

Zieve's Syndrome: a Case Report

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Abstract

A case of Zieve's syndrome. We describe a patient with hemolytic anemia, cholestatic jaundice, hypercholesterolaemia, fatty liver and alcoholism. Zieve has described this syndrome in 1958.

Key words: Zieve's syndrome, cholestasis, haemolysis, hypercholesterolaemia, fatty liver, alcoholism.

Introduction

The association, in an alcoholic patient, of hyperlipidaemia, hemolytic anemia, jaundice and hepatic steatosis, was described by Zieve in 1958 as a distinct physiopathological entity, becoming known by the name of Zieve's Syndrome^{1,2,3}.

Clinically, it can be seen the insidious onset of nausea, vomiting, diarrhea, anorexia, weight loss and abdominal pain of variable intensity³. All these signs and symptoms are followed by a febrile or sub-febrile temperature³. In the objective exam it is detected, usually stigma of chronic alcoholism, as telangiectasias, star angiomas, jaundice, hepatomegaly, extremity shaking, and more rarely ascites, peripheral edemas and pleural effusion³.

In laboratory, it can be found as main features – hemolytic anemia, hyperlipidaemia, cholestatic jaundice and hepatic steatosis^{1,3,4}.

All clinical and laboratorial changes will be back to normal, more or less shortly, with alcoholic abstinence^{3,5,6}.

Clinical case

M.J.J.P, male, 26 years old, born in Castelo Branco and residing in Alcains-Castelo Branco, married and a locksmith as occupation.

The patient was admitted in the Medicine II Service of Coimbra University (HUC) on the 23rd August 1991, transferred from Castelo Branco Hospital (HCB) where he was hospitalized in the Gastroenterology Service, due to cholestatic jaundice and dyslipidaemia.

Around 2 months ago, he noticed a yellowish color in the skin, "loaded" urine and uncolored feces. Simultaneously the patient mentioned asthenia and easy tiredness, reduction on the strength of the lower limbs and anorexia, although without apparent weight loss. He also mentioned oliguria for 2 to 3 days, followed by facial edema, not long before being admitted in HCB. As during the referred hospitalization it was detected a 3 fingers hepatomegaly below the coastal edge, on the medium-clavicular line, with a round edge, an jaundice color on the skin and mucosa, and no other changes were visible.

The patient confirmed marked alcoholic habits for the last 6 months, around 20g/day, denying the intake of any other kind of drink. Smoker, 360 packs/year.

Regarding the personal history the most important to mention, was a drug addiction between 16 and 22 years of age, using marijuana, benzodiazepines, denying the use of injectable drugs.

With a family history worth of note only a grandfather with dyslipidaemia.

On table 2 and 3 we can see the main laboratorial changes detected in HCB from which we highlight hyperbilirubinemia due essentially to the conjugated fraction, the high value of alkaline phosphatase and γ -GT, marked hypercholesterolaemia and anemia. It has also been performed in this hospital an abdominal echotomography, with a liver image suggestive of steatosis, as well as a myelography, showing only a red serial hyperplasia.

In the objective exam, performed already in our

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TABLE I

Anemia and Alcoholism^{5,6}

Ethanol direct toxicity
Folic acid deficiency
Sideroblastic anemia
Hemolytic anemia
Iron deficiency anemia

service, no changes in the skin color or mucosa were verified, no edema was seen and pulmonary and cardiac auscultation were normal. Blood pressure of 180/90 mmHg. Abdomen was normal to inspection, palpation was depressible, painless and without organomegaly. Apyretic.

Before the association of marked alcoholic habits, dyslipidaemia, probable hepatic steatosis (suggested by ultrasound and confirmed later by biopsy), cholestatic jaundice and hemolytic anemia, was advanced the diagnosed hypothesis of Zieve's Syndrome.

From the supplementary exams performed in our service it is worth of notice the hemogram with Hb = 11 g/dL, 3,250 T/L G.V, MCV of 95.7 fl, 6.6 G/L white blood cells with 49% lymphocytes, 42% neutrophils, 4% eosinophils, 5% monocytes and 160 g/L reticulocytes; 306 G/L platelets and an erythrocyte sedimentation rate of 78 mm in the first hour; biochemistry where it was detected calcium in the upper limit of normality (10.8 mg/dL), total protein and albumin of 7.2 and 3.9 g/dL respectively, phosphorous of 2.9 mg/dL, high total cholesterol (357 mg/dL), triglycerides of 120 mg/dL, lipid gram with an increase on beta-fraction (67.7%), uric acid of 8.0 mg/dL, total and direct bilirubin of 0.9 and 0.4 mg/dL, respectively TGO of 19 U/L, TGP of 13 U/L, alkaline phosphatase of 52 U/L, LDH of 203 U/L, amylemia of 128 U/L and prothrombinemia of 80%. Serum tests for Hepatitis A, B and C, as well as toxoplasmosis, syphilis, typhoid fever and brucellosis were negative or normal. The summary of urine was normal, as well as calcium and urinary phosphorous. The study of lymphocyte populations was normal. The serum immunoelectrophoresis was normal. The Anti-nuclear antibodies (DNA, SSA, SSB, Sm, RNP) were negative. The swab of peripheral blood has shown a spherocytosis and in the myelography were found normocellular fragments,

with a megakaryocytic series well represented and erythroid hyperplasia. A liver biopsy was also carried out, being detected a diffuse macrovacuolar steatosis, discreet portal inflammatory infiltrate, Mallory bodies and sinusoidal distension.

The finding of spherocytosis led us to exclude other possible pathologies (Table 4). Thus, the haptoglobin dosed outside the haemolysis period, was within the normal upper limit (174 mg/dL < N-18-173- mg/dL); the direct and indirect Coombs test were negative; the complement study showed a C3 of 0,96 g/L (0.7-1.7) and a C4 of 0.35 g/L (0.15-0.45); the research of cold agglutinin and alo-antibodies was negative; the globular resistance, auto-haemolysis and spectrin dosage, were within normal parameters; serial copper was 1.2 mg/L (0.7 – 1.4 mg/L); ceruloplasmin was of 44.9 mg/dL (21-53 mg/dL). Hemogram were also carried out to direct relatives (parents and uncles) and no case of spherocytosis was detected.

To clarify the high calcium, which was normalized in the meantime, thyroid tests were asked and were normal, as well as the thyroid scintigraphy, the Serum Angiotensin Conversion Enzyme (SACE) dosage which was found high: 100 U/L (N=8-52 U/L), the dosage of parathormone, what was normal, the skeleton X ray which showed no change, and the neck and upper mediastinum CAT Scan which did not detect any anomalous formation, namely at parathyroid level.

The patient improved without any therapy, referring the disappearance of asthenia and tiredness, as well as an appetite recovery.

He was discharged on the 17th September 1991, and has been followed ever since as an outpatient. The last clinical and laboratorial control was made on the 23rd October 1991, the patient did not express any complaint, having a complete normalization of the hemogram, lipidic, calcium and hepatic tests. The patient was kept in alcoholic abstinence.

Comments

Table 1 shows the main causes of secondary anemia to an excessive consumption of ethanol.

1 - Any of the changes described in our clinical case can, isolated, to follow an excessive consumption of ethanol; therefore, is frequent to find an alcoholic and hepatic steatosis, a dyslipidaemia (almost always a hypertriglyceridaemia), an anemia and/or jaundice. The simultaneity verified, in the current

TABLE II

Date	26/07/91	29/07/91	01/08/91	07/08/91	09/08/91
Creatinine	2.1	1.09	1	1.2	1
Uremia	8	13	10	16	14
Glucose	124	113	127	87	101
K	3.9	4	4.2	5.1	
Na	131	139	136	136	
Uricaemia				5,2	
Triglycerides			160	162	160
Total cholesterol			607	454	695
Direct bilirubin	8.4		1.6	0.5	0.5
Total bilirubin	9.3		3.7	1.7	1.8
SGOT	161	110	66	25	27
SGPT	106	84	73	24	24
LDH		436	358	243	256
Alkaline phosphatase	237	163	93	72	72
G.transpeptidase	1910	2112	963	318	317
Total protein		6.4	6.5		
Albumin		2.9	2.9		
Globulin					
Alpha 1		0.32	0.26		
Alpha 2		0.64	0.85		
Beta		1.15	1.23		
Gamma		1.34	1.23		
Amylasemia		59	51		
Serum iron		136	101		
Iron fix cap		240	218		

case, of marked alcoholic habits, hemolytic anemia, cholestatic jaundice, hypercholesterolaemia and hepatic steatosis is, by some authors, classified as Zieve's syndrome.^{6,7,8}

Regarding the anemia found in Zieve's Syndrome it is admitted its hemolytic nature, of extracorporeal cause although a precise mechanism is still a motive for controversy.⁹ For Zieve, the hyperlipidaemia would be a main cause. According to this author, as a lysolecithin has strongly hemolytic properties; the presence of this fatness in the blood, even in a small

quantity would lead to hemolysis³. Another mechanism responsible by a globular destruction would be the unbalance between substance favoring haemolysis (lysolecithin, lysocephalin, free fatty acids) and another one with anti-hemolytic properties (lecithin, albumin and globulin).^{3,5,10}

For Maxwell et al, it would verify an increase on the plasmatic lipids and cell (red blood cells), in the haemolysis crisis. For this author it would be the increased cellular lipids (cholesterol, lecithin), the main responsible for the globular destruction, returning to normal, as well as the red blood cells survival, with alcohol withdrawal.⁴

For other authors, hyperlipidaemia would play a secondary role in haemolysis; the acute development of fatty liver, with the simultaneous increase on portal hypertension and splenomegaly, would be the main haemolysis leading factor of Zieve's Syndrome.^{5,6}

Dyslipidaemia, particularly due to triglycerides, is a common finding in alcohol consumers, even moderate and its mechanism will have to do with the fact of ethanol hepatic metabolism to provide a 'savings', on free fatty acids that will be afterwards transformed in triglycerides.^{11,12} In the Zieve's Syndrome we find whether an isolated hypercholesterolaemia or hypertriglyceridaemia or a mixed hyperlipidaemia. Its pathogenesis was related with hepatic steatosis and an

increase mobilization of fatty substances, effect of alcohol on the hepatic metabolism and the pancreatic lesion with lipases deficits.^{1,3,11}

A hepatic steatosis, particularly if associated to the presence of Mallory bodies, is a common finding in people having alcohol consumption, although in moderate quantities, without having sometimes any clinical or laboratorial manifestation denouncing this histological change.⁸ The liver steatosis is usually a benign disease, solving itself within 4 to 6 weeks after an alcoholic abstinence, particularly if it is a 1st

TABLE III

Date	26/07/91	29/07/91	01/08/91	07/08/91	12/08/91
Erythrocytes	3.52	3.03	2.74	2.64	2.76
Hgb gr/cm ³	11.6	9.8	8.9	8.6	8.9
Hematocrit	33.3	28.7	25.8	25.6	26.7
MCV	94.6	94.8	94.3	96.9	96.7
MCH	33.0	32.3	32.5	32.6	32.2
CHGM	34.8	34.1	34.4	33.6	33.3
Leucocytes	8.9	7.4	6.6	8.6	7.6
N	50%	74%	60%	50	50%
E		2%	2%		
B					
L	47%	20%	35%		42%
M	3%	4%	3%		3%
Platelets	170.000	197.000	324.000	522.000	392.000
ESR		67mm		131 mm	
Prothrombin				100%	

TABLE IV

Spherocytosis differential diagnosis^{5,11}

Hereditary spherocytosis
Immuno-hemolytic haemolysis
Microangiopathy
Infections (<i>Clostridium welchii</i>)
Enzymopathy
Wilson Disease

degree steatosis.⁸

A cholestatic jaundice, sometimes serious, can occasionally follow a hepatic steatosis.⁸

Regarding the therapy, it is not necessary any special step apart of the obvious absolute abstinence of ethanol consumption.^{2,3,5} It is anticipated a symptomatic medication whenever necessary (withdrawal syndrome) folic acid and thiamin in case of lack of these vitamins. The recovery (clinical, laboratorial and histological) is frequently total, being possible the recurrence if the alcohol consumption is resumed.^{2,3,5}

Being common among chronic alcoholic the occurrence of neurologic changes, some serious, it is not odd the association of Zieve's syndrome with cerebrovascular accidents. It is described the clinical case whereas an alcoholic patient, hyperlipidaemic and with an asteatotic liver, suffered an intracerebral hemorrhage, having been detected a high lipidic concentration in the CSF, a rare fact in the references we searched.¹³

2 - The presence of spherocytes in the peripheral blood, although common in a haemolysis by hypersplenism, one of the underlying mechanisms to anemia in the Zieve's Syndrome, led us to a differential diagnosis.

An immuno-hemolytic anemia was excluded, with some certainty, due to the test negativity by direct and indirect Coombs, normal complement and absence of hot cryoglobulins and immunoglobulins.¹⁴

The normality of auto-haemolysis tests, osmotic resistance, spectrin dosage and the relatives study enabling us to exclude a hereditary spherocytosis.⁷

Normal copper and serial ceruplasmin as well as the hepatic biopsy are against the hypothesis of the Wilson disease as cause of spherocytosis and it is not possible its absolute exclusion due to the impossibility of dosing the liver copper.⁷

3 - A laboratorial finding, for which we have no explanation, it was the value of the high serum calcium (more concretely, the normal upper limit). The concomitance of a high SACE did not provide any diagnostic help; as a matter of fact, it is about a not very specific marker and in the absence of any other clinical and histological change compatible with sarcoidosis, this diagnosis was excluded by us; on the other hand it is described the association of high levels of the mentioned enzyme with hepatic pathology, namely a viral hepatitis, a chronic hepatitis and alcoholic hepatic disease, and we think the latter is the most likely reason to increase the SACE in the current case.¹⁵ Other hypercalcemia possible causes were researched through the PTH dosage, performing the myelography, immunoelectrophoresis of serial

proteins, X Ray and skeleton scintigraphy. There was a normalization of the calcium value, without any other therapy, at the end of 15 days of admission.

4 – The normalization of all clinical and laboratorial endpoints after the alcohol abstinence, and without any other therapy reinforces the possible relation with the ethanolic toxicity with the presented clinical condition, being for some authors another crucial feature of Zieve's Syndrome.^{2,3} ■

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