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Hepatogenous diabetes in primary care practice – a case study

Diabetes hepatogenicus w podstawowej opiece zdrowotnej – opis przypadku

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Summary

This case study describes a patient who admitted to a family physician and was denied basic laboratory tests although being hospitalized due to symptoms of liver insufficiency 4 years before. The laboratory test results which the patient did on her own revealed glucose level of 418 mg/dl in the blood and 7277 mg/dl in the urine. The case illustrates the importance of investigating the patient's whole medical history. It is an example of therapeutic difficulties following primary care practitioner's clinical inertion. It also highlights the prominent need for creating standards and guidelines on follow-up treatment of patients with diagnosed cirrhosis. *Geriatria 2010; 4: 130-134.*

Keywords: hepatogenous diabetes, hepatic coma, hepatic insufficiency

Streszczenie

Pacjentka 54-letnia zgłosiła się do lekarza celem wykonania podstawowych badań laboratoryjnych. Lekarz poz odmówił zlecenia badań, mimo iż pacjentka przed czterema laty była hospitalizowana z powodu objawów niewydolności wątroby, dokumentacja medyczna z okresu hospitalizacji była niekompletna a od tego czasu pacjentka nie zasięgała porady lekarskiej ani nie miała wykonywanych żadnych badań kontrolnych. Badania wykonane „na własną rękę" przez pacjentkę wykazały obecność glukozy w moczu na poziomie 7277 mg/dl oraz 418 mg/dl we krwi. Przedstawiony przypadek przemawia za koniecznością czynnego poszukiwania bezobjawowej cukrzycy w grupach podwyższonego ryzyka rozwoju choroby, wskazując jednocześnie trudności terapeutyczne i diagnostyczne wynikające z zaniedbania takich działań. Podkreśla również rolę lekarza rodzinnego w kompleksowej opiece nad pacjentem obciążonym wieloma chorobami przewlekłymi i pozostającym pod opieką wielu specjalistów. Artykuł dowodzi tez konieczności stworzenia ujednoliconych diagnostycznych i terapeutycznych schematów postępowania z pacjentem z przewlekłą niewydolnością wątroby. *Geriatria 2010; 4: 130-134.*

Słowa kluczowe: diabetes hepatogenicus, niewydolność wątroby, śpiączka wątrobowa

Case report

A 54 year-old woman presented to her family physician laboratory tests results that the patient had performed on her own (blood tests: CBC with differential, erythrocyte sedimentation rate, glucose level, alanine transferase, AST, creatinine level, thyroid-stimulating hormone, urine testing and urinary sediment analysis).

Biochemical abnormalities were glycemia 418, 94 mg/dl. The urine testing revealed the presence of glucose levels exceeding 1000 mg/dl. The test was repeated from the same urine sample with the glucose level reaching 7277,22 mg/dl.

Further investigation of the patient's medical history revealed that the patient had been abusing alcohol and had been hospitalised four years earlier due to

a hepatic coma. Since then, her previous physician had not referred the patient for any laboratory tests. The hospital documentation also was determined to be incomplete. A few days before admission to the hospital, the patient had been showing signs of physical deterioration, and inability to stay awake.

Basic laboratory tests on admission showed: isochromic anemia, metabolic alkalosis with respiratory acidosis, total bilirubin of 3,71 mg/dl, AST 76 U/l, alanine transferase 9U/l, GGTP 306 U/l, cholesterol 124 mg/dl, alcohol 2 mg/dl.

On the second day of hospitalisation, the patient lost consciousness with maintained pain reaction. She underwent neurological consultation and CT of the head that revealed no significant pathology. After two days, the patient regained consciousness. Further investigation was performed. The abdominal ultrasound examination revealed evidence of liver steatosis, chronic pancreatitis, three liquid cavititations in the pancreas, and one in each kidney. HBs antigen was negative. Gastroscopy revealed erosive gastritis, oesophagitis and biliary reflux. No varices of the oesophagus were found. Considering the general clinical state, laboratory and radiology tests liver cirrhosis in state of decompensation with transient hepatic coma, ascites, secondary normocytary anemia was diagnosed.

Instituted pharmacological treatment and peritoneal punction with evacuation of the remaining fluid led to improvement of the patient's state. The patient was not referred for follow-up treatment in a primary care unit. Despite the serious detriment to her health, the patient was not referred to undergo any care by a specialist.

Considering the significance of her past medical history and current tests results, the general practitioner diagnosed DM and referred the patient to the hospital.

On admission, blood and urine samples were collected for CBC, electrolytes, alanine transferase and AST, amylase, bilirubin, creatinine level, glycemia, lipidogram, acid-basic balance, coagulation tests and urine testing.

The glucose level was 171 mg/dl.

Urine testing revealed glucose levels of 3,7 g/dl; ketones on a vestigial level. Glucose profile was done and HbA1c level reaching 14,5%.

Due to the laboratory test results, DM type 2 was diagnosed. Insulin therapy and liquid infusion were initiated. Tightly controlling the glucose level and liquid balance were held. When the patient attained a good general status, she was discharged to the following ambulatory treatment and recommended that she undergo regular follow-ups with specialists (diabetologist, cardiologist, ophthalmologist and hepatologist).

Discussion

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism.

Today, DM is an increasing social health problem. According to the American Diabetes Association (ADA), the estimated prevalence of diabetes among

Table 1. Criteria for testing for pre-diabetes and diabetes in asymptomatic adult individuals (American Diabetes Association Standards of Medical Care in Diabetes - 2009)

1. Testing should be considered in all adults who are overweight (BMI 25 kg/m^2*) and have additional risk factors: • physical inactivity • first-degree relative with diabetes • members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander) • women who delivered a baby weighing >9 lb or were diagnosed with GDM • hypertension (140/90 mmHg or on therapy for hypertension) • HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250 mg/dl (2.82 mmol/l) • women with polycystic ovarian syndrome (PCOS) • IGT or IFG on previous testing • other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans) • history of CVD
2. In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at age 45 years
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

* At-risk BMI may be lower in some ethnic groups

Table 2. Diagnostic criteria for diabetes, impaired fasting glucose and impaired glucose tolerance

	Fasting plasma glucose	Casual plasma glucose	OGTT (2h after glucose intake)
DM	≥7,0 mmol/l (126 mg/dl)	≥11,1 mmol/l (200 mg/dl) + diabetes symptoms	≥11,1 mmol/l (200 mg/dl) 2h after glucose intake
IFG (impaired fasting glucose)	≥5,6 & ≤6,9 mmol/l (≥100 & ≤125 mg/dl)		IGT (Impaired glucose tolerance) ≥7,8 & ≤11,0 mmol/l (≥140 & <200 mg/dl) after 2h
Normal	<5,6 mmol/l (<100 mg/dl)		<7,8 mmol/l (<140 mg/dl)

adults was 7,4% in 1995, and is expected to reach 9% by 2025 [1]. Morbidity is growing in all age groups, especially the middle-aged (45-65 years old) (Table 1).

The risk of developing DM type 2 increases with age, obesity, and lack of physical activity. Type 2 diabetes is more common in individuals with a family history of the disease and in members of certain ethnic groups. It occurs more frequently in women with prior gestational DM or polycystic ovary syndrome, and in patients with hypertension, dyslipidemia, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG).

Clinical manifestation of diabetes occurs in only 50-60% of the suspected cases, the rest 40-50% are asymptomatic- showing no signs of the disease. Due to a long pre-clinical period, DM remains undiagnosed for many years, while the complications are inevitably developing [2-6]. Chronic hyperglycemia leads to nephropathy, neuropathy, ophthalmic complications such as retinopathy, glaucoma and cataracts, skin and joint pathologies. It also contributes to the development of atherosclerosis, ischemic heart disease, peripheral ischemia, and stroke.

In view of the severity of this complication, patients suffering from diabetes should undergo complex care, including tight control of glycaemia as well as prophylaxis of complications. On the other hand, it is highly recommended to identify and to start treating patients with type 2 DM at the earliest stage. Although there are no randomised clinical trials proving that population screening towards diabetes decreases mortality and morbidity, it seems to be very useful in definite groups (the so-called targeted screening). According to the UKPDS, intervention either at earlier stages of diabetes or at lower levels of FPG (fasting plasma glucose) may influence the severity of the disease, as a substantial percentage of patients already have evidence of micro vascular complications of diabetes. Even in asymptomatic patients testing yields regarding to pre-diabetes therefore providing an opportunity for education, lifestyle interventions or initial treatment if necessary. One of the principles of screening for diabetes is the reduction of cardiovascular risk in patients with glucose metabolism impairment. Screening seems to be the favored recommendation, and currently there are no reports regarding adverse effects of it [1,2,7]. The ADA recommends screening in people from the age of 45 and above with one or more of the risk factors for type 2 diabetes, as mentioned in the ADA position statement (table 2). The WHO recommends screening in patients with hypertension.

Chronic liver disease-related diabetes

Chronic liver disease results in hepatocellular functional loss and insulin resistance, which manifests as disturbances of glucose metabolism. Up to 80% of patients with chronic liver diseases suffer from impaired glucose tolerance and around 30-60% develop overt diabetes [8-12]. Diabetes ensuing as a complication of cirrhosis is known as hepatogenic diabetes. Glucose intolerance in cirrhosis results from two coexisting abnormalities- insulin resistance of muscles, and inadequate response of the B-cells to appropriate secretion of insulin to overcome the defect in insulin action. Therefore, diabetes develops as a result of a progressive impairment in insulin secretion, together with progressive peripheral and hepatic insulin resistance [8,11,13,14]. Insulin sensitivity is decreased in nearly all cirrhotic patients before impaired glucose tolerance is present. Development of diabetes can be a marker of liver function deterioration [9,16]. On the other hand diabetes is an independent negative prognostic factor in cirrhosis. The survival rates of patients with liver cirrhosis and diabetes differ significantly from those with NGT (normal glucose tolerance). Serum albumin, total bilirubin, increased prothrombin rates, Child- Pugh scores and glucose intolerance are the most important prognostic factors whereas albumin and diabetes are the most powerful independent negative predictors of survival [17].

The clinical manifestation of hepatogenous diabetes is different from type 2 diabetes mellitus. An overwhelming majority of patients suffer from and expire more often due to complications of cirrhosis. In comparison with type 2 diabetes mellitus, hepatogenous diabetes less frequently includes cardiovascular and retinal complications. In a given patient, one cannot determine whether hepatogenous diabetes or non-insulin-dependent diabetes mellitus has occurred [8,11].

Currently, no recommendations for therapy of cirrhosis-related diabetes were established. Due to liver insufficiency, hypoglycemic treatment should be complex, involving adequate diabetes adjustment and low incidence of hypoglycemia episodes, as well as prevention of complications from cirrhosis. Hepatotoxicity of oral anti-diabetics considerably limits the assortment of drugs that can be used. Side effects in liver insufficiency exclude the usage of biguanide and PPARγ agonists. Glinides and short-acting sulfonylureas should be applied as a first-line therapy. If diabetes is not sufficiently controlled by oral anti-diabetics, the physician should institute a prandial insulin therapy using short- acting insulin or rapid- acting insulin analogues [16].

On the other hand, special attention should be paid to eliminate the risk of hypoglycemic episodes, which may be especially inclined and harmful in patients with co-existing chronic liver disease. Optimisation of diabetic metabolism not only prevents from or delays the development of diabetic late complications but also cirrhosis – associated complications such as gastrointestinal bleeding, hepatocellular carcinoma or hepatic encephalopathy.

Conclusions

Presently, there are no recommendations that are comparable to guidelines for metabolic adjustment in cirrhotic patients, such as goals for hypoglycemic treatment, lipid management or adequate protein supply. Neither therapy schemes nor definitive contraindications have been established. Nevertheless, such patients require combined specialized care as well as frequent monitoring by a primary care physician. Treatment must be delivered on an individual basis, in relation to aetiology of cirrhosis, present complications, age, concomitant diseases and more.

It is certain that patients with liver cirrhosis should undergo special multi-modal care, including regular specialist control. Prophylaxis of complications - both liver insufficiency and diabetes, may significantly increase survival rates and the quality of life for these patients. Therefore, complex care appears to be necessary, combining oversight by different specializations, including hepatologists, diabetologists, cardiologists, nephrologists, gastroenterologists and ophthalmologists. This multi-dimensional approach should provide sufficient metabolic adjustment, as well as prevention of cirrhosis and diabetes associated complications. Additional research is necessary to discover the pathological mechanisms, and to arrive at the best treatment strategies for these patients.

As the case above illustrates, the patient condition improved after she underwent hospitalisation, in spite of the fact that her possible complications were ignored. The aim of this study was to highlight the obvious necessity for close cooperation between primary and secondary care physicians. In this case, the hospital documentation was incomplete and contained no information regarding any follow up. After the patient's stay in hospital when chronic pancreatitis and hepatic coma were diagnosed, she was not referred for follow-up evaluation to any outpatients' department. Neither the patient nor the general practitioner received any suggestions about the subsequent treatment. Consequently the patient developed diabetes which remained asymptomatic for years and was diagnosed incidentally. High HbA1c level together with lack of symptoms at high hyperglycaemia indicate the prolonged duration of hyperglycaemia and patient's adaptation to it. The patient is now in a good general condition, and still under treatment. The case illustrates the importance of reviewing the entire medical history of any patient, not just focusing on the present symptoms and complaints. Conversely, close cooperation between primary and secondary care providers is necessary to provide complete and effective treatment of health issues, as well as an adequate follow-up.

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References

1. American Diabetes Association Standards of Medical Care in Diabetes - 2009. Diabetes Care January 2009.
2. Screening for Type 2 Diabetes Report of a World Health Organization and International Diabetes Federation meeting; World Health Organization 2003.
3. Dunstan DW, Zimmet PZ, Welborn TA, De Court, Cameron AJ, Sicree RA, et al.The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. Diabetes Care 2002;25:829-34.
4. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 1992;15:815-9.
5. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes Care 1998;21:518-24.
6. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ, et al. Prevalence and determinants of glucose intolerance in a Dutch caucasian population. The Hoorn Study. Diabetes Care 1995;18:1270-3.
7. Sheehy AM, Coursin DB, Gabbay RA. Revisiting Screening for Type 2 Diabetes Mellitus: To Screen or Not to Screen, That Is the Question–Reply - I 2009 Mayo Foundation for Medical Education and Research
8. Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, patophysiology, clinical implications and management. World J Gastroenterol 2009;15:280-8.
9. Garcia-Compean D, Jaquez-Quintana JO, Maldonado-Garza H. Hepatogenous diabetes. Current views of an ancient problem. Ann Hepatol 2009;8:13-20.
10. Holstein A, Hinze S, Thiessen E, Plaschke A, Egberts EH. Clinical implications of hepatogenous diabetes in liver cirrhosis. J Gastroenterol Hepatol 2002;17:677-81.
11. Petrides AS. Hepatogenic diabetes: pathophysiology, therapeutic options and prognosis. Z Gastroenterol 1999; Suppl 1:15-21.
12. Singal AK, Ayoola AE. Prevalence and factors affecting occurrence of type 2 diabetes mellitus in Saudi patients with chronic liver disease. Saudi J Gastroenterol 2008;14:118-21.
13. Petrides AS, Vogt C, Schulze-Berge D, Matthews D, Strohmeyer G. Pathogenesis of glucose intolerance and diabetes mellitus in cirrhosis. Hepatology 1994;19:616-27.
14. Kim MG, Choi WC. Differential diagnosis of diabetes mellitus caused by liver cirrhosis and other type 2 diabetes mellitus. Korean J Hepatol 2006;12:524-9.
15. Kato M, Asano H, Miwa Y, Tajika M, Yamato M, Tomita E, et al. Both insulin sensitivity and glucose sensitivity are impaired in patients with non-diabetic liver cirrhosis. Hepatology Research 2000;17:93-101.
16. Gundling F, Schumm-Draeger PM, Schepp W. Hepatogenous diabetes – diagnostics and treatment. Z Gastroenterol 2009;47:436-45. Epub 2009 May 5.
17. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Haruna Y, Imano E, et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. Am J Gastroenterol 2006;101:70-5.