RJDNMD, **18**(3):265-271 *http://www.jrdiabet.ro*

DIABETIC NEUROPATHY UNDER THE CONDITIONS OF CHRONIC ALCOHOL CONSUMPTION

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received: May 14, 2011 *accepted*: July 23, 2011
available online: August 15, 2011

Abstract

Numerous studies regarding the association between diabetes and chronic alcohol consumption have approached various aspects such as the effects of alcohol on the control of blood sugar levels in diabetic patients, alcohol consumption and the increased risk for developing and exacerbating diabetes related chronic complications- retinopathy and neuropathy. In addition, there are also studies which have investigated adverse reactions and medical interactions in alcoholics who are under treatment with oral antidiabetic drugs or insulin, and alterations of lipid metabolism in the same category of patients. Peripheral neuropathy occurs when both the sensory and the motor nerves are damaged. Diabetes and alcoholism are the two most common causes of peripheral neuropathy. In non-alcoholic diabetic patients the prevalence of symptomatic peripheral neuropathy increases with disease duration. However, in diabetic patients with a history of chronic alcohol comsumption studies have demonstrated a greater prevalence of symptomatic peripheral neuropathy. This increase in prevalence was most apparent in patients with a disease duration of less than four years. The following case study is suggestive of the above mentioned data- diabetes and alcohol predispose patients to peripheral nerve injuries and can enhance each other's effects in terms of causing nerve damage.

keywords*: type 2 diabetes, chronic alcohol consumption, peripheral neuropathy, autonomic neuropathy, diabetic foot, pain rating scale.*

Case presentation:

The patient is a 55-year-old man from the countryside working in the logging industry, diagnosed with type 2 diabetes at the age of 47. His diabetes was discovered on routine laboratory testing, the patient being asymptomatic. Considering his age- over 40,

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grade I obesity- BMI=33,5kg/m², abdominal obesity- waist circumference of 110 cm, high serum triglyceride - TAG=277mg/dL, low high density lipoprotein cholesterol-HDL=32mg/dL, the diagnosis was easily established: type 2 diabetes and metabolic syndrome. For dyslipidaemia he started treatment with fenofibrate 160mg/day and simvastatin 20mg/day.

For diabetes, besides lifestyle modifications (healthy diet and meal schedule, regular exercise, avoidance of toxic habits like smoking, excessive alcohol consumption) medical therapy was also introduced-metformin 2x500mg/day. The patient being in such a good condition, the treatment was initiated without hospital admission. The dose was gradually increased up to 2x1000mg/day, the patient being unable to tolerate a higher dose. At the next appointment, after 4 to 5 months of medical therapy, because he failed to achieve the treatment goal (glycosilated haemoglobin- HbA1c <7%), a new oral agent was introduced –glimepiride 2mg/day. The daily dose was increased to 2mg twice a day. With a combined treatment of glimepiride and metformin the patient experienced frequent episodes of hypoglicaemia, most probably a side effect of the sulfonylurea therapy. No additional risk factor was identified such as kidney failure, liver failure and the patient was not undergoing simultaneous treatment with acetylsalicylic acid, beta-adrenergic blocking agents, allopurinol and denied heavy alcohol consumption, factors which could have explained hypoglicaemia.

The therapeutic decision was to initiate combined treatment with metformin 2000mg/day and basal insulin 20U, less than 18 months after the diabetes was diagnosed. The HbA1c was still above 7%, and with this new treatment the gastrointestinal adverse events associated with metformin doses higher than 2000mg/day and the hypoglicaemia related with the sulfonylurea therapy have been avoided.

Shortly afterwards, the patient returned to hospital, complaining of numbness, paraesthesias, burning pain with spontanous nocturnal exacerbation distally located in the lower limbs. The pain was the most distressing symptom and the main reason for seeking medical attention. The patient was hospitalised for the assessment of the symptoms.

The following causes were considered: pain due to ischemic vascular disease or neuropathic pain. The ischemic pain is exacerbated by physical activity in comparison to the neuropathic pain.

After the pain was established as being neuropathic pain, the following possible diagnoses were analyzed:

– acute painful neuropathy – occurs after a long period of poor glycaemic control, shortly after initiation of insulin treatment. The pain typically disappears after a few months of continued insulin therapy and blood glucose control. The prognosis is good with complete disappearance of symptoms.
– chronic painful peripheral diabetic neuropathy - over the years the painful symptoms progress to the upper limbs.The pain is associated with signs of sensory loss and reduced or absent osteotendinous reflexes.
– other causes of painful peripheral neuropathy in a patient with diabetes were

excluded by either clinical or paraclinical criteria: chronic inflammatory demyelinating polyneuropathy, uraemia, myxoedema, sarcoidosis, amyloidosis, paraneoplastic neuropathy.

– polineuropathy associated with excessive alcohol intake or with vitamin deficiency-B12,B6 couldn't be excluded or included because of insufficient evidence.

The peripheral neurological examination comprised the following steps:

1. 10g monofilament test of pressure sensation proved sensory loss – the ability to perceive pressure was lost on each foot, on the plantar surface of distal hallux and on the first and third metatarsal.

2. test of vibration using the 128 Hz tuning fork over apex of the great toe proved inability to sense vibration.

3. pinprick test. The pain sensation was lost on each foot on the plantar surface of the distal hallux.

4. test of temperature sensation using the Tiptherm device. The patient lost his temperature sensation, he was unable to distinguish the difference between hot and cold.

5. test of the ankle reflexes revealed reduced ankle reflexes bilaterally.

It was concluded that the patient was suffering from diabetic peripheral sensorymotor chronic painful polineuropathy, based on the criteria:

– the symptoms experienced by the patient with a distal symmetrical distribution, affecting the lower limbs.
– nocturnal spontanous exacerbation of the symptoms.
– the association between spontanous severe pain and loss of pain sensation at the assessment of the peripheral nervous system.
– motor nerve injury confirmed by reduced ankle reflexes.

The short form of the McGill Pain Questionnaire was used to assess the characteristics and the intensity of the neuropathic pain. The questionnaire comprises 15 descriptors, representing the sensory dimension of the pain experience. Each descriptor- e.g. burning, shooting, stabbing, aching, cramping pain- is ranked on an intensity scale 0=none, 1=mild, 2=moderate, 3=severe. Out of 15, 6 sensations have been perceived by the patient as being severe.

About 6-8% of the type 2 diabetic patients develop chronic peripheral neuropathy at such an early stage, after being diagnosed. Usually there is a clear relationship between the intensity of the pain and the glycaemic control. Our patient responded adequately to a combined treatment of metformin and basal insulin, with a reduction of the HbA1c to 6,4%. No risk factor- duration of diabetes or elevated level of glycosilated haemoglobin - as a measure of metabolic control was identified to explain the neuropathic pain.

Vascular investigations have also been performed. Palpable peripheral pulse, ankle brachial index above 0,9 bilaterally suggested there was no peripheral artery disease. The patient was placed in the diabetic foot risk category 1 because he had lost his protective sensation. Because he was likely to develop a foot ulceration, to prevent this complication, he was given the following advice :

– to maintain an optimal glycaemic control.
– to self-examine his feet for any signs of injury, to daily wash his feet with warm water and to dry it thoroughly especially

between the toes, to take care of his skin, nails, to treat any corns or calluses, minor traumatic or thermal injuries considered as being insignificant, but potentially severe because they may become seriously infected, never to walk barefoot , always to wear socks and shoes that fit.

– to take benfotiamine in combination with vitamin B6/ B12 twice daily and to undergo a clinical examination after 6 months to evaluate the efficacy of the treatment.

During hospitalisation paraclinical investigations were also performed. The ophtalmoscopic examination revealed preproliferative retinopathy. The abdominal ultrasonography detected hepatomegaly and multiple gallstones. Elevated alanine and aspartate aminotransferase levels AST=73u/L , ALT=52u/L as well as elevated gamma glutamyl transpeptidase levels GGT= 167u/L were detected incidentally on blood tests. The patient had normal values for viral markers. Considering the obesity, the hyperglycemia and the dyslipidaemia (decreased HDL levels, hypertrigliceridemia) with elevated aminotransferase levels, the most probable diagnosis was NASH- nonalcoholic steatohepatitis.

The prescribed treatment for NASH was silibinin and phospholipids with vitamin B complex 3 times a day.

After approximately 6 months, the patient was hospitalised in the surgery department for acute calculous cholecystitis as a complication of gallstone disease. Conventional open cholecystectomy was performed, as well as a liver biopsy. The histological findings after liver biopsy - the presence of steatosis, apoptotic hepatocytes, hepatocellular ballooning, Mallory bodies- were typical of steatohepatitis. The hepatic enzymes levels were still elevated: AST=116u/L, ALT=56u/L and GGT=320u/L, the aspartate aminotransferase value was twice the alanine aminotransferase value and a high GGT level indicated alcoholic steatohepatitis. The MCV- mean corpuscular volume was above normal range=101,8fl also associated with alcoholism. Because the patient also had other risk factors, obesity, type 2 diabetes and dyslipidaemia, the final diagnosis was multiple aetiologic steatohepatitis.

Based on the laboratory results, and because no significant improvement of the neuropathic pain was achieved with a benfotiamine monotherapy, the diagnosis and the treatment were reconsidered. The patient received ALA- alfa lipoic acid at a dose of 600mg intravenously for 10 days, and afterwards benfotiamine in combination with vitamin B6/ B12, three times a day and an oral dose of alfa lipoic acid 600mg once daily. Furthermore, every 6 months intravenous administration of 600mg ALA.

The patient's evolution was unfavourable, with multiple admissions in the department of plastic surgery. The first hospital admission was for left hallux ulcer. The patient was thoroughly investigated for peripheral vascular disease to assess if the foot ulcer is of neuropathic, ischaemic or neuroischaemic aetiology**.** The peripheral pulses were palpable, the ankle brachial index above 0,9 bilaterally. The angiography examination revealed no significant occlusion of the iliac femoral arteries or the tibioperoneal trunk. The evaluation concluded it was neuropathic hallux ulcer with bone infection classified as grade IIIB, according to the University of

Texas diabetic wound assessment classification system. Because the wound penetrated the bone, minor amputation was required to avoid the extent of the infection. After a few months, the patient returned to hospital with neuropathic ulcer on the lateral side of the left foot with infection, grade IB. The wound culture and the sensitivity tests identified staphylococcal infection, responding to cefuroxime, a second generation cephalosporin. The response to treatment was slow, under tight glucose control, HbA1C<7%.

Alcoholic and metabolic steatohepatitis, as well as peripheral diabetic neuropathy complicated by multiple infections under tight glycaemic control suggest the posibility of a polineuropathy influenced by alcohol consumption.

The prevailing of the above mentioned risk factors, diabetes or alcohol, on the peripheral nervous system is difficult to determine because of the following:

- diabetes and alcoholism are the most common causes of peripheral sensorymotor polineuropathy.
- the most common presentation of diabetic and alcoholic neuropathy is distal symmetric dysfunction, explaining the additional effect of the two factors, resulting in exacerbation of the symptomatology. The same cumulative effect applies in patients with paraneoplastic neuropathy treated with cytotoxic drugs, the peripheral neuropathy being among the serious side-effects of chemotherapy, or the combined effect of HIV infection and neurotoxicity of the antiretroviral therapy:
- in diabetes and alcoholism, sensory disturbance predominates, but as the disease advances motor manifestations become apparent.
- ireversible nerve damage.
- chronic pain, affecting the patient's quality of life.
- the pathology and aetiology of diabetic and alcoholic neuropathy involve thiamine and other neurothropins deficiency.
- the development of the neuropathic pain after the diagnosis of the metabolic disease, even though the patient is a chronic alcohol consumer proves the association between the two aetiologic factors.
- autonomic neuropathy is very common in patients with peripheral neuropathy. Numerous functional abnormalities can be demostrated in organs receiving an autonomic innervation-postural hypotension, gastroparesis, constipation, diarrhoea, neuropathic bladder, gustatory sweating, erectile failure. The patient was diagnosed with erectile failure, with a multifactorial aetiology, diabetic and alcoholic.

The alcohol consumption explains:

- hypoglicaemia episodes during sulfonylurea treatment.
- premature chronic complications, symptomatic neuropathy and retinopathy in less than 2 years after diagnosis.
- alteration of the lipid panel including elevated triglyceride levels - alcohol promotes hepatic syntesis of triglyceride.

Regarding the disease's progression, some studies suggest that the painful symptoms improve once the sensory loss increases, other studies support the opinion that there is no

significant pain remission. In case that no substantial recovery is obtained with the alfa lipoic acid and benfotiamine in combination with vitamin B6/ B12, the following alternatives are available, with limited efficacy and the treatment usually doesn't completely abolish the pain.

A) Drugs acting upon the central nervous system, interrupting the conduction of pain signals. The therapy is symptomatic, with pain alleviation, with no effect on the development and the progression of neuropathy, their use being limited by the high frequency of adverse events:

- tryciclic antidepressants: imipramine, amitriptyline- used in patients with painful diabetic peripheral neuropathy for pain reduction. Not advised because of the antimuscarinic side effects such as xerostomia and sedation amplified by the alcohol, a central nervous system depressant.
- serotonin norepinephrine reuptake inhibitors: duloxetine with adverse reactions such as sleep disorders, somnolence, insomnia, nausea, dizziness. Furthermore duloxetine should not be prescribed in patients with liver disease.
- anticonvulsivants: pregabalin, gabapentin, carbamazepine – alcohol should be avoided during treatment, because it magnifies the adverse reactions, the sedative effect, the somnolence.
- opioids: tramadol- should be avoided in patients with a history of substance abuse, and furthermore alcohol is strictly forbidden during therapy, because it can possibly cause respiratory depression when associated with opiods.

B) Drugs for topical use, with less side effects. Further clinical trials are required to testify the long term efficacy:

- lidocaine patches applied on the affected area have been found to relieve neuropathic pain without systemic drug accumulation, which explains the lack of antiarrhythmic effect.
- topical capsaicin cream, lotion or patches used for temporary relief of neuropathic pain.

The patient was informed of available non-pharmacological treatments he could benefit from if pain control is still inadequate, such as acupuncture, low intensity laser therapy, magnetic field therapies and transcutaneous electrical stimulation. Further evidence is needed to sustain the safety and efficacy of the non pharmacological treatments.

The prognosis depends on:

A) tight glycaemic control – to improve the neuropathic pain, the first step is to maintain the blood glocose values within normal range.

B) interruption of the alcohol abuse.

C) compliance to the combined treatment with metformin, basal insulin, benfotiamine and phospholipids with vitamin B complex, alfa lipoic acid, silibinin, fenofibrate, simvastatin. Nutritional deficits in vitamin B1, B6, B12 and folic acid related to alcohol abuse contribute to the development of the disease.Acid folic was prescribed 5mg/day, the daily requirement of vitamins B being fulfilled by the administration of benfotiamine and phospholipids with vitamin B complex. The patient has to follow the treatment on a long term basis and even though complete

recovery is unusual, the treatment helps to diminish the symptomatology.

D) avoidance of acute/chronic complications related with diabetes and alcohol consumption, the prevention depending on the patient's involvement and interest:

- hyperglycaemia if the patient doesn't follow the dietary recommendations, consuming large amounts of alcohol, sugar, saturated fats.
- hypoglycaemia if the patient doesn't eat properly, consuming alcohol instead as an only source of nutrients.
- ketoacidosis, acute complication associated with high concentrations of ketone bodies may develop in diabetes and also because of prolonged alcoholism.
- hypertriglyceridemia induced pancreatitis.
- rapid progression of diabetic retinopathy.
- deterioration of liver function, resulting in cirrhosis.
- depression, anxiety caused by the severe pain.

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