (Mexican Poppy) oil. The outbreak of epidemic dropsy in the Indian capital, New Delhi, during the rainy season of 1998 was of one of the most severe forms and had repercussions in both health and political circles. Some 2552 cases were reported and 65 deaths occurred between 5 August and 12 October, causing untold misery and economic loss to the affected families. The actual figures are likely to be much higher due to nonreporting of milder cases to the hospitals. The aim of this article is to consolidate and update the available information on clinical aspects of epidemic dropsy.

The condition was first reported by Lyon in 1877 from Calcutta[1] and has since occurred in other countries including the Fiji Islands, Mauritius, Madagascar, South Africa and Burma (Myanmar).[2] In India, it has been reported from time to time from the States of West Bengal, Bihar, Orissa, Madhya Pradesh, Uttar Pradesh, Gujarat, Maharashtra and Delhi,[3–13] generally sparing South Indian States where the predominant cooking fat is coconut oil.

The word *Argemone* is derived from the Greek *argema* meaning cataract in the eye, as the juice of the plant was used as a remedy in diseases of the eye. In India the plant has numerous vernacular names of which *Satyanashi* meaning devastating seems most appropriate.[14] The Prickly Poppy has been used as a medicinal plant in several cultures.

Aetiology

Based upon numerous epidemiological and clinical studies and human and animal feeding trials, it has been firmly established that *Argemone* oil is responsible for epidemic dropsy.[5 15–19] It occurs due to the use of contaminated mustard oil (with which *Argemone* oil is completely miscible)[20] for cooking and massage.[21] Adulteration of other types of oils (linseed, rapeseed, groundnut, and other vegetable oils) has also been reported.[22–24] In South Africa, an epidemic occurred due to contamination of wheat flour. Other contributory factors are the consumption of a diet rich in carbohydrates and low in proteins, as well as poor premorbid nutritional status. It has been observed that those consuming a protein-rich diet tend to develop a relatively mild form of dropsy.[25] The active toxic principle of *Argemone* oil, the alkaloid sanguinarine, is able to withstand normal cooking temperatures and hence appears to be heat stable. While Lal and Dasgupta observed that a minimum concentration of 1% of *Argemone* oil as an adulterant was necessary to produce clinical features,[17] Ramasastri and Babu have proposed a maximum permissible upper limit of 0.01% in edible oils.[26] The duration of exposure is also of vital importance. Sanguinarine can be retained in the gastrointestinal tract, liver, lung, kidney, heart and serum, for up to 96 hours after ingestion, due to binding to plasma proteins.[27 28] This may lead to cumulative toxicity even with low-dose exposure over prolonged period.[29]

Pathophysiology

The exact pathophysiology of epidemic dropsy is not well understood. Sanguinarine has been shown to produce widespread capillary dilation coupled with increased capillary permeability, and produces clinical features similar to epidemic dropsy under experimental conditions.[30] The chief effects of *Argemone* oil are on the blood vessels,[31] where they cause leakage of protein-rich plasma components into the extravascular compartment, leading to a state of hypovolemia and reduced plasma osmotic pressure. The resultant decrease in renal blood flow sets into motion compensatory mechanism with activation of the renin–angiotensin–aldosterone system, and retention of sodium and water. The fluid and salt thus conserved may compensate for the expanded vascular capacity and increased permeability in mild cases of epidemic dropsy. However, in severe cases these compensatory mechanisms may prove to be inadequate because fluid and salt conserved by kidneys is poorly held in the vascular com-

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Mechanism of toxicity of *Argemone* alkaloids

- inhibition of Na⁺, K⁺-ATPase[40–45]
- destruction of cytochrome P-450[16 46]
- depletion of endogenous hepatic glutathione content[27]
- enhanced glucogenolysis leading to depletion of glycogen levels in liver[27]
- formation of glucose-1-phosphate, exhausting glycogen levels in liver[27]
- inhibition of the oxidation of pyruvate, lactate and succinate[47]
- binding at multiple sites on DNA which may decrease capacity for DNA repair[48 49]
- phototoxicity,[50 51] blocking of hepatic enzymes[52] and inhibition of RNA and DNA polymerase activities

Box 1

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partment due to low plasma osmotic pressure. As a result, a state of relative hypovolemia exists, which provides a constant stimulus for renal conservation of salt and water, which in turn causes marked anasarca. The hypoproteinaemia observed in dropsy may result from leakage of protein-rich plasma into extravascular tissue, poor intake, diarrhoea, and perhaps from mild hypotoxicity or protein-losing enteropathy. Increased total protein content of the aqueous humor of the eye has been demonstrated.[32] Widespread capillary dilatation and proliferation in the subcutaneous tissue, surrounded by proliferating endothelial cells, which produces mottling and blanching of the skin has also been reported.[32–36] Increased permeability of these small capillaries leads to oedema, which in the later stages may be worsened by right-sided heart failure. The dependent oedema in epidemic dropsy is relatively resistant to diuretics and resolves gradually over months. It may be firm at times, perhaps indicative of the high protein content of the oedematous fluid.

Similar exudation of protein-rich fluid from the pulmonary capillaries in the interstitial tissues of the alveoli produces interstitial or frank pulmonary oedema of non-cardiac origin with manifestations of mild hypoxia, respiratory alkalosis, restrictive ventilatory defects, increased alveolar to arterial oxygen gradient, and derangement of diffusion capacity. Resultant pulmonary hypertension leads to a rise in right ventricular systolic pressure as well as dilation of right-sided cardiac chambers and right-sided failure independent of left ventricular systolic function. Histopathology of the lungs reveals congestion and exudation of fluid and red cells into the alveoli. High output cardiac failure with a wide pulse pressure, tachycardia, dyspnoea, orthopnoea and gallop rhythm may result from the peripheral vasodilatory effects of sanguinarine and moderate to severe anaemia. The onset of cardiac failure, which is predominantly right-sided, further worsens oedema formation and leads to congestive hepatomegaly. Autopsy studies reveal a thinning of the walls of the heart with muscle fibres separated by dilated capillaries.[27] Similar mechanisms may underlie effusions in the pleural, pericardial and peritoneal cavities. Haemodynamic and vascular changes in the kidney, and possibly an additional direct effect of *Argemone* alkaloids, are responsible for the azotemia and renal failure seen in some patients. The kidneys show vascular and glomerular congestion and patchy tubular lesions.[27]

The diarrhoea and vomiting observed in the acute stage may be due to direct toxicity of *Argemone* oil to the enterocytes and congestion of the gut mucosa due to vascular leakiness. Some patients demonstrate nodular haemangiomata called sarcoids in the gut, which can cause severe blood loss necessitating blood transfusion. The liver shows swollen hepatocytes with hydropic changes and degenerated nuclei. There is marked dilation of the veins and sinusoids separating the liver cells. Fatty infiltration is also seen and fibrosis and hyperplasia of bile ducts may be observed in some cases.[27 29 37 38] Anaemia is common and may be multifactorial in origin due to bleeding from the gastrointestinal tract, bone marrow suppression, and shortened red cell life span.[39]

The mechanism of toxicity of *Argemone mexicana* is summarised in box 1.

Clinical features

Persons of all ages are affected, except breast-fed infants and toddlers who have no mustard oil in their diets. The disease is seen mostly in epidemic form but isolated cases also occur occasionally.[18] Both sexes are affected equally. In India the incidence reaches its peak in July to August when newly extracted oil harvested towards the end of summer is sold. Due to a decrease in toxicity during storage of oil, the incidence is lowest in April.[53]

Onset is usually subacute or insidious with watery diarrhoea and vomiting. This lasts from a few days to more than a week. In a few outbreaks diarrhoea was not a common feature at the outset but it usually precedes the onset of oedema. Gastrointestinal disturbances at onset have been reported by various investigators in 52–80% of cases.[25] Intermittent or continuous fever, ranging from 99°F to 100.5°F, is noted commonly but is seldom high-grade. Arthralgias, myalgias, and low backache are also seen. Significant hair loss is observed occasionally.[54]

Bilaterally symmetrical pitting oedema of the lower limbs extending from the ankles up to the scrotum and abdominal wall is a constant feature. The oedema increases after standing, typically reaching a maximum at the end of the day and decreasing on recumbency. Marked cutaneous flush with tenderness and blanching of oedematous parts on pressure, burning sensations, itching and paresthesias are usually observed. The oedema is only partially responsive to diuretics. Vascular naevi, small and dilated superficial veins and hyperpigmentation may be seen.[36 55] Telangiectases and sarcoids under the skin and mucus membranes, including anal mucosa, may appear. These can cause blood loss, which may be severe and contribute to anaemia.

Palpitations, exertional breathlessness and orthopnoea may be seen. Tachycardia, elevated jugular venous pressure and wide pulse pressure are common. Clinical evidence of cardiomegaly may be found. Gallop rhythm and an apical systolic murmur due to functional mitral incompetence may be present.[56] Flow murmurs at the base are common due to associated anaemia and high output state. Pulmonary oedema may be seen in severe cases. Pericardial effusion may also occur. Cough and breathlessness are common symptoms. Initially exertional, the breathlessness may be seen at rest and on recumbency when cardiac failure develops. Pneumonia is seen in some cases.[57] High fever, chest pain and purulent sputum may not be present and occult infection may be discovered on a routine chest X-ray. The condition responds to the usual antibiotics although microbiological evidence of aetiology is lacking. Pleural effusions are occasionally seen. Though not a feature in previous epidemics, mild to moderate derangement in renal function was occasionally encountered in the recent Delhi epidemic. The renal size is normal on ultrasonography, and the urine sediment is bland. Dialysis may be required and recovery is normally complete.

Sensorium is normal. No objective sensory loss is demonstrable and all peripheral reflexes are present. Electrophysiological studies of peripheral nerves and muscles are normal.[58] However, paresthesias and pain in the oedematous limbs are prominent early complaints. Fundus examination shows venous dilation and tortuosity, haemorrhages and disc oedema. Flurorescein angiographic findings include dilated and tortuous retinal veins, prominent vascular staining, microaneurysms, disc oedema and pericapillary dye spillage.[59 60] Glaucoma has been reported in various epidemics in 0–12% of cases.[61 62] This is a later manifestation occurring after about 4 weeks. During the early stages, there may be no dimness of vision and perimetry may also reveal no field defects. During later stages glaucomatous field defects may be present.[32] If undetected, it may lead to severe visual impairment. All cases of epidemic dropsy should be subjected to regular eye examinations for 8–12 weeks. The severity of the glaucoma is independent of the severity of the systemic features. The glaucoma is always bilateral with no aqueous outflow obstruction. There is no sign of anterior segment inflammation and the chamber depth is normal.[63] Moderate to severe anaemia is one of the commonest manifestations.[39] It is usually normocytic, and normochromic but may be hypochromic in those cases which develop bleeding manifestations.

Diagnosis

Epidemic dropsy must be distinguished from hypoproteinaemic states, filariasis, venous insufficiency, and Beri-Beri, hypothyroidism and nephrotic syndrome. The diagnosis must be considered during an outbreak of bilaterally symmetric oedema in more than one member of a family or community consuming mustard oil, especially if peripheral tendon jerks are well preserved. Beri-Beri occurs among poor persons living on a diet of milled rice, has an acute onset, prominent peripheral neuropathy and responds rapidly to thiamine therapy with brisk diuresis. No laboratory parameter is considered specific for epidemic dropsy. Anaemia may be severe and is of microcytic hypochromic or normocytic normochromic type. Liver function tests are usually normal. Blood urea and creatinine may be raised if renal failure is present. Hypoalbuminaemia, raised alpha-2 globulin and reversal of albumin:globulin ratio has been reported by some investigators. Urinalysis is usually normal.

Raised plasma pyruvate levels may be seen. Chest X-ray may show cardiomegaly, pulmonary oedema or pneumonia. Electrocardiogram may show non-specific ST segment, and T-wave changes or atrial or ventricular extrasystoles.

Identification of the *Argemone* seed

Adulteration of light-yellow mustard seeds (*Brassica dompestris*) by *Argemone* seeds can be visually detected. However, they are more similar in colour to the dark mustard seeds (*Brassica nigra*), and are thus less easily detected. The specific gravity of *Argemone* seeds is 1.03 compared to 1.3 for mustard seeds. Hence, in normal saline solution, the mustard oil seeds settle at the bottom while *Argemone* seeds remain suspended.[25]

Composition of *Argemone* oil

Mukerjee *et al* isolated a toxic substance from *Argemone* oil in 1941, with an empirical formula $C_{20}H_{15}NO_4$ that was later identified as sanguinarine.[15] Sarkar *et al* in 1948 reported the presence of at least two toxic alkaloids, sanguinarine and dihydrosanguinarine.[47]

Alkaloid composition of *Argemone* **oil**
Major alkaloids
● dihydrosanguinarine 87%
● sanguinarine 5%
Minor alkaloids
● berberine 0.57%
● protopine 0.34%
● cheletrythrine 0.12%
● coptisine 0.03%

Box 2

Argemone seeds yield 32–35% of *Argemone* oil (v/w)[16] which contains 0.13% total alkaloids. The alkaloid composition of *Argemone* is given in box 2.

Detection of *Argemone* oil adulteration in edible oils

The following tests are useful[64]:

Nitric acid test: 5 ml oil is shaken with an equal volume of nitric acid. On standing, the acid layer turns yellow, orange-yellow or crimson, depending upon the amount of *Argemone* oil . The test is sensitive to a concentration of >0.25%. It has a high false-positive rate and a positive test must be confirmed.

Ferric chloride test: 2 ml of oil and 2 ml of concentrated hydrochloric acid are mixed and heated in a water bath at 33.5–35°C for 2 minutes. Then 8 ml of ethyl alcohol is added and the mixture is heated in the bath for 1 minute. Finally, 2 ml of ferric chloride is added and the tube is heated in the bath for a further 10 minutes. If *Argemone* oil is present, an orange-red precipitate is formed.

Cupric acetate test: a green colour is formed.

Paper chromatographic method: the most sensitive method; can detect down to 0.0001% *Argemone* oil adulteration.

Treatment

Withdrawal of the contaminated cooking oil is the most important initial step. Bed rest with leg elevation and a protein-rich diet are useful. Supplements of calcium, antioxidants (vitamin C and E),[37 55] and thiamine and other B vitamins are commonly used.[47] Corticosteroids and antihistaminics such as promethazine have been advocated by some investigators,[25 65] but demonstrated efficacy is lacking. Diuretics are used universally but caution must be exercised not to deplete the intravascular volume unless features of frank congestive cardiac failure are present, as oedema is mainly due to increased capillary permeability. Cardiac failure is managed by bed rest, salt restriction, digitalis and diuretics. Pneumonia is treated with appropriate antibiotics. Renal failure may need dialysis therapy and complete clinical recovery is seen. Glaucoma may need operative intervention, but generally responds to medical management.

Prognosis

Mortality is usually due to heart failure, pneumonia, respiratory distress syndrome or renal failure and is around 5%.[25] Long-term follow-up studies are scanty so the long-term effects of *Argemone* oil toxicity have not been documented. Wadia *et al* reported that 25% of cases will have oedema beyond 2 months and 10% beyond 5 months.[54] Shanbag *et al* noticed pigmentation of skin and excessive loss of hair, which lasted 4–5 months following the disease.[6] The majority of patients completely recover in about 3 months.

Prevention

A number of measures may help to prevent epidemic dropsy in India:
- selective cultivation of yellow-seeded mustard with which neither black-coloured *Argemone* seeds nor dark-brown *Argemone* oil mixes well so that adulteration can easily be detected even with the naked eye
- a strict ban on the sale of unbranded and unpacked mustard oil, and a statutory certificate from manufacturers of labelled mustard oils about the freedom of the contents from *Argemone* alkaloids
- education and motivation of farmers to cultivate yellow-seeded mustard and to make them aware of the identity of *Argemone* plants which grow as weeds in mustard fields
- government agencies involved in enforcing the provisions of the Prevention of Food Adulteration Act must be made accountable in the event of occurrence of such epidemics. This means exemplary punishments for unscrupulous traders.

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