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Case Study

Patient with Cirrhosis of the Liver and Hepatic Encephalopathy

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Norgine Limited proposed the patient type for the case study but had no further input other than carrying out medical approval to ensure compliance with regulations.

Because patients inspire us

Prescribing information can be found on page 6.

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Background and history:

A 67-year-old former plumber was hospitalised with ascites for further examination and therapy. The abdominal circumference had increased continuously in recent weeks and the patient felt increasingly less resilient. He felt exhausted with light exertion; however, climbing 2 flights of stairs was not a problem. His mood was poor, his sleep pattern worse and he was often tired and unfocused during the day.

COPD GOLD B, group A, is known to cause chronic fatigue, and he received inhalation therapy with a LAMA-LABA combination of indacaterol / glycopyrronium. He also had hypertension which was treated with 5 mg ramipril and 5 mg amlodipine. He was a regular beer drinker (usually 0.5 litres in the evening) and had smoked a pack of cigarettes a day for 40 years. Since adolescence, he has been overweight but in the last 2 months this has increased with a significant increase in abdominal circumference.

Findings:

In the case of anamnesis, the patient appeared unconcentrated, at times slightly drowsy, and showed significant memory impairment.

Low-grade spasticity with crepitations in the auscultation of the lungs were detected with no heart murmurs. Examination of the abdomen suggested pronounced ascites, no skin signs of liver disease, no jaundice, and no spider naevi.

Height	183cm
Weight with ascites	110.3Kg
Weight after ascites puncture	104.1Kg
BMI	31.1
Obesity grade	1
Blood pressure	120/75mmHg
Pulse	68/min
Bilirubin	1.5mg/dl
GOT	1.9ULN
GPT	2.2 ULN
GGT	2.7 ULN
INR	1.34
total protein	6.1 mg/dl
HDL	32 mg/dl
LDL	142 mg/dl

Ultrasound of the abdomen confirmed ascites. The liver was large, the parenchyma had a spotty-inhomogeneous effect, the surface was slightly irregular and not smooth and there was an otherwise unremarkable abdominal status.

After a diagnosis of cirrhosis (sonographically), further laboratory values were measured:

cholinesterase	4870 U/l
Albumin in serum	28 g/l
protein electrophoresis	albumin decreased; gamma globin correspondingly increased
hepatitis serology	no chronic hepatitis B or C
ferritin	no indication of haemochromatosis
ceruloplasmin in serum	normal range
AMA	not increased
antibodies for autoimmune hepatitis	not increased
AFP	not increased

On the day of the review, the ascites was tapped and 6 litres of ascites fluid was drained with i.v. substitution of 40 g albumin. Serum albumin gradient 1.3 g/dl (portal hypertension), nucleic cells 220/ul (no spontaneous-bacterial peritonitis) and there was no growth in the incubated blood culture bottles.

Gastroscopy was performed to exclude esophageal varices, and no abnormalities were detected. Due to the psychological abnormalities, a critical flicker test along with a number connection test was conducted.

Diagnosis and differential diagnostic consideration:

On the basis of the findings, liver cirrhosis (Child B) was diagnosed with overt hepatic encephalopathy (HE), West Haven Grade 2. Cause of the HE was not determined.

Without a liver biopsy, the distinction between cirrhosis resulting from NASH or alcohol-related was not possible. Alcohol consumption was slightly above the limit of 20 g of alcohol per day, which in this case would be assumed to be NASH-related cirrhosis. Due to the lack of therapeutic benefit (a strict alcohol abstention was strongly recommended in this patient) the patient was not advised to undergo liver puncture.

Therapy and inpatient treatment:

For ascites the patient received topazide 20 mg and spironolactone 200 mg. Hepatic encephalopathy was treated with lactulose 10ml b.d. and rifaximin 550mg b.d.

The patient was advised he may be at an increased risk of accidents and advised to arrange a trial driving lesson with a driving instructor. He was also given advice on nutrition and alcohol intake, the goal was to achieve a weight reduction of 5-10% within 12 months.

For treatment of hypercholesterolemia, atorvastatin 20 mg was initiated in addition to the remaining medication which was unchanged.

At the time of discharge after 5 days, the patient showed clinical improvement of overt HE, and the ascites was under control with only a slight increase.

Recommendations to the GP:

The patient was discharged on medical treatment with a request to the GP to monitor closely for weight control, kidney values and electrolytes under diuretic therapy and, if necessary, adjustment of dosage. Lactulose and rifaximin were to be maintained for at least 6 months for the recurrence prophylaxis of the HE, but then to be discussed further regarding extending therapy depending on the course of liver disease.

Interpretation of the preliminary findings of the family doctor (requested) and comments on the procedure:

The patient had been with the same GP who treated COPD and hypertension for 8 years. The increased liver values were first noticed during a laboratory inspection as part of a febrile illness 6 years ago (GOT 1.5 ULN, GPT 1.7 ULN, GGT 2.2 ULN). The GP had checked the values and after they showed no regression tendency, he ruled out chronic hepatitis B and C. He had related liver values to alcohol due to higher consumption than normal. He advised the patient on his alcohol intake, but the patient did not comply. He monitored the values at longer intervals, most recently more than a year ago.

Since the patient had now presented himself to the GP with an increase in the circumference of the abdomen, the GP performed an ultrasound examination, in which he detected ascites and instructed the patient for further clarification and therapy.

The possibilities of an earlier diagnosis of cirrhosis were missed. Although the family doctor had checked liver values occasionally, he had not ruled out the possibility of cirrhosis (laboratory values with INR, albumin, cholinesterase, ultrasound examination). It should be noted that in early stages of cirrhosis these investigations can be inconspicuous, but nevertheless it is essential to strive for them to be done.

The patient also reported having suffered a traffic accident almost two years ago. It could be assumed that at least, minimal HE was already present at that time.

What does the German guideline for the diagnosis of HE recommend?

The German S2k guideline (Gerbes *et al*., Z Gastroenterol 2019; **57**: 611-680) recommends a critical flicker frequency analysis (CFF) and/or fully performed Psychometric Hepatic Encephalopathy Score (PHES) as the preferred examination methods for early stages of HE, including minimal HE. The PHES test is a battery of tests consisting of five neuropsychological tests.

Both examination techniques are not established in either primary care or in the gastroenterological-specialist field as the critical flicker frequency testing is not common and the PHES test too complex.

Evoked potentials and the EEG are also mentioned in the guideline but are not specific and are not widespread in the established field in question.

The guideline mentions psychometric individual tests such as the number connection test, the line drawing test or the Animal Naming Test as possible screening tests. The EncephalApp, based on the Stroop test, is also mentioned and changes in the typeface are also a possible indication of HE. Ammonia determinations are not recommended as a search test by the guideline.

What would have been practically possible for the family doctor to prevent the progression of cirrhosis to Grade 2 (ascites and hepatic encephalopathy)?

1. Further examination in liver function test (LFT) value increase, rather than simple exclusion of viral hepatitis:
   - Laboratory parameters evaluating the synthesis performance of the liver (cholinesterase, albumin, INR).
   - Ultrasound liver with the search for cirrhosis (but is not remunerated in the established health insurance department in Germany without further indications).
   - Alternatively, referral to a gastroenterologist on the question of etiology of LFT value increase and the presence of cirrhosis.
2. Early detection of hepatic encephalopathy (minimal HE or early clinical stages):
   - Ask the patient about abnormalities such as traffic accidents, unexplained falls, changes in nature, sleep disturbances, increased fatigue during the day (these are possible symptoms of HE Grade 1 or 2 according to West Haven); if points are affirmed, a diagnosis should be made of HE.
   - Tests such as number connection test, line drawing test, animal naming test in patients with chronic liver disease, when the presence of cirrhosis needs to be considered; in the event of abnormalities in these tests, refer to a gastroenterologist.

What benefit would the patient have had in an earlier diagnosis of cirrhosis and HE?

An earlier diagnosis could have prevented progression to decompensated cirrhosis with overt HE and the corresponding limitations of quality of life and the expected longer-lasting cognitive deficits. It remains speculative whether even the traffic accident could have been avoided by management of the then presumed minimal HE.

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Professor Dr. Dr Med. Manfred Gross is Chief Physician and Medical Director of the Internal Clinic of Munich South. He is an internist and specialist in diseases of the stomach, intestine, liver and pancreas gastroenterology.

Professor Gross studied medicine from 1978 to 1985 at the University of Saarland. He completed his studies of Psychology at the Saarland University and received his diploma with distinction in 1987. After his license in 1985 and the acquisition of the doctorates in medicine and human biology in 1986 and 1990, he completed his training as a specialist in internal medicine.

Professor Gross has published more than 100 original papers and six medical books. He has held numerous scientific lectures and further training events. The main focus of his scientific activities is on acid-associated diseases (reflux, ulcer), NSAID therapy, hereditary colorectal cancer, chronic inflammatory diseases and purine metabolism. Professor Gross is also a member of the board of directors of the commission sonography of the regional chamber of Bavaria as well as the DEGUM seminar leader (Germany Society for Ultrasound in Medicine); thus, acquiring the highest qualification for ultrasonography in internal medicine in Germany.

INTERNATIONAL ABBREVIATED PRESCRIBING INFORMATION: XIFAXAN® / TARGAXAN® 550 mg (rifaximin-α)

Presentation: Blister pack with film-coated, pink tablets containing 550 mg rifaximin for oral administration.

Indication: Reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.

Dosage and administration: 550 mg twice a day orally with a glass of water, with or without food. No specific dosing adjustment is necessary for patients with hepatic insufficiency or for the elderly. The safety and efficacy of rifaximin have not been established in paediatric patients under 18 years of age.

Contraindications: Hypersensitivity to rifaximin, rifamycin derivatives or any of the excipients. Cases of intestinal obstruction.

Warnings and precautions: *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out. Caution should be used in patients with impaired renal function. Concomitant administration of rifaximin with other rifamycins is not recommended. Rifaximin may cause a reddish discolouration of the urine. Use caution in patients with severe hepatic impairment (Child-Pugh C) and in patients with MELD (Model for End-Stage Liver Disease) score >25. Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein such as ciclosporin is needed.

Interactions: No experience administering rifaximin to subjects taking another rifamycin antibacterial agent to treat a systemic bacterial infection. *In vitro* data show rifaximin did not inhibit major cytochrome P450 (CYP) drug metabolizing enzymes. Rifaximin did not induce CYP1A2 and CYP2B6 but was a weak inducer of CYP3A4. In healthy subjects studies demonstrated rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates, however in hepatic impaired patients rifaximin may decrease exposure of CYP3A4 substrates administered concomitantly (e.g. warfarin, antiepileptics, antiarrhythmics, oral contraceptives) due to higher systemic exposure. Increases and decreases in international normalised ratio have been reported in patients on warfarin and rifaximin. Carefully monitor international normalised ratio if co-administration is necessary. Dose adjustments of anticoagulants may be necessary. *In vitro* work suggests rifaximin is a moderate substrate of P-glycoprotein (P-gp) and metabolised by CYP3A4. It is unknown if concomitant drugs which inhibit P-gp and/or CYP3A4 increase systemic exposure of rifaximin. Clinical interaction between rifaximin and compounds that undergo efflux via P-gp and other transport proteins is unlikely (MRP2, MRP4, BCRP and BSEP).

Pregnancy and lactation: No or limited data on the use of rifaximin in pregnant women. Animal studies showed transient effects on ossification and skeletal variations in the foetus. Use of rifaximin during pregnancy is not recommended. It is unknown whether rifaximin/metabolites are excreted in human milk. A risk to the child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy.

Undesirable effects: Adverse effects observed in the placebo-controlled study RFHE3001 and long-term study RFHE3002: Common (>1/100 to <1/10): Depression, dizziness, headache, dyspnoea, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia, oedema peripheral. Prescribers should consult country approved Summary of Product Characteristics for further information in relation to undesirable effects.

Overdose: No case of overdose has been reported. In patients with normal bacterial flora, rifaximin in dosages of up to 2,400 mg/day for 7 days did not result in any relevant clinical symptoms related to the high dosage. In case of accidental over-dosage, symptomatic treatments and supportive care are suggested.

Price and pack sizes: PVC-PE-PVDC/Aluminium foil blisters in cartons of 28 or 56 tablets. A 98-tablet carton is also available in some markets. Contact local distributor for price.

Legal category: POM

Prescribing information: Medicinal product subject to medical prescription.

Marketing authorisation holder: Norgine BV, Antonio Vivaldistraat 150, 1083 HP Amsterdam, The Netherlands.

Product licence number: PL20011/0020

ATC code: A07AA11

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