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Zieve's Syndrome

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In 1958, Leslie Zieve published data on 20 alcoholic patients seen at the Minneapolis Veterans Hospital during a period of eight years. The complex of jaundice, hyperlipaemia and haemolytic anaemia in these patients was 'so strikingly similar' that he concluded that this clinical picture was a 'definite syndrome'.

The author stated that the data had been assembled largely retrospectively from records made by physicians unaware of the correlated changes taking place.

Since 1958, relatively small series of patients with Zieve's syndrome have been described (Kuhn *et al.*, 1966; Warembourg *et al.*, 1968; Balcerzak *et al.*, 1968; Heck *et al.*, 1970; Thämmig, 1970; Alexander *et al.*, 1971; Lischner *et al.*, 1971; Galambos, 1972a, b; Bosseckert *et al.*, 1972; Sudre *et al.*, 1973; Galambos and Shapira, 1973; Galambos, 1974; Birschbach *et al.*, 1974; Goebel *et al.*, 1975). These studies do not contain fresh arguments to confirm or deny Zieve's concept of a definite syndrome.

In a period of 42 months (1973-77) we diagnosed Zieve's syndrome during 15 periods of observation on 11 patients in a 35 bedded general medical ward.

The present authors were aware of the existence of Zieve's syndrome during the study period. Nevertheless, in several of the reported 15 observations, diagnostic problems arose. Our data illustrate that in a period of still increasing alcohol abuse, the diagnosis of Zieve's syndrome should be a matter of concern to every physician, general practitioner, surgeon and, last but not least, general internist.

ILLUSTRATIVE CASES

Case 1: A 49-year-old housewife was admitted to the department of gynaecology with the presumptive diagnosis of acute abdomen caused by ovarian pathology. Because of jaundice, the internist was consulted. The woman was jaundiced, had a tender abdomen with guarding and absent peristalsis. The liver was enlarged 10 cm below the costal margin. Alcohol abuse was admitted (1 litre of Geneva gin a day). Revised diagnosis: acute liver steatosis due to alcohol abuse.

Case 2: A 50-year-old tramp was admitted to the department of surgery with the presumptive diagnosis of acute appendicitis. His abdomen was tender with guarding. Peristalsis was present. The liver was enlarged. Milky serum and mild

hypercholesterolaemia (8.2 mmol/litre) did suggest the existence of Zieve's syndrome. Liver function tests appeared at that time to be normal. Twelve hours later, peristalsis ceased. At laparotomy, a huge fatty liver was found. Postoperatively, alcohol abuse (12 litres of beer and unspecified amounts of hard liquor) was admitted.

Case 3: A 29-year-old salesman presented with severe abdominal discomfort. The blood taken showed milky serum. He was known for alcohol abuse. After admission to the hospital the patient showed jaundice, hepatomegaly, hyperlipaemia, and later developed signs of haemolytic anaemia.

Case 4: A 31-year-old unemployed former barkeeper with known diabetes mellitus (40 units of insulin daily) was admitted to the emergency service because of acute epigastric pain. Alcohol abuse (6 litres of beer daily) was admitted. On physical examination, the sclerae were subicteric, and hepatomegaly was found. The epigastrium was very tender. Peristalsis was normal. Signs of ketoacidosis were absent. Haemoglobin concentration was elevated to 14 mmol/litre. Total bilirubin was not measurable because of milky serum. Serum amylase was elevated to 256 units/litre, and in the urine to 2,048 U/litre. During the first two weeks of observation, Hb concentration fell to 7.9 mmol/litre and the reticulocyte count rose from 9 to 58 per thousand. X-ray of the duodenum showed enlargement of the duodenal sweep. The diagnosis of Zieve's syndrome, complicated by alcoholic pancreatitis, was made. Liver biopsy showed severe steatosis with signs of alcoholic hepatitis. The clinical course was uneventful, with the disappearance of all abnormalities.

RESULTS

Clinical Data

Table 1 summarises the data. The age range was 28 to 65 years. Of the 11 patients, 4 were women. In the patients' history, abdominal pain and discomfort appeared to be more prominent than anorexia and vomiting. Alcohol abuse was denied by one, and a number of the patients minimised the amount of alcohol taken. Of the 11 patients, 4 had been treated for peptic ulcers in the past; 3 were being treated for diabetes mellitus: all remained in good control during the course of Zieve's syndrome. Only one patient had clear-cut alcoholic delirium and another suffered from alcoholic neuropathy.

In 10 of the 15 admissions, low-grade fever ranging from 37.7 to 38.9°C was observed during the first five days. On admission, 4 patients were not clinically jaundiced. The total bilirubin levels (*see* below) ranged from 16 to 36 μmol/litre. The liver was palpable in all the patients. In most of them, hepatomegaly was prominent but the spleen was only slightly enlarged in one.

Table 1. Data of history and clinical signs on admission.

Patient	Sex	Age yrs	History	Alcoholic abuse	Low-grade fever* (° C)	Jaundice noticed at admission	Hepato-megaly	Spleno-megaly	Other diagnoses
1a	♂	28	Abdominal colicky pain.	± 12 litres beer daily	38.0	–	12 cm	–	diabetes mellitus Novolente insulin
1b (Case report No. 4)	♂	31	Fulminating pain in epigastrium and vomiting.	± 6 litres beer daily	38.2	±†	4 cm	–	id. alcoholic pancreatitis
2 (Case report No. 2)	♂	50	'Acute abdomen' due to acute appendicitis?	± 12 litres beer + unspecified amounts of hard liquor	38.2	–	15 cm on per-cussion	–	alcoholic neuropathy Billroth II gastrectomy at age 20
3	♀	33	Upper abdominal pain. In last years periodic fever and jaundice.	unspecified amounts of beer and wine	38.0	–	6 cm	±‡	–
4	♀	56	Jaundice	abuse denied; hetero-anam-nesis/heavy drinking	38.0	+++	20 cm	–	maturity onset diabetes mellitus hypoglycaemic drugs
5 (Case report No. 1)	♀	49	'Acute abdomen' jaundice	± 1 litre gin daily	38.9	+++	10 cm	–	duodenal ulcer at age 41 yrs. Strumiprival hypoparathyroidism.
6	♂	41	Abdominal discomfort	± 3 litres beer and whiskey	37.4	++	7 cm	–	duodenal ulcer in the past and at admission
7	♂	41	Anorexia jaundice	± 5 litres beer and hard liquor	38.1	++	2 cm	–	duodenal ulcer → vagotomy + pyloroplasty at age 35 yrs.

8a	♂	*63*	*Anorexia*	*± 150 ml gin daily*	*37.2*	*+++*	*6 cm*	–	hypertension and nephrolithiasis at age 52 yrs.
8b	♂	65	Jaundice	± 3 litres beer and wine + hard liquor	37.8	+++	8 cm	–	
9	♂	43	Anorexia	± 300 ml gin daily	37.1	–	6 cm	–	diabetes mellitus
10a	♀	30	Anorexia	non specified	37.5	+	4 cm	–	
10b	♀	31	Anorexia	amounts of all	37.7	±	4 cm	–	
10c	♀	32	Anorexia, diffuse abdominal pain and vomiting.	types of alcoholic beverages	38.1	±	5 cm	–	
11	♂	29	Severe abdominal discomfort; alcholic delirium at age 27.	unspecified amounts of beer	37.4	++	4 cm	–	

* highest temperature during first 5 days in hospital.
† yellow tinge of the sclerae
‡ tip of the spleen palpable.

Biochemical Indices of Liver Damage (Table 2)

During the observations the highest levels of serum total bilirubin ranged from 16 to 430 μmol/litre. The concurrent conjugated bilirubin levels ranged from 3 to 350 μmol/litre. From the individual pairs of data, it was calculated that the higher the total bilirubin levels rose, the higher were the percentages of bilirubin conjugated ($r = 0.86$, $n = 15$). The highest levels of SGOT were, in 13 of the 15 observations, higher than the coincident SGPT levels. In the eight observations during which serum gamma-glutamyl transpeptidase (GGTP) activities were measured, the levels were 5 to 35 times the highest levels observed in normal control subjects. In 10 patients, the serum alkaline phosphatase was pathologically elevated. Total lactic dehydrogenase activity of the serum was normal in 9 of the patients. It was raised in 2 patients with an impressive increase of fraction V of the iso-enzyme system. Both presented with acute abdominal discomfort and marked signs of pancreatitis.

Table 2. Biochemical indices of liver damage (maximum values measured). (Maximal abnormality observed with each measurement in each patient.)

Patient No. and sex	Direct bilirubin* μmol/L	Total bilirubin* μmol/L	Aminotransferases SGOT U/L	Aminotransferases SGPT U/L	Serum GGTP† U/L	Serum AP‡ U/L	Serum LDH§ U/L
1a ♂	3.0	21	48	116	–	91	–
1b ♂	8.2	28	115	110	130	91	870
2 ♂	17.0	31	82	118	–	110	90
3 ♀	7.0	16	275	250	181	165	59
4 ♀	350.0	430	600	164	700	530	152
5 ♀	51.0	86	615	189	–	267	953
6 ♂	18.0	40	125	63	–	210	99
7 ♂	31.0	55	125	85	–	500	66
8a ♂	150.0	230	144	53	–	275	–
8b ♂	178.0	225	154	60	–	213	66
9 ♂	23.0	36	237	117	990	133	72
10a ♀	38.0	62	260	80	600	156	73
10b ♀	18.0	38	241	91	360	245	–
10c ♀	12.0	29	173	65	471	215	76
11 ♂	16.0	31	375	148	730	193	109
Normal Values	<4.3	<17	<50	<50	♂ <28 ♀ <18	<95	<240

* Bilirubin data obtained from milky serum samples have not been taken into account because of spurious values due to opalescence.

† GGTP: gamma glutamyl transpeptidase activity

‡ AP: alkaline phosphatase activity

§ LDH: lactic dehydrogenase activity

Biochemical Indices of Hyperlipaemia

Table 3 shows the marked variability of disordered lipid metabolism in Zieve's syndrome. From additional data not shown in the table, one of the factors determining this variability is the 'fugitive' character of hyperlipaemia in patients using very variable amounts of alcohol and admitted to hospital for various reasons (Tables 1 and 2). During 15 observations, the disturbances in lipid metabolism disappeared in 3 to 30 days.

Table 3. Biochemical indices of hyperlipaemia. (Maximal abnormality observed with each measurement in each patient.)

Patient No.	Serum fasting total cholesterol mmol/L	Serum fasting triglycerides mmol/L	Serum opalescence	Serum fasting chylomicrons	Lipoproteins pre β−	Lipoproteins β−
1a ♂	28.4	137.4	+	++	+	−
1b ♂	25.0	130.0	++	?	?	?
2 ♂	8.2	3.85	++	++	+	+
3 ♀	6.2	3.03	−	−	+	−
4 ♀	13.1	3.27	−	−	+	−
5 ♀	11.8	327	+	−	+	+
6 ♂	7.8	3.4	−	−	+	−
7 ♂	14.0	4.14	+	++	+++	+
8a ♂	11.2	n.d.*	n.d.	n.d.	n.d.	n.d.
8b ♂	15.6	4.71	n.d.	n.d.	n.d.	n.d.
9 ♂	11.8	34.7	+	n.d.	n.d.	n.d.
10a ♀	7.6	4.05	−	−	+	−
10b ♀	6.1	2.7	−	−	++	−
10c ♀	6.3	4.0	−	−	++	−
11 ♂	20.1	10.7	+	+++	−	−
Normal Values	<6.5	< 2.4				

* not determined

Haematological Data

Table 4 illustrates that in 8 of the 9 observations on men and in 5 of the 6 observations on women with Zieve's syndrome, haemoglobin concentrations after admission were lower than found in normal subjects. Reticulocytosis was noted in all 15 observations. Serum iron levels were elevated in 4 of the 6 females and in 5 of the male patients, whereas in 2 male patients with subnormal serum iron levels, gastrectomy had been performed previously. Serum iron binding capacities were normal. Figure 1 illustrates a lowering of the mean haemoglobin levels in the first 12 days after admission and after stopping alcohol abuse. After a nadir at about the twelfth day of the observation period the mean haemoglobin level (7.6 mmol/litre) rose significantly ($P < 0.05$) to a mean of 8.7 mmol/litre after 37

Table 4. Haematological data. (Maximal abnormality observed with each measurement in each patient.)

Patient No. and sex	Haemoglobin content mmol/L	Reticulocyte count/1000	Serum iron µmol/L	Serum iron binding capacity µmol/L
1a ♂	8.7	37	n.d.*	n.d.
1b ♂	7.9	58	11.2	44.0
2 ♂	8.0	51	8.2†	61.2
3 ♀	8.1	135	19.9	59.0
4 ♀	8.7	140	25.0	48.7
5 ♀	6.3	210	30.4	53.7
6 ♂	8.2	122	31.3	49.4
7 ♂	7.3	132	11.1†	41.3
8a ♂	7.4	55	n.d.	n.d.
8b ♂	8.0	200	26.8	45.1
9 ♂	6.8	54	31.3	52.1
10a ♀	6.8	81	37.6	52.6
10b ♀	6.6	83	15.2	47.2
10c ♀	5.8	126	27.0	49.2
11 ♂	7.7	76	42.6	47.1
Normal Values	♀ 7.5-10.0	7-15	14.3-21.5	45.0-63.0
	♂ 8.7-11.2	7-15	16.1-25.1	54.0-71.0

* not determined.
† gastrectomy in the past

days in hospital. The mean reticulocyte count in this group of patients was clearly elevated on admission and decreased thereafter to normal values after about four weeks. The figure suggests a reciprocal relation between the mean haemoglobin levels and the mean reticulocyte counts. In fact, the mean values of the reticulocyte counts and the corresponding mean haemoglobin levels from the sixth day in hospital till the end of the observations are correlated negatively and significantly ($r = -0.98$, $n = 8$).

Histological Data (Table 5)

The prominent feature of the liver morphology was massive steatosis in all 13 samples obtained from the 11 patients. Unequivocal histological signs of liver cirrhosis were present in only two of these 13 biopsies. Minimal signs of cirrhosis were found in one additional biopsy. In all except two of these biopsies, mild to severe signs of hepatitis were found. The distribution of granulocytic and/or mononuclear infiltrates was not peculiar in any of the biopsies. Varying degrees of septal and/or pericentral fibrosis in 10 biopsies might indicate previous liver damage. Signs of cholestasis were prominent in 4 biopsies and minimal in one.

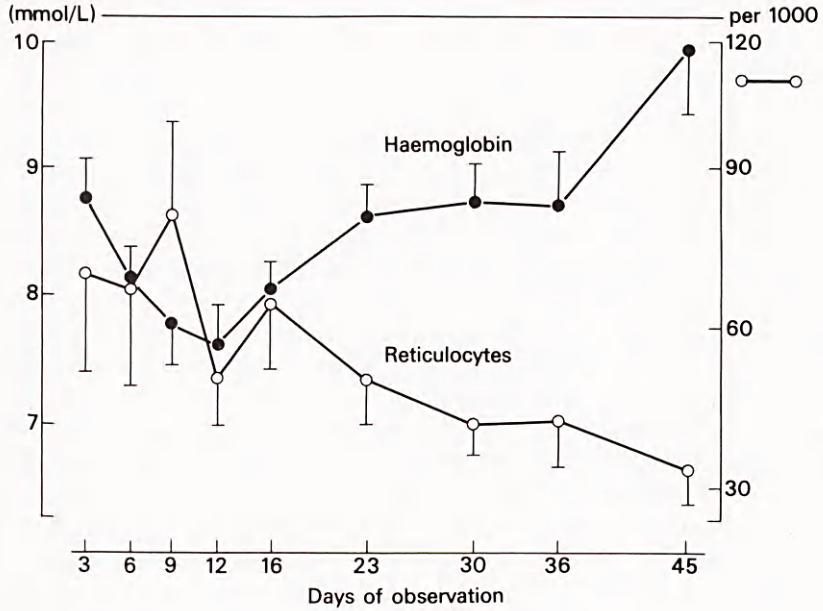

Fig. 1.

Table 5. Signs of alcoholic liver damage in biopsies.

Patient No.	Steatosis	Focal necrosis		Fibrosis		Cholestasis	Cirrhosis
		Granulocytic infiltrates	Lymphocytic infiltrates	Septal	Pericentral		
1a	+++	+	–	–	–	–	–
1b	+++	+	–	+	–	–	–
2	+++	–	–	–	–	–	–
3	++	+++	++	–	–	–	–
4	++	+	+	++	+	++	++
5	+++	+	–	+	+	–	–
6	++	++	+	++	+	++	±
7	+	++	+	+	+	+	–
8b	++	++	+	+++	–	++	+
9	+	–	+	++	–	±	–
10a	++	+	+	++	+	–	–
10c	++	+	+	++	+	–	–
11	+++	–	–	+	–	–	–

DISCUSSION

One of the main characteristics of Zieve's syndrome is the marked variability of the clinical picture and of the biochemical and histological findings.

Alcohol abuse can induce a broad spectrum of disorders, too broad for any single specialty. It is the 'general practitioner' in internal medicine who is confronted in daily practice with the capricious nature of the syndrome earlier described as an entity by Leslie Zieve. We do not intend to discuss the rather academic question of whether or not Zieve's syndrome has to be considered as an entity. As with many multi-system disorders caused by drugs, the clinical picture can be very variable indeed.

Attention is drawn to the well-known increase in frequency of alcohol-induced disorders. In the period in which the 11 patients of this study were observed, about 1,100 patients were admitted to the ward. So Zieve's syndrome had a frequency of about 1.0 per cent in our department of general medicine. In comparison, Heck *et al.* (1970) found a frequency of 1 in 1,600 hospital admissions. It is interesting that three of the patients had been treated for peptic ulcer in the past and one patient had an active ulcer during hospitalisation for alcohol abuse. Low-grade fever observed in our patients was described in Zieve's original paper.

Two of the patients had serious symptoms of acute abdomen and one of them underwent laparotomy. One of Zieve's patients also had a laparotomy. Thus, Zieve's syndrome has to be considered in the differential diagnosis of acute abdomen.

From the data in Tables 1 and 2, it appears that jaundice is clinically discernible when total bilirubin levels amount to more than twice normal values. The data illustrate that the degree of liver damage in terms of disturbed bilirubin metabolism is quite variable. Obviously, patients with alcohol abuse are hospitalised in different stages of Zieve's syndrome. In Zieve's original paper, a similar picture of variable hyperbilirubinaemia was illustrated. In our cases there was a relationship between the degree of histologically discernible cholestasis and the degree of hyperbilirubinaemia.

From the data on direct and total bilirubin collected in Table 2, it can be deduced that, in Zieve's syndrome, bilirubin glucuronyl transferase activity is not impaired. Indeed, the higher total bilirubin rose, the higher was the percentage of bilirubin conjugated. Thus, the disturbance in bilirubin metabolism seems to be caused by obstruction of bile outflow rather than by the co-existing haemolysis. This observation accords with published data. Another argument against haemolysis in Zieve's syndrome being a dominant factor in the development of hyperbilirubinaemia is the observation that signs of haemolysis often reach their maximum when bilirubin levels are already declining. In fact, haemoglobin concentration often declines and reticulocyte counts reach their maximum values after several days in hospital when alcohol abuse has been stopped.

A number of liver cellular enzymes are used to diagnose liver diseases. In Zieve's syndrome, the most prominent abnormality was the huge rise in the activity of the GGTP. This enzyme's activity remained elevated for a much longer period than other enzyme abnormalities in Zieve's syndrome. In one case (No. 15) the GGTP activity was very high, but total bilirubin was only mildly elevated. No correlation was found between the height of this enzyme's activity and any of the histological abnormalities in the liver biopsies specified in Table 5. In most of the cases studied, the pattern of activity of the aminotransferases shows preponderance of SGOT over SGPT in accordance with published data. The highest alkaline phosphatase activities observed were quite variable.

Lactic dehydrogenase activity was within the normal range except in two cases in which this enzyme's activity reached extremely high values. One of these patients had pancreatitis; in the other, this diagnosis could not be excluded.

Thus, the combination of relatively mild or moderate increases in the activities of the aminotransferases with preponderance of SGOT over SGPT, with extremely elevated activity of the GGTP, and highly variable increases in direct and total bilirubin and serum alkaline phosphatase, could be a poor laboratory guide to the diagnosis of alcohol-induced liver disease.

The data in Table 3 on the abnormalities in lipid metabolism illustrate that by measuring fasting serum total cholesterol, serum triglycerides, serum opalescence, and indices of serum lipoproteins, abnormal values have been found in all 15 observations. The pattern of lipid abnormalities was extremely variable. It was observed that the abnormalities were evanescent after stopping alcohol abuse, as shown by other authors. It is important to realise that these disturbances in lipid metabolism during alcohol abuse can give rise to unreliable laboratory data obtained by colorimetric techniques.

It appears that reticulocytosis is the most sensitive indicator of the haemolysis generally accepted to occur in Zieve's syndrome; in most cases, the haemolytic disorder is of the compensated type. The data of this study strongly suggest that haemolysis in these patients occurred in the first two weeks in the hospital after stopping alcohol abuse. This observation has not been reported by others, although in Zieve's original series the haemoglobin decreased in 11 of 20 patients after admission. The serum iron changes also suggest a haemolytic disorder.

Meaningful correlation of the histological findings with the clinical and laboratory data is hampered by the fact that the biopsies were taken at various intervals (2 to 28 days) after admission. Histological evidence of cholestasis was found only in patients whose total bilirubin was higher than 36 μmol/litre. No correlation was found between the degree of hyperlipaemia and that of hepatic steatosis. Nor were any of the laboratory indices of haemolysis discernibly related to any of the histological characteristics.

In this series of patients with histologically proven marked steatosis, 10 of 11 showed signs of alcoholic hepatitis, and only 3 had signs of minimal (1) or

moderate (2) cirrhosis. Correlating the occurrence and disappearance of the clinical and chemical signs of Zieve's syndrome with the histological data suggests that this peculiar reaction to alcohol abuse can happen in patients with or without pre-existent alcoholic liver damage. This might indicate that an acute bout of alcoholism is the cause of Zieve's syndrome in a predisposed segment of the population of alcoholics. In fact, such bouts of alcoholism have been admitted (in retrospect) by a number of these patients.

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