Whipple's triad as a clinical manifestation of hepatolenticular degeneration

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Abstract: Hepatolenticular degeneration (Wilson's disease) is a rare condition characterised by a defect in biliary excretion of copper resulting in excessive copper accumulation and toxicity. To the most frequent symptoms of this disorder belong liver, neurological or psychiatric disturbances, although other less common clinical features may sometimes be present. Since the clinical presentation of the disease is highly heterogeneous, it may mimic the symptoms of many various disorders. Diagnosis of the condition depends primarily on clinical features, biochemical parameters and the presence of the Kayser-Fleischer ring. Early detection and treatment protect patients from devastating organ damage. We describe an atypical case of Wilson's disease in a 23-year-old woman, whose clinical presentation suggested the presence of an insulin-secreting tumour. After the diagnosis was established and zinc sulphate treatment implemented, her clinical status improved remarkably. The presented case suggests that hepatolenticular degeneration should be taken into consideration in a differential diagnosis of hypoglycaemia of an unknown origin.

Key words: clinical presentation, diagnosis, hypoglycaemia, insulinoma, Wilson's disease

INTRODUCTION

Hepatolenticular degradation (Wilson's disease) is an autosomal recessive inherited disorder characterized by copper biliary excretion defect resulting in excessive copper accumulation in the liver, brain, kidney and cornea [1]. Development of severe, potentially life-threatening injury of the liver and central nervous system – if not treated with penicylamin, trientin or zinc – inevitably leads to total outcome [2].

Hepatolenticular degradation is characterized by a heterogeneous clinical feature partially depending on age at the diagnosis time [2,3].

As demonstrated on a large group of patients, in 42% of cases the first Wilson's disease clinical sign was liver injury, in 34%- neurological symptoms mainly resulting from injury of the extra pyramidal system, in 12%- hematological dysfunction, in 10%- mental disorders, in 1%- kidney dysfunction [3]. Thus hepatolenticular degradation should be taken into account in the differential diagnosis of several diseases. As a first case described we present here a atypical clinical feature of Wilson's disease imitating *insulinoma* symptoms.

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CASE REPORT

A 23-year-old woman admitted to hospital due to recurrent hypoglycemia (glucose blood level 37–55 mg/dl measured with glucometer on the ambulatory basis). The patient reported symptoms of paroxysmal hyperhidrosis, pallor, hand tremor and palpitations that occurred approximately 30 months earlier. The symptoms appeared mostly in the morning, late in the afternoon, on exertion and while fasting. Though irregular and of various duration, episodes of hypoglycemia became more frequent and severe in the last three months. During that period of time sight disorders, hypersomnia, seizures, and transient motoric disorder were observed. Prodromal symptoms preceding syncope, which occurred for the first time in 2003, became more frequent. Fainting episodes were mild due to patients awareness (sugar intake in a prodromal period) although one of them resulted in non-severe head injury. Family history was negative except type 2 diabetes in his grandfather on the father's side. The patient was hospitalized twice in the internal hard and once in the neurological ward. The last hospital stay preceded the present odmission by 2 weeks. The patient presented hypoalbuminemia, coagulation abnormalities, indicator liver enzymes elevation and normal ultrasound scan of the liver and therefore had been discharged from hospital with the liver injury diagnosis after symptomatic therapy. According to clinical feature *insulinoma* a specific diagnostic procedure was performed. Diagnostic fasting test, performed as "gold standard" in *insulinoma* [4,5] had to be interrupted after 36 hours because of a sudden presyncope with neuroglyco-

penia and autonomic nervous system hypersensitivity. A test result negated the *insulinoma* diagnosis because serum glucose, insulin and peptide C levels decreased concurrently during 6 hours' interval blood tests. Hypoglycemia (42 mg/dl) with no measurable insulin and peptide C levels after the test completion were observed (at the beginning of the test: 15.2 mIU/l and 1.2 ng/ml respectively). Therefore, normal pancreatic insulin secretion (absent in *insulinoma*) was proven. Furthermore, low normal glucose serum level increase in glucagon test was observed with maximum of 35 mg/dl after 30 minutes. NMR spectroscopy of the liver and pancreas was negative.

Other plausible reasons of hypoglycemia [6,7], presented below, were excluded:

1) insulin and sulphonylurea derivatives drug-induced hypoglycemia
2) chronic renal failure
3) nesidioblastosis
4) other pancreas dysfunction
5) hormone deficiency:
   a) hypothyroidism (TSH–1.67 mIU/l, fT_4–15.2 pmol/l, fT_3–5.2 pmol/l)
   b) hypercorticoidism (fasting cortisol serum level – 17 μg/dl; normal cortyzol diurnal rhythm; free cortisol urine level – 103ug/24h; ACTH 10.2 pmol/l)
6) glucagon deficiency (serum level – 41 pmol/l)
7) hypopituitarism (TSH, thyroid hormones, ACTH, FSH, LH, insulin-like growth factor 1, cortisol in the fasting test and diurnal rhythm, as well as urinary excretion of cortisol in normal ranges)
8) glycogenosis (no signs of hyperlipidemia in lipid profile, normal serum level of free fats acid, 442 μmol/l)
9) hyperketosis (fasting serum beta- hydroxybutanoic acid 0.15 mmol/l)
10) metabolic acidosis
11) lactic acid elevation (serum lactic acid level 1.5 mmol/l)
12) hyperuricemia (serum uric acid level 5.2 mg/dl)
13) inherited disorders of galactose and fructose metabolism (medical history negative, absence of clinical symptoms, urine galactose and fructose test negative)
14) malnutrition
15) increased urine glucose loss
16) increased catabolism
17) autoimmunological hypoglycemia (normal insulin serum level, absence of insulin and insulin receptor antibodies)
18) ethanol intoxication
19) heterogeneous reactive hypoglycemia (neurovegetative dysfunction, gastrectomy).

Several clinical signs that confirm the diagnosis of Wilson's disease were observed: low serum ceruloplasmine level (14 mg/dl, N: 20–60), low serum copper level (78 μg/dl, N: 80–130), increase of twenty-four-hour copper elimination (101 μg/24hrs, N: <80), corneal Kaiser-Fleischer ring and hyperintensity of the basal ganglia in NMR spectroscopy. According to diagnostic criteria of the 8th International Conference on Wilson Disease and Menkes Disease [8] the patient obtained 4 points (2 for the Kaiser-Fleischer ring; 1 for ceruloplasmine serum level between 10 and 20 mg/dl; 1 for mild neurological symptoms) and therefore met the diagnostic criteria for Wilson's disease [8]. Notwithstanding ultrasound of the liver remained normal as well as NMR liver spectroscopy with mild hypertension of portal system in Doppler ultrasonography (no esophageal varices in endoscopy). The biopsy of the liver was not done due to clinical and laboratory signs of bleeding. The patient received penicylamin ands symptomatic treatment (albumins, plasma concentrate, and vitamin K). Penicylamin had to be replaced with zinc sulphate (75 mg/d in three doses) after two weeks of treatment because of thrombocytopenia. A significant improvement of patients general condition was observed with hipoproteinemia and normalization of hemorrhagic abnormalities. Currently hypoglycemia has been absent despite two episodes at the beginning of treatment. The patient now remains in good condition, with no symptoms or signs present, and he leads an active life.

DISCUSSION

The case presented here is the first from published data with clinical picture of Wilson's disease resembling *insulinoma*. Whipple's triad, typically occurring in *insulinoma* was described: 1) clinical signs triggered off by fasting or exertion; 2) hypoglycemia (<45 mg/dl) with clinical manifestation, and 3) yielding of clinical signs after food intake. As observed in *insulinoma,* the patient presented symptoms of neuroglycopenia as well as increased catecholamine level. The only difference was no weight gain usually observed in *insulinoma* and young age of patient (*insulinoma* usually is diagnosed between 40 and 60 years of age).

While it is true that Wilson's disease leads to hypoglycemia, it is usually observed in the late stage of disease when liver failure develops [2] and therefore hypoglycemia was associated with typical manifestation of hepatolenticular degeneration [2]. Normal ultrasound scan and NMR spectroscopy, and mild hypertension of portal system, confirmed that hypoglycemia can develop on an early stage of the disease and can appear as the first clinical manifestation. Other causes of hypoglycemia were excluded [6,7]. It has been, therefore, confirmed that the patient does not suffer from other hypoglycemia-associated disorder. Overlapping concurrent diseases were also excluded.

Efficacy of zinc sulphate treatment suggested two further conclusions. Hypoglycemia recovery together with clinical improvement (diathesis, hypoalbuminemia and liver dysfunction recovery) confirms a straightforward dependence of hypoglycemia with hepatolenticular degeneration. Secondly, hypoglycemia in Wilson's disease is reversible, if early and effective treatment has been initiated.

The case report presented proves that hepato-lenticular degeneration must be taken into consideration if hypoglycemia of unknown origin occurs. It should be also a component

of differential diagnosis when clinical symptoms suggest *insulinoma* while biochemical markers (especially the fasting test) are negative. Normal or slightly abnormal liver scan does not exclude the diagnosis of Wilson's disease and therefore, should be verified by biochemical blood tests.

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