

# An outbreak of veno-occlusive disease of the liver in northern Iraq

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فاشية مرض انسداد أوردة الكبد في شمال العراق  
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**خلاصة :** تصف هذه المقالة فاشية مرض انسداد الأوردة الكبدية، حدثت في الموصل بشمال العراق في سنة 1994. ولقد وقعت هذه الفاشية بسبب تناول قمح تلوث بشكل غير مقصود بحبوب «سينيشيو» (شيخ الربيع) التي أنتجت قلوانيات البيروليزيدين السامة. وشملت الفاشية 14 شخصاً (ثمانية من الذكور وستة من الإناث) كانوا من أفراد ثلاث عائلات بدوية. وكانت الأعمار في نصف الحالات تقل عن خمسة عشر عاماً. كما كانت الملامح السريرية اللافتة للنظر هي آلام البطن بالاستسقاء السريع التكوين وتضخم الكبد. وتوفي مريضان أثناء علاجهما بالمستشفى، وذلك يعني أن معدل وفيات الحالات كان يقدر بنسبة 14%.

**ABSTRACT** This paper describes an outbreak of veno-occlusive disease of the liver which occurred in Mosul, northern Iraq in 1994. It was caused by the consumption of wheat accidentally contaminated with *Senecio* seeds which produced toxic pyrrolizidine alkaloids. The outbreak involved 14 people (eight males and six females) who were members of three Bedouin families. Half of the cases were under the age of 15 years. The striking clinical features were abdominal pain, rapidly filling ascites and hepatomegaly. Two deaths occurred during hospitalization, with an estimated case fatality rate of 14%.

## Flambée épidémique de maladie veino-occlusive du foie dans le nord de l'Iraq

**RESUME** Cet article décrit une flambée épidémique de maladie veino-occlusive du foie qui s'est produite en 1994 à Mossoul, ville située dans le nord de l'Iraq. Cette flambée épidémique a été provoquée par la consommation de blé accidentellement contaminé par des graines de Sénéçon qui ont produit des alcaloïdes pyrrolizidiniques toxiques. Elle a touché 14 personnes (huit de sexe masculin et six de sexe féminin) appartenant à trois familles de bédouins. La moitié des cas étaient âgés de moins de 15 ans. Les signes cliniques marquants étaient des douleurs abdominales, une ascite se formant rapidement et une hépatomégalie. Deux décès se sont produits au cours de l'hospitalisation et le taux de létalité a été estimé à 14%.

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## Introduction

Veno-occlusive disease of the liver is produced by the hepatotoxic effects of pyrrolizidine alkaloids (PAs), and these alkaloids are derived from plants, of the genus *Senecio*. This wild weed can be inadvertently harvested with grain crops and consumption of flour contaminated by these plants is the cause of liver disease [1,2].

Liver disease caused by the contamination of grain has been reported in rural populations around the world. Outbreaks result from the growth of an exceptionally high proportion of the alkaloid-containing weeds in the crops [3-6]. These outbreaks of veno-occlusive disease have been reported among infants, children and adults, and mortality is reported to be high. Human poisoning through the medicinal use of herbs containing PAs has also been reported [7-9].

The molecular structures of almost all of these PAs are known and the main outlines of the structure-toxicity relationship have been established [10]. The alkaloids occur in all parts of the plant and are often present as the *N*-oxide derivatives, which are also toxic when ingested orally.

The toxic effects of PAs are due to their activation in the liver leading to the formation of metabolites [2]. These react with constituents of the liver cell in which they are formed and cause liver cell necrosis. The metabolites are released into the circulation and may pass beyond the liver to the lung causing vascular lesions characteristic of primary pulmonary hypertension and right ventricular hypertrophy [11,12]. The toxic alkaloids have widespread effects, the main symptom being rapidly filling ascites. Children appear to be the most vulnerable group and mortality is high among the very young and old [2].

In the acute stage of the disease, the liver shows characteristic centrilobular haem-

orrhagic necrosis, which is accompanied by occlusion of the hepatic veins [2]. A single acute episode of illness following brief consumption of food containing PAs may lead to progressive chronic liver disease resulting in cirrhosis which is not distinguishable from that resulting from other causes. Various PAs have been shown to be carcinogenic in experimental animals [13].

The disease generally has an acute onset, characterized by progressive upper abdominal discomfort, pain in the right hypochondrium, rapidly developing ascites and sometimes oliguria and oedema of the feet; nausea and vomiting may also be a feature [2]. Jaundice and fever are uncommon. The liver is enlarged and tender, often associated with massive pleural effusion; splenomegaly has also been observed. Liver function tests may show only mild disturbance. Mortality in veno-occlusive disease is high at the start and death often occurs after oesophageal haemorrhage. A subacute or chronic onset may lead to cirrhosis.

The present study describes an outbreak of veno-occlusive disease among Bedouin nomads near Mosul in northern Iraq and aimed to ascertain that the cause of the epidemic outbreak was the consumption of wheat contaminated by PAs from the weed plant *Senecio*.

## Subjects and methods

During the harvest of 1993, Bedouin families who lived near Mosul in northern Iraq buried their grains under their houses. These grains had been inadvertently mixed with *Senecio* weeds containing PAs during harvesting. The practice of burying grains underground is a traditional method used by the Bedouin to store their grains for a later date in winter.

From January 1994 to April of the same year, 14 patients were admitted to Mosul Teaching Hospital with rapidly developing ascites and hepatomegaly. The 14 cases came from three Bedouin families (33 members) who inhabited the neighbouring area of Albaagh near Mosul. A household survey involving 45 Bedouin families (556 members) in the area was conducted to disclose any undiagnosed cases, but no other such cases were found. However, two people died apparently from severe fulminant liver disease before being referred to Mosul Teaching Hospital.

### Laboratory Investigations

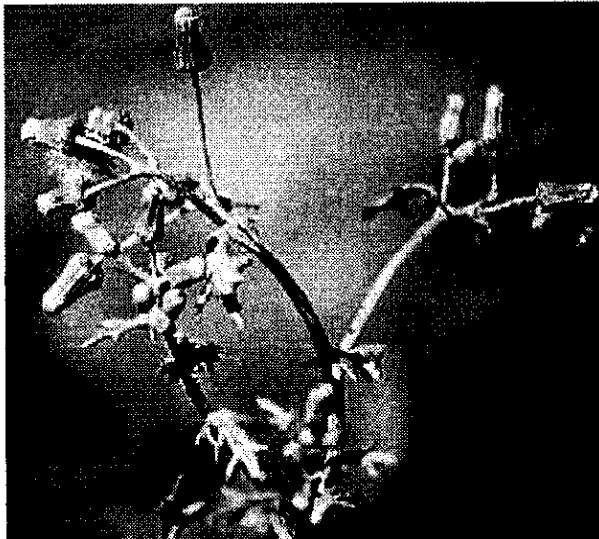
Samples of the stored wheat and flour were tested for heavy metals, organophosphorous compounds and aflatoxins. The tests were negative. The presence of PAs in the stored wheat and flour was confirmed by Ehrlich's reaction according to Mattocks and Jukes [14]. The plant which was isolat-

ed from the contaminated grain was identified as *Senecio vulgaris* (Figure 1).

Biochemical variables that were tested included: ascitic protein, haemoglobin, white blood cell count, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, plasma protein and prothrombin time.

All patients were tested for HBsAg by radioimmunoassay. Noninvasive ultrasound examinations were carried out for all the patients, which revealed no obliteration of the hepatic veins and no reversal of flow in the portal vein. Patients were also subjected to endoscopic examinations to detect oesophageal varices.

Liver biopsy in all 14 patients was done when the haemostatic mechanism was intact as indicated by a prothrombin time of not more than four seconds longer than the control and a platelet count of less than  $100 \times 10^9$  per litre. This confirmed that all pa-



### WARNING

The plant *Senecio vulgaris* and others of the same family contain an alkaloid which is highly toxic and causes extensive liver damage, as described in the article.

These plants should never be used for tea or as herbal remedy and great care must be taken to avoid contamination of harvested or stored grain with these plants.

Figure 1 *Senecio vulgaris* (*sheikh al-rabi*)—weed responsible for the outbreak of veno-occlusive disease in Mosul in 1994

tients were suffering from veno-occlusive disease of the liver.

## Results

The 14 patients were admitted to the hospital during the first four months of 1994 as follows: three patients were admitted in January, seven in February (two died), two in March and two in April. Seven of the 14 patients were children under the age of 15 years; ages ranged from 3 to 70 years. Eight of the patients were males.

All patients presented with abdominal pain and ascites; liver enlargement and

vomiting were also observed (Table 1). Table 2 shows the results of the biochemical tests together with the normal ranges of the biochemical variables investigated. The mean of ascitic protein indicates a transudative ascitic fluid. The white blood cell count was on the high side of the normal range. Alanine aminotransferase and aspartate aminotransferase levels were above the normal range. The high levels of the mean of the biochemical variables studied were due to the contribution of patients with severe veno-occlusive disease, especially those patients who died (numbers 8 and 10) (Table 3). The prothrombin time was prolonged in the 14 patients.

There were two deaths, a female aged 45 years and a male aged 18 years; both died from bleeding oesophageal varices and acute liver coma. The other 12 patients remained symptom-free on follow-up 12 months later.

**Table 1 Clinical presentation of the 14 patients, Mosul 1994**

Clinical presentation	No.	%
Ascites	14	100
Abdominal pain	14	100
Hepatomegaly	8	57
Vomiting	7	50
Jaundice	6	43
Splenomegaly	5	36

## Discussion

This is the first study of an outbreak of veno-occlusive disease caused by PAs in northern Iraq. An earlier study, which appeared in 1970, described a similar out-

**Table 2 Results of biochemical tests in the 14 patients, Mosul 1994**

Biochemical test	Mean	$\pm s$	Normal range
Ascitic protein (g/dl)	1.60	0.6	—
Haemoglobin (g/dl)	12.70	2.2	13–18
White blood cell count ( $10^9/l$ )	10.06	1.1	4–11
Bilirubin (mg/dl)	4.60	4.8	0.2–1.0
Alanine aminotransferase (IU/l)	51.90	74.2	5–20
Aspartate aminotransferase (IU/l)	37.40	30.8	5–20
Alkaline phosphatase (KAU/dl)	14.60	4.5	3–13
Plasma protein (g/dl)	6.30	1.0	6–8
Prothrombin time (s)	+8.07	9.4	10–12

Table 3 Biodata on the 14 patients with veno-occlusive disease

Patient No.	Month of presentation	Age (years)	Sex	Duration (days)	Vomiting	Liver span (cm)	Spleen (cm)	Oesophageal varix	Ascitic protein (g/dl)
1	Jan 94	60	F	30	+	11	8	+	0.2
2	Jan 94	70	M	7	-	12	10	+	1.6
3	Jan 94	18	M	7	-	15	0	-	2.8
4	Feb 94	14	M	10	-	17	10	+	1.6
5	Feb 94	4	F	7	-	16	0	-	2.3
6	Feb 94	3	F	90	-	11	0	-	2.9
7	Feb 94	14	M	10	-	18	8	+	1.5
8	Feb 94	45	F	10	+	10	10	+	2
9	Feb 94	18	F	5	+	12	9	+	1.95
10	Feb 94	18	M	7	+	18	10	+	2.8
11	March 94	30	F	30	-	12	0	-	1.5
12	March 94	7	M	2	+	16	0	-	1.2
13	April 94	10	M	3	+	16	0	-	0.5
14	April 94	8	M	7	+	16	10	+	2.1

\*The values shown were the highest obtained during the study  
Hb = haemoglobin WBC = white blood cell count

ALT = alanine aminotransferase

break involving nine patients who were members of three Bedouin families living outside Baghdad city [15]. In that study, the cause of the veno-occlusive disease was not investigated and the authors did not ascertain whether PAs were the causative agents. No other studies from Iraq have been cited in the recent past. A recent search in the registers of all Mosul hospitals showed that no similar illness had occurred in the past.

The 14 patients had veno-occlusive disease of the liver as confirmed by histopathological examination, and the underlying causative agents were isolated from the contaminated wheat and flour and found to be pyrrolizidine alkaloids. The association of PA-contaminated wheat grain as the causative agent of the outbreak is apparent from the fact that on chemical testing, the wheat and flour were found to contain PAs. On the other hand, the wheat and flour and

other items of food commonly consumed by the families were free of heavy metals, organophosphorous compounds and aflatoxins.

The effects of both qualitative and quantitative changes in diet on the hepatotoxicity of PAs have been investigated in several studies. A restriction of protein levels in the diet has been shown to enhance the acute hepatotoxic effects of alkaloids in rats [16], whereas a high protein diet has been reported to have a protective effect [17]. Such findings may explain the susceptibility of the patients in the present outbreak to the toxic action of PAs, as their malnourished state may have made them more vulnerable to the toxic effects.

Reliable estimates of the level of intake of PAs, especially in outbreaks of disease caused by the contamination of cereal crops with the seeds of toxic plants, are extremely difficult to make [2]. Furthermore, no accu-

Hb (g/dl)	WBC (10 <sup>9</sup> /l)	Bilirubin (mg/dl)	ALT <sup>a</sup> (IU/l)	AST <sup>a</sup> (IU/l)	ALP <sup>a</sup> (KAU/dl)	Plasma protein (g/dl)	Prothrombin <sup>b</sup> time (s)	Outcome A/D
10.0	9.7	3.9	14	31	7	7.2	+ 6	A
16.5	10.4	1.2	18	29	26	6.5	+ 5	A
15.6	11	1.5	16	31	17	7.3	+ 6	A
13.0	10.5	1.0	37	35	20	5.8	+ 4	A
12.0	11.2	1.7	6	18	14	6.3	+ 3	A
12.5	10.4	1.5	30	20	15	6.4	+ 6	A
13.5	11	1.3	37	27	14	3.5	+ 7	A
14.3	11.2	18.0	280	140	10	7.6	+ 40	D
12.5	7.5	7.3	9	21	15	7.3	+ 8	A
14.7	8.2	10.0	144	51	16	6.3	+ 10	D
8.8	9.8	2.0	22	19	13	5.7	+ 6	A
10.0	9.5	2.0	20	30	13	6.2	+ 3	A
11.2	10.3	7.5	34	35	14	6.3	+ 2	A
13.1	10.1	6.0	59	37	11	5.9	+ 7	A

<sup>a</sup>Prothrombin time is the difference between the patient and the laboratory control

AST = aspartate aminotransferase

ALP = alkaline phosphatase

A = alive

D = dead

ate record is possible of the amount of contaminated food consumed over an uncertain length of time. The levels of toxic PA-intake in the earlier reports of human toxicity have not been recorded.

Prevention of poisoning can only be achieved by minimizing or eliminating the ingestion of the alkaloids. Two effective methods are: control of PA-containing plants in agricultural areas and educational programmes. Some measures which have been implemented and found effective are [2]:

- certification and prohibition of the sowing of wheat, rye, barley or oats contaminated by the seeds of weed plants;
- agricultural measures to ensure minimum contamination of crops and harvested grain, including appropriate cultivation methods and timing, weeding of crops prior to maturing of the grain and mechanical cleaning of grain;

- monitoring of levels of contamination of flour, bread and similar products;
- publication of educational booklets for communities at risk describing the toxic weeds and the causes of toxicoses experienced;
- promotion of weed control by governmental authorities and provision of legislation to enforce the control measures.

## Conclusion

PA-containing plants produce their toxic effects through contamination of wheat during the harvest season. In this incident, the rainfall, humidity and warmth helped the PA-containing seeds to grow and mix with the badly stored wheat, which led to the contamination. Toxicity was potentiated by the associated poor nutritional status

of the patients, which resulted in the outbreak of veno-occlusive disease. Children were at a higher risk. The overall case fatality was 14% resulting from acute liver failure and bleeding oesophageal varices.

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