RESEARCH

Prognostic significance of hyperammonemia in neuroendocrine neoplasm patients with liver metastases

Julie Refardt[1,2], **Caroline M den Hoed**[3], **Janneke Langendonk**[4], **Wouter T Zandee**[5], **Ayoub Charehbili**[6], **Richard A Feelders**[1], **Wouter W de Herder**[1], **Tessa Brabander**[6] and **Johannes Hofland**[1]

[1]ENETS Center of Excellence, Department of Internal Medicine, Section of Endocrinology, Erasmus Medical Center and Erasmus Cancer Institute, Rotterdam, The Netherlands
[2]ENETS Center of Excellence, Department of Endocrinology, University Hospital Basel, Basel, Switzerland
[3]Department of Gastroenterology and Hepatology, Erasmus MC Transplant Institute, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[4]Department of Internal Medicine, Center for Lysosomal and Metabolic Diseases, Erasmus Medical Center, Rotterdam, The Netherlands
[5]Division of Endocrinology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[6]ENETS Center of Excellence, Department of Radiology & Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence should be addressed to J Refardt: julie.refardt@usb.ch

Abstract

Neuroendocrine neoplasms (NENs) are rare, usually slow-growing tumors, often presenting with extensive liver metastases. Hyperammonemia due to insufficient hepatic clearance has been described in NEN cases; however, no systematic evaluation of risk factors and outcomes of NEN-associated hyperammonemia exists so far. This case report and retrospective review of NEN patients developing hyperammonemia from the years 2000 to 2020 at the Erasmus Medical Center in Rotterdam, the Netherlands, aimed to describe these patients and determine prognostic factors to improve evaluation and treatment. Forty-four NEN patients with documented hyperammonemia were identified. All patients had liver metastases with 30% (n = 13) showing signs of portal hypertension. Patients who developed encephalopathy had higher median ammonia levels, but there was no association between the severity of hyperammonemia and liver tumor burden or presence of liver insufficiency. Eighty-four percent (n = 37) of patients died during follow-up. The median (IQR) time from diagnosis of hyperammonemia to death was 1.7 months (0.1–22.7). Hyperbilirubinemia, hypoalbuminemia, elevated international normalized ratio, presence of liver insufficiency, encephalopathy and ascites were associated with worse outcomes. Their role as independent risk factors for mortality was confirmed using the Child–Pugh score as a summary factor (P < 0.001). No difference was seen concerning overall survival between our hyperammonemia patients and a propensity score-matched control stage IV NEN cohort. In conclusion, hyperammonemia comprises a relevant and potentially underdiagnosed complication of NEN liver metastases and is associated with worse outcomes. Assessment of signs of encephalopathy, risk factors and the Child–Pugh score could be helpful in selecting patients in whom ammonia levels should be measured.

Key Words
- neuroendocrine tumor
- liver metastases
- encephalopathy
- shunting
- Child–Pugh score
- MELD-Na score

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Background

Hyperammonemia occurs when there is a defect in the detoxification or overproduction of ammonia. It can lead to encephalopathy, ranging from mild cognitive impairment to coma (Willson *et al.* 2013, Haj & Rockey 2020). While the metabolism of ammonia to urea and excretion via the kidneys is primarily impaired in inborn errors of metabolism, there are also several secondary causes that can be grouped into four main categories (Willson *et al.* 2013). The first are factors inhibiting the conversion of ammonia to urea such as severe malnutrition with low carnitine or arginine levels, drug-induced mitochondrial dysfunction or urea cycle disorders. Secondly are factors that reduce the urea cycle capacity, as observed in liver insufficiency. The third cause of secondary hyperammonemia is the presence of shunting of the liver, such as portosystemic shunting as in portal hypertension or intrahepatic shunting due to high liver tumor load. Fourthly, hyperammonemia can occur due to overproduction or due to infections with urease-producing bacteria, for example, urinary tract or skin infections (Stergachis *et al.* 2020).

Ten cases of hyperammonemia in neuroendocrine neoplasm (NEN) patients have been described in the literature to date (Turken *et al.* 2009, Broadbridge *et al.* 2010, Erinjeri *et al.* 2010, Vandamme *et al.* 2012, Shea *et al.* 2013, Pande *et al.* 2017, Monardo *et al.* 2020). NENs are a diverse group of rare malignant tumors arising from neuroendocrine cells and are mainly localized in the intestine, pancreas and lung (Hofland *et al.* 2020). NENs are graded based on histological differentiation into well-differentiated neuroendocrine tumors or poorly differentiated neuroendocrine carcinomas (Perren *et al.* 2017). Around one-fourth of NENs produce amine or peptide hormones and are called functional tumors (Zandee *et al.* 2017). Due to their usually slow growth, NENs are often diagnosed at a metastatic stage and are prone to develop liver metastases (Riihimäki *et al.* 2016, Dasari *et al.* 2017). However, liver failure in NEN patients is rare, even in cases with extensive metastatic liver disease (Willson *et al.* 2013). Treatment of metastatic NENs depends on their presentation and includes surgery, liver-directed therapy, (radiolabeled) somatostatin analogs, targeted treatment and chemotherapy (Pavel *et al.* 2016). The majority of the previously reported cases of hyperammonemia in NEN patients suffered from high liver tumor burden, with different triggering factors leading to elevated ammonia levels.

Based on an index case of a NEN patient with hyperammonemia presenting in our clinic, awareness of this NEN-related complication was increased. Subsequently, all NEN cases treated at our center of excellence during the last 20 years were reviewed. As no cohort of NEN patients developing hyperammonemia has been described to date, our aim was to describe clinical characteristics and outcome as well as to define prognostic factors in order to ameliorate evaluation and management of these patients.

Methods

Collection of clinical data

Clinical data of this case report and retrospective case review were obtained from the years 2000 to 2020 from the database of the ENETS Center of Excellence for Neuroendocrine Tumors Erasmus MC Rotterdam, the Netherlands. The Local Institutional Review Board of the Erasmus MC approved the database and a waiver of patient informed consent for the retrospective analysis was issued.

While an extensive work-up was performed in the index patient, data were assessed retrospectively for other patients. Patients were selected if they had hyperammonemia defined as an ammonia level above the upper reference limit of 45 µmol/L. Patient, tumor, laboratory and radiological characteristics were recorded at the time point of hyperammonemia occurrence according to careful review of patient files as well as evaluation of the liver images by a radiologist. Tumor grade and stage were documented according to the 2010 WHO grading and ENETS guidelines (Klöppel *et al.* 2017, Nagtegaal *et al.* 2020). Treatments were recorded over the entire follow-up period.

Liver insufficiency was defined as the simultaneous presence of bilirubin and international normalized ratio (INR) levels above the normal range and albumin levels below the normal range. Signs of portal hypertension were defined as having thrombopenia and/or splenomegaly, presence of collaterals or thrombotic occlusions of the portal or liver veins or ascites without peritoneal carcinomatosis (Simonetto *et al.* 2019). The Child–Pugh and model for end-stage liver disease-sodium (MELD-Na) prognostic scores were calculated according to the published scoring systems (Kim & Lee 2013, Peng *et al.* 2016). The Child–Pugh score includes the factors ascites, bilirubin, albumin, INR of prothrombin time and encephalopathy, while the MELD-Na score includes the factors creatinine, bilirubin, INR and sodium. Due to missing values, the Child–Pugh

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and MELD-Na scores could not be calculated in $n = 12$ and $n = 11$ patients, respectively.

For survival comparison, our previously presented cohort of metastatic (=stage IV) grade 1 or 2 NEN patients (Refardt *et al.* 2020) was used. The data of this cohort were obtained from 2000 to 2019 and are derived from two prospective observational studies of NEN patients from the ENETS Center of Excellence for Neuroendocrine Tumors Erasmus MC Rotterdam, the Netherlands, and the Swiss national register of neuroendocrine tumors SwissNET. Of the total 325 patients, 7 patients were also in the hyperammonemia cohort and hence excluded. To make the data more comparable, only patients with reported liver metastases were included, leaving a total number of 247 patients.

Statistics

Descriptive statistics were used to characterize demographic and clinical data, expressed as median with interquartile range (IQR) or frequencies with percentage (%). Binary variables were analyzed using logistic regression models and continuous variables were analyzed with linear regression models. A Cox proportional hazard model was used to calculate mortality hazard ratios (HR) and 95% CIs, with time to event counting from the first onset of hyperammonemia until death or loss of follow-up. The proportionality of hazards was evaluated using the Cox regression analysis with time-dependent covariates. The assumption of proportionality of hazards was tested and was not broken in any of the Cox regression models.

For the control cohort, propensity score (PS) matching was used. PS matching is used to optimize the post-weighting balance of covariates between groups (Austin 2009, 2013). Using the PS methodology, all hyperammonemia patients and all control patients with liver metastases were assigned a weight between 0 and 1 according to the covariates age, sex, hormonal syndrome, site of origin and additional metastases. Grading was not used as a covariate, since this variable is not known in 23% of the hyperammonemia cohort. PSs were then used to match hyperammonemia patients to control patients with liver metastases in a 1:1 ratio using the nearest neighbor matching method. Successful matching was indicated by the absence of statistical significance between the variables.

Overall survival rates, that is survival from the date of diagnosis to the last date of follow-up or death, were calculated with the Kaplan–Meier method. The log-rank test was used to compare overall survival differences between groups.

Statistical analyses were performed using SPSS version 26.0 (IBM Corp.) and R 3.3.3 open-source. P values <0.05 were considered statistically significant.

Results

Index case

A 65-year-old patient with a metastatic pancreatic NEN presented with progressive liver metastases 2 years after diagnosis in our center. Peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-DOTATATE was initiated. In the meantime, however, the patient became disoriented in time and place, nauseous and developed a fine hand tremor. Interestingly, symptoms transiently improved within 1 day of the administration of PRRT. Diagnostic work-up revealed hyperammonemia of 138 µmol/L without signs of liver dysfunction. MRI showed liver tumor burden mainly concentrated in the left hepatic lobe without signs of intra- or extrahepatic portosystemic shunts. Diagnostic angiography showed signs of portal hypertension with a recanalized umbilical vein, high portal venous pressure and retrograde flow in the left portal vein but no evidence for shunting. After initial improvement under treatment with lactulose and rifaximin, the patient again developed progressive encephalopathic symptoms. Despite negative imaging, intrahepatic shunting was suspected and selective intra-arterial radiotherapy (SIRT) injecting ^{90}Yttrium-labeled microspheres to the left hepatic artery was performed to reduce the liver tumor burden. Two weeks after the SIRT, the patient already reported a significant improvement in quality of life. Ammonia levels taken 3 weeks after the procedure decreased to 70 µmol/L. The procedure was repeated 2.5 years after the first intervention due to a relapse in symptoms and recurrent hyperammonemia of 144 µmol/L, in the absence of radiological signs of progressive disease. Again, SIRT was successful and hyperammonemia remained controlled with lactulose and rifaximin. One year after the second intervention, the patient's symptoms recurred and plasma ammonia levels rose to 139 µmol/L. Arginine treatment was started after which the ammonia levels decreased to 80 µmol/L.

Retrospective analysis of hyperammonemia cases

Patient characteristics

Our analysis revealed 75 NEN patients with available ammonia levels, of which 44 NEN patients had documented

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hyperammonemia during their disease course (Table 1). The median (IQR) ammonia level in this NEN cohort was 83 µmol/L (59–141). Patients were predominantly male (64%) and presented with well-differentiated (93%) NENs of the pancreas (36%), small intestines (31%) and other origins (33%). All patients had stage IV metastatic disease with liver metastases. Additional metastatic sites were identified in 68% of patients. The main treatment modalities before the onset of hyperammonemia involved somatostatin analogs (71%) or PRRT (59%) and surgical interventions (41%). Eighty-four percent of the patients died, with a median (IQR) follow-up time of 55 months (31–105) since NEN diagnosis and a median (IQR) follow-up time of 1.7 months (0.1–22.7) since the diagnosis of hyperammonemia.

The main reasons for ammonia measurement were encephalopathy in 31%, general deterioration in 30% and post-interventional evaluation or evaluation due to acute triggers (e.g. sepsis) in 16%, respectively. The suspected underlying cause for hyperammonemia was tumor progression in the majority of patients (57%), followed by post-interventional complications in 18%, for details see Table 1.

Risk factors associated with hyperammonemia

In our cohort of hepatic-metastasized NEN patients, abnormal liver transaminases were present in 71%, with 39% fulfilling the criteria of liver insufficiency at the time of hyperammonemia diagnosis (Table 2). Eighty-two percent of patients had an impaired kidney function and cardiac failure was observed in 7% of patients.

In the majority (68%) of the patients, both liver lobes were affected by metastases with a liver tumor burden greater than 50% in 46% of all patients. On imaging, ascites (both malignant and non-malignant) was present in 68% of the patients. Other signs of portal hypertension were seen in 29% of the patients.

The maximum levels of plasma ammonia did not correlate with liver transaminases ($R^2 < 0.001$) There was also no difference in hyperammonemia severity according to liver tumor load ($P = 0.15$) or between patients with and without liver insufficiency or signs of portal hypertension ($P = 0.29$ and $P = 0.16$, respectively) (Fig. 1).

In patients with extensive liver disease, tumor progression was identified as the main cause for hyperammonemia, while in patients with a low tumor liver burden, acute triggers such as interventions or surgery were the main cause (Supplementary Table 1, see section on supplementary materials given at the end of this article). There was no difference in survival time between the two groups from the moment of hyperammonemia.

The median (IQR) plasma ammonia levels in patients developing encephalopathy were higher at 107 µmol/L (76–157) compared to 65 µmol/L (53–90) in patients without encephalopathy (Fig. 1).

Impaired kidney function was observed in the majority of the hyperammonemia patients (Table 1); however, no correlation was observed between maximum levels of plasma ammonia and creatinine levels ($R^2 = 0.025$, $P = 0.31$).

Risk factors associated with mortality

To identify variables associated with mortality in NEN patients with hyperammonemia, a univariable regression analysis was performed on known risk factors associated with liver failure or hyperammonemia (Fig. 2). The maximum level of plasma ammonia was not associated with increased mortality in our cohort. In contrast, hyperbilirubinemia (bilirubin levels HR (95% CI) = 1.013 (1.003–1.024), $P = 0.01$), hypoalbuminemia (albumin levels HR (95% CI) = 0.95 (0.91–0.99), $P = 0.007$) and elevated INR (INR levels HR (95% CI) = 1.92 (1.26–2.94), $P = 0.003$) were markers for worse outcome. The presence of liver insufficiency (HR = 3.53, 95% CI = 1.69–7.38), $P = 0.01$), encephalopathy (HR = 2.4, 95% CI = 1.2–4.5, $P = 0014$) and ascites (HR = 2.66, 95% CI = 1.21–5.83, $P = 0.015$) were also associated with increased mortality risk.

Since our cohort size and event rate did not allow us to combine all identified factors in a multivariable regression analysis, we decided to test classic prognostic scores for end-stage liver diseases: Child–Pugh and MELD-Na. While the Child–Pugh score includes all defined factors, the MELD-Na score includes only bilirubin and INR. Both scores were associated with an increased mortality risk in NEN patients with hyperammonemia with a HR (95% CI) of 1.50 (1.21–1.87, $P < 0.001$) for the Child–Pugh score and 1.14 (1.06–1.22, $P < 0.001$) for the MELD-Na score. Median (IQR) survival time from the onset of hyperammonemia was 51 months (31–105) for Child–Pugh class A (=5–6 points), compared to 0.8 month (0.3–19) for class B (=7–9 points) and 0.1 month (0.1–1.7) for class C (=10–15 points), $P = 0.004$ (Fig. 2).

To evaluate the impact of hyperammonemia on overall survival, we compared our patients with 44 PS-matched stage IV NEN patients. PS matching led to two well-balanced groups (Supplementary Table 2), which showed no difference in overall survival ($P = 0.65$, Supplementary Fig. 1). Accordingly, no evaluation concerning the possible identification of risk factors could be performed.

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Table 1 Characteristics of the patients with hyperammonemia. Values are shown as frequencies (%) or median (IQR).

Patient characteristics	Value
(A) Characteristics of the 44 NEN patients with hyperammonemia	
Sex, male, *n* (%)	28 (64)
Age, years, median (IQR)	65 (54–70)
BMI, kg/m^2, median (IQR)	21.8 (18.5–25.6)
NEN origin, *n* (%)	
Gastro-duodenal	3 (6.7)
Midgut	14 (31)
Hindgut	0
Pancreas	16 (35,6)
Lung	3 (6.7)
Unknown	8 (17.8)
Grade, *n* (%)	
NET grade 1	11 (25)
NET grade 2	20 (45.5)
NET grade 3	1 (2)
NEC	2 (4.5)
Unknown	10 (23)
Metastases, *n* (%)	
Liver	44 (100)
Non-mesenteric lymph nodes	17 (39)
Mesenteric lymph nodes	15 (34)
Lung	5 (11)
Bone	6 (14)
Hormonal syndrome, *n* (%)	19 (43)
Laboratory, median (IQR)	
Ammonia, µmol/L	83 (59–141)
Chromogranin A, ng/L	3724 (293–56468)
Treatment during follow-up period	
Somatostatin analogs, *n* (%)	32 (73)
Before HA	18 (56)
After HA	1 (3)
Before and after	13 (41)
PRRT, *n* (%)	30 (68)
Before HA	22 (73)
After HA	4 (13.5)
Before and after	4 (13.5)
Chemotherapy, *n* (%)	9 (21)
Before HA	4 (44.5)
After HA	4 (44.5)
Before and after	1 (11)
Targeted treatment, *n* (%)	8 (18)
Before HA	3 (38)
After HA	3 (38)
Before and after	2 (25)
Surgery, *n* (%)	19 (43)
Before HA	17 (90)
After HA	1 (5)
Before and after	1 (5)
Liver embolization, *n* (%)	11 (25)
Before HA	8 (73)
After HA	3 (27)
Before and after	0
Follow up time, months, median (IQR)	55 (31–105)
Time from diagnosis of HA to death or loss of follow-up, months, median (IQR)	1.7 (0.1–22.7)
Patients died, *n* (%)	37 (84)

(Continued)

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Table 1 Continued.

Patient characteristics	Value
(B) Triggers leading up to ammonia measurement	
Reason for measurement	
Encephalopathy, *n* (%)	14 (31)
Post-interventional/surgical complications, *n* (%)	7 (16)
General deteriation, *n* (%)	13 (30)
Acute trigger (e.g. sepsis), *n* (%)	7 (16)
Liver tumor bulk, *n* (%)	3 (7)
Main clinical problem at time of measurement	
Tumor progression, *n* (%)	25 (57)
Tumor lysis syndrome, *n* (%)	3 (7)
Intervention/operation, *n* (%)	8 (18)
Cardiac failure, *n* (%)	1 (2)
Infection, *n* (%)	4 (9)
Elective evaluation, *n* (%)	3 (7)

HA, hyperammonemia; IQR, interquartile range; NEN, neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; PRRT, peptide receptor radionuclide therapy.

Treatment of hyperammonemia in our cohort

The majority (59%) of our patients did not receive specific treatment for hyperammonemia. Of the 18 treated patients, 83% received lactulose orally, in 7 cases in combination with rifaximin. Additional supportive medication with L-arginine and dexamethasone was given in three cases. Two patients, among them our index case, received SIRT with 90Yttrium-labeled microspheres. One patient was treated with PRRT with 177Lu-DOTATATE to lower the liver burden, and in one patient, portal hypertension was successfully treated with portal vein stenting.

Of the patients who received only lactulose and/or rifaximin, the majority (61%) died within 3 months of hyperammonemia-onset (median (IQR) plasma ammonia level, 151 (86–162) µmol/L). All patients with interventional treatment had a survival of at least 11 month from hyperammonemia-onset (median (IQR) plasma ammonia level, 69 (60–138) µmol/L).

Discussion

Hyperammonemia is an underrecognized complication of liver metastases in NEN patients. The presence of hyperammonemia is accompanied by a high short-term mortality rate and several risk factors for worse outcomes could be defined. The commonly used Child–Pugh score proved to be a useful tool for assessing mortality risk in these patients.

Hyperammonemia in NEN patients can occur due to several causes. Because NENs are usually slow-growing tumors, progressive hepatic tumor infiltration can lead to intrahepatic shunting. Decreased liver capacity due to tumor infiltration contributes to the reduced clearance of ammonia. This was likely the main cause in 46% of our patients presenting with a liver tumor burden above 50% and has also been described in previous case reports (Broadbridge *et al.* 2010). Hepatic failure due to tumor infiltration however is rare in NEN patients (Willson *et al.* 2013). This was also reflected by our cohort where the majority of patients had an intact liver function and only four patients showed signs of liver failure. The second main cause for hyperammonemia in our cohort was portosystemic shunting, caused by obstructions of the portal venous system or microvascular portosystemic shunting within the liver metastases. Portosystemic shunting as a cause of encephalopathy in NEN patients has been described in other case reports (Erinjeri *et al.* 2010, Vandamme *et al.* 2012) and was most likely also one of the main causes in 13% of our patients. Additional causes include decreased ammonia excretion due to impaired kidney function or acute stressors such as surgical or other interventions, infections or medication-associated toxicities (Shea *et al.* 2013, Willson *et al.* 2013, Gupta *et al.* 2016). In 27% of our patients, the occurrence of hyperammonemia was indeed associated with an acute trigger factor. Interestingly, this was the main cause in our patients with a tumor liver load below 10%.

Lastly, an alternative mechanism involving the production of hormones or neurotransmitters has been proposed (Monardo *et al.* 2020). The fact that no difference was seen in hyperammonemia severity according to liver tumor load, liver insufficiency or signs of portal hypertension indicates different mechanisms. In addition, the number of patients with functional active NENs (43%) was higher in this cohort than the control cohort (32%) (Refardt *et al.* 2020) and functional active NENs

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Table 2 Risk factors associated with hyperammonemia in neuroendocrine neoplasm patients. Values are shown as frequencies (%) or median (IQR).

Laboratory parameters at time point hyperammonemia	Value
Liver function, *n* (%)	
Liver transaminase levels, normal	13 (29)
>normal, <10× elevated	20 (46)
>10×/<100× elevated	7 (16)
>100× elevated	4 (9)
Bilirubin, (normal 0–16 µmol/L), median (IQR)	20 (10–33)
Hyperbilirubinemia, *n* (%)	23 (52)
Albumin, (normal 35–50g/L), median (IQR)	27 (23–36)
Hypalbuminemia, *n* (%)	31 (71)
Kidney function	
Creatinine, (normal 55–90 µmol/L), median (IQR)	116 (78–154)
GFR, median (IQR)	53 (37–81)
GFR 60–90mL/min, *n* (%)	7 (16)
GFR 30–59mL/min, *n* (%)	22 (50)
GFR <30 mL/min, *n* (%)	7 (16)
Coagulation factors	
Thrombocytes, (normal 150–370 10^9/L), median (IQR)	184 (95–288)
Thrombopenia, *n* (%)	16 (36)
Prothrombin time, (normal 10.9–13.3), median (IQR)	16.5 (14.6–23.4)
INR, (normal <1.1), median (IQR)	1.4 (1.3–1.8)
Assessment liver function	
Liver insufficiency (high bilirubin, low albumin, elevated INR), *n* (%)	17 (39)
Signs of encephalopathy, *n* (%)	14 (31)
Child–Pugh score, median (IQR)	8 (7–10)
MELD-Na score, median (IQR)	17 (11–23)
Radiology, *n* (%)	
Tumor burden liver	
0–10%	10 (22,7)
11–25%	2 (4,5)
26–50%	7 (15,9)
>50%	20 (45,5)
Missing	5 (11,4)
Bilobar metastatic involvement liver	32 (73)
Hepatomegaly	24 (55)
Portal/superior mesenteric vein thrombosis	7 (16)
Splenomegaly	5 (12)
Collateral vessels	6 (14)
Ascites (malignant and non-malignant)	30 (68)
Ascites due to portal hypertension	9 (30)
Signs of portal hypertension (thrombopenia, splenomegaly, large portal vein/collaterals, thrombotic occlusions)	13 (29)

GFR, glomerular filtration rate; INR, international normalized ratio of prothrombin time; IQR, interquartile range; MELD-Na, model for end-stage liver disease-sodium.

that could interfere with the complex detoxification process of ammonia seems plausible and should be further investigated.

Given the likely underreporting of hyperammonemia in NEN patients, the main challenge will be to identify the patients in whom ammonia levels should be measured. An important clinical indicator is the development of encephalopathy, which was documented in 31% of our patients. Encephalopathy can be missed in patients presenting with mild symptoms (Rose *et al.* 2020) like mild behavior changes but still alert. This is likely underreported in the presented cohort. Awareness of the treating physician prompting ammonia measurement in metastatic NEN patients presenting with behavior changes, disorientation, memory problems or hand tremor is critical. These symptoms are debilitating and severely reduce the quality of life of the patient and/or patient's family. Furthermore, although patients who developed encephalopathy had higher levels of ammonia, lower levels were not exclusive of the development of symptoms. Similar findings have been described in other studies (Ong *et al.* 2003, Haj & Rockey 2020). Interestingly, the severity

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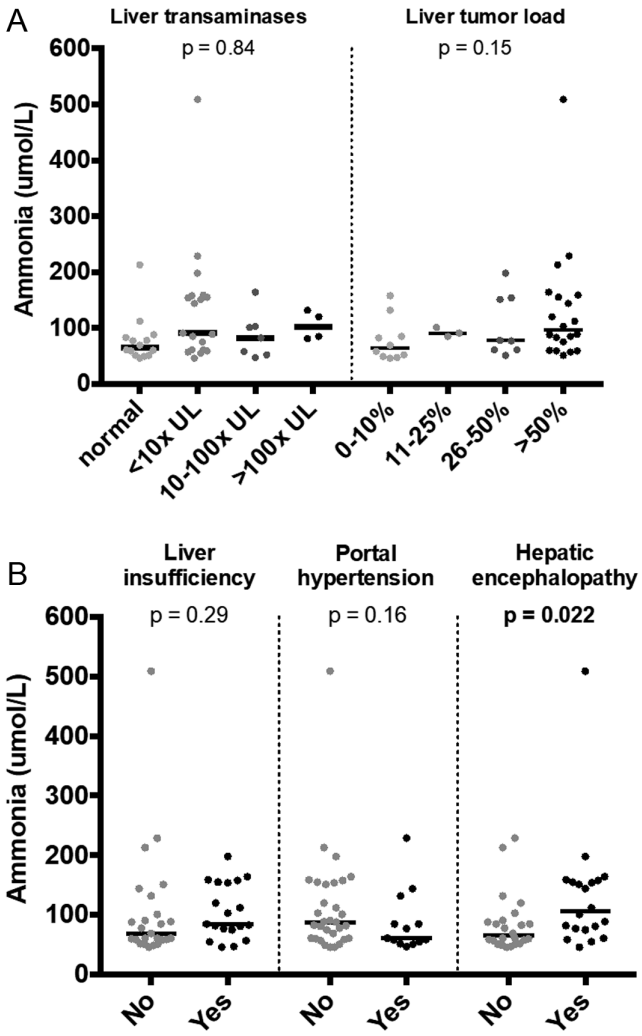

Figure 1
Plasma ammonia levels in neuroendocrine neoplasm patients stratified according to different risk factors. (A) Liver transaminases and liver tumor load; (B) Liver insufficiency, signs of portal hypertension and hepatic encephalopathy. Data are shown as median with individual data points. The *P* -values depict the difference within the groups and bold writing indicates significance. UL, upper limit of normal.

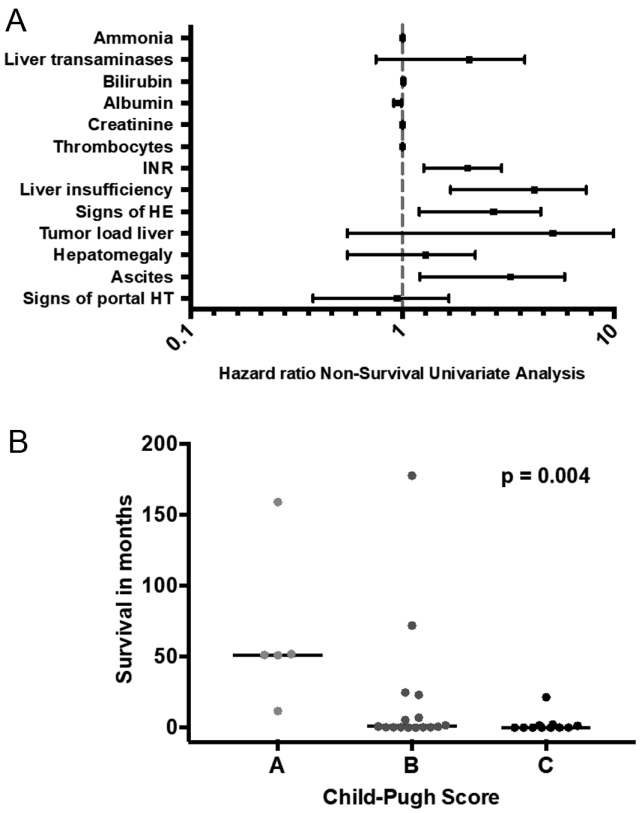

Figure 2
Risk factors associated with hyperammonemia in NEN patients. (A) Forest plot showing the effect of the pre-defined risk factors on mortality risk according to univariable regression analysis. The black squares reflect the hazard ratio, while the whiskers indicate the lower and upper limits of the 95% CI. HE, encephalopathy; HT, hypertension; INR, international normalized ratio of prothrombin time. (B) Survival time from onset of hyperammonemia to death in relation to Child–Pugh scores. Data are shown as median with individual data points. The *P* -value depicts the difference within the groups and bold writing indicates significance. Control, NEN control population, HA, hyperammonemia population; NEN, neuroendocrine neoplasm.

of hyperammonemia failed to identify patients at risk for a reduced outcome, which underlines the need for additional prognostic factors.

In our cohort, the parameters hyperbilirubinemia, hypoalbuminemia, elevated INR as well as the presence of ascites and hepatic encephalopathy were associated with increased risk of mortality. Since these factors might be challenging to combine for the individual patient, we chose to evaluate the use of the known risk scores for liver insufficiency Child–Pugh and MELD-Na. While a higher rating was associated with an increased mortality risk in both scores, the Child–Pugh score included all defined risk factors and showed a higher association with worse outcome. The Child–Pugh score was developed as a predictive tool for mortality in cirrhotic patients and categorizes patients into good liver function (A), moderately impaired liver function (B) and advanced liver dysfunction (C) (Peng *et al.* 2016). The clear association between Child–Pugh score and survival in our NEN patients with liver metastases shows that this score can be employed for prognostication.

Although overall survival rate of hyperammonemia patients did not differ from PS-matched stage IV control NEN patients, the median survival time after diagnosis of hyperammonemia was only 1.7 months. This underlines that these patients require prompt recognition and initiation of specialized treatment for hyperammonemia and underlying causes. Hyperammonemia is also accompanied by reduced survival rates in patients with

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acute and chronic liver failure and irrespective of complete liver failure (Sakusic *et al.* 2018, Shalimar *et al.* 2020).

A careful evaluation of possible causes and specific treatment options is crucial following the demonstration of hyperammonemia. Treatment for hyperammonemia given to the patients in the presented cohort was limited, with the majority receiving no treatment. This is most likely due to the low awareness of the impact of hyperammonemia. Evaluation should include nutritional status assessment as well as carnitine and arginine measurement, since both are important intermediates in ammonia detoxification via the urea cycle (Hanai *et al.* 2020). Late-onset or acquired urea cycle disorders may also become apparent in patients with chronic malnutrition, rapid weight loss or other factors causing metabolic stress (Stepien *et al.* 2019). For patients in whom the cause of hyperammonemia is not easily reversible, treatment focuses on lowering ammonia levels. This can be achieved in most cases by reducing ammonia production and absorption from the intestines, as with the antibiotic rifaximin. Lactulose can also reduce absorption by converting ammonia to ammonium, which is then excreted in the stool (Bass *et al.* 2010, Hudson & Schuchmann 2019). Other treatment options are L-arginine, a non-essential amino acid that reduces ammonia levels by increasing urea production (Harper & Najarian 1956, Fahey *et al.* 1957). In the presented case, the administration of L-arginine resulted in a transient amelioration of symptoms, since L-arginine is given together with PRRT for nephroprotection.

In case of hyperammonemia due to shunting, reduction of liver tumor mass could be the preferred strategy, for example with SIRT as in our case or with interventions such as transarterial embolization (TAE) or transarterial chemo-embolization (TACE) (Turken *et al.* 2009, Erinjeri *et al.* 2010, Vandamme *et al.* 2012, Pande *et al.* 2017). According to the available limited data, TAE might be preferred in severely symptomatic patients aiming at rapid reduction of ammonia levels (Vandamme *et al.* 2012). While these procedures might prolong survival in patients with otherwise high mortality rates, they could also trigger hyperammonemia due to acute deterioration of liver function. Therefore, their use should be carefully evaluated in a multidisciplinary setting.

The main limitation of our study is its retrospective design and likely selection bias. All but three patients were diagnosed with hyperammonemia due to patient deterioration or the appearance of an acute trigger factor. Patients with mild symptoms could have been missed, especially in view of the low awareness of hyperammonemia in NEN patients. This is also reflected in the low number of NEN patients with available ammonia levels. In addition, due to the limited number of actively treated patients, no statement can be made about the effect of ammonia-lowering treatments on the outcome. Despite these limitations, this study is the first to systematically evaluate risk and possible prognostic factors in NEN patients with hyperammonemia.

In conclusion, our study revealed that NEN patients developing hyperammonemia have a worse outcome independent of the severity of hyperammonemia. Ammonia levels should be measured when neurocognitive symptoms or risk factors are present. Child–Pugh scoring could be helpful for risk stratification in these patients.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-21-0346.

Declaration of interest

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Author contribution statement

J R, W Z, R F, W W D H, T B and J H collected the data. J R and J H designed the study and performed the analyses. C H and J L advised on the analyses and interpretation of the data. J R wrote the initial draft of this article; all authors revised the manuscript. All authors contribute to the article and approved the submitted version.

References

Austin PC 2009 Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine* **28** 3083–3107. (https://doi.org/10.1002/sim.3697)

Austin PC 2013 The performance of different propensity score methods for estimating marginal hazard ratios. *Statistics in Medicine* **32** 2837–2849. (https://doi.org/10.1002/sim.5705)

Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, Sigal S, Sheikh MY, Beavers K, Frederick T, *et al.* 2010 Rifaximin treatment in hepatic encephalopathy. *New England Journal of Medicine* **362** 1071–1081. (https://doi.org/10.1056/NEJMoa0907893)

Broadbridge V, Townsend A, Pittman K, Kimber R, Patterson W, Sukumaran S & Price TJ 2010 Reversing hyperammonemia in neuroendocrine tumors. *Journal of Clinical Gastroenterology* **44** e186–e189. (https://doi.org/10.1097/MCG.0b013e3181d96aad)

Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T & Yao JC 2017 Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncology* **3** 1335–1342. (https://doi.org/10.1001/jamaoncol.2017.0589)

Erinjeri JP, Deodhar A, Thornton RH, Allen PJ, Getrajdman GI, Brown KT, Sofocleous CT & Reidy DL 2010 Resolution of hepatic encephalopathy following hepatic artery embolization in a patient with well-differentiated neuroendocrine tumor metastatic to the liver. *Cardiovascular and Interventional Radiology* **33** 610–614. (https://doi.org/10.1007/s00270-009-9698-0)

Fahey JL, Nathans D & Rairigh D 1957 Effect of L-arginine on elevated blood ammonia levels in man. *American Journal of Medicine* **23** 860–869. (https://doi.org/10.1016/0002-9343(57)90295-4)

Gupta S, Fenves AZ & Hootkins R 2016 The role of RRT in hyperammonemic patients. *Clinical Journal of the American Society of Nephrology* **11** 1872–1878. (https://doi.org/10.2215/CJN.01320216)

Haj M & Rockey DC 2020 Ammonia levels do not guide clinical management of patients with hepatic encephalopathy caused by cirrhosis. *American Journal of Gastroenterology* **115** 723–728. (https://doi.org/10.14309/ajg.0000000000000343)

Hanai T, Shiraki M, Imai K, Suetugu A, Takai K & Shimizu M 2020 Usefulness of carnitine supplementation for the complications of liver cirrhosis. *Nutrients* **12** 1915. (https://doi.org/10.3390/nu12071915)

Harper HA & Najarian JS 1956 A clinical study of the effect of arginine on blood ammonia. *American Journal of Medicine* **21** 832–842. (https://doi.org/10.1016/0002-9343(56)90097-3)

Hofland J, Kaltsas G & De Herder WW 2020 Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. *Endocrine Reviews* **41** 371–403. (https://doi.org/10.1210/endrev/bnz004)

Hudson M & Schuchmann M 2019 Long-term management of hepatic encephalopathy with lactulose and/or rifaximin: a review of the evidence. *European Journal of Gastroenterology and Hepatology* **31** 434–450. (https://doi.org/10.1097/MEG.0000000000001311)

Kim HJ & Lee HW 2013 Important predictor of mortality in patients with end-stage liver disease. *Clinical and Molecular Hepatology* **19** 105–115. (https://doi.org/10.3350/cmh.2013.19.2.105)

Klöppel G, Couvelard A, Hruban R, Klimstra D, Komminoth P, Osamura R, Perren A & Rindi G 2017 *WHO Classification of Tumours of Endocrine Organs*. Lyon, France: World Health Organization.

Monardo AS, Marcus AJ & Berry AC 2020 Pancreatic neuroendocrine tumor-induced hyperammonemic encephalopathy in the absence of hepatic involvement. *ACG Case Reports Journal* **7** e00425. (https://doi.org/10.14309/crj.0000000000000425)

Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA & WHO Classification of Tumours Editorial Board 2020 The 2019 WHO classification of tumours of the digestive system. *Histopathology* **76** 182–188. (https://doi.org/10.1111/his.13975)

Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, Arroliga AC & Mullen KD 2003 Correlation between ammonia levels and the severity of hepatic encephalopathy. *American Journal of Medicine* **114** 188–193. (https://doi.org/10.1016/s0002-9343(02)01477-8)

Pande A, Philips CA & Patidar Y 2017 Successful management of refractory hyperammonemia in metastatic neuroendocrine tumor. *International Journal of Advances in Medicine* **3** 431–434. (https://doi.org/10.18203/2349-3933.ijam20161105)

Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, Knigge U, Salazar R, Pape UF, *et al.* 2016 Enets consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* **103** 172–185. (https://doi.org/10.1159/000443167)

Peng Y, Qi X & Guo X 2016 Child-Pugh versus score for the assessment of prognosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. *Medicine* **95** e2877. (https://doi.org/10.1097/MD.0000000000002877)

Perren A, Couvelard A, Scoazec JY, Costa F, Borbath I, Delle Fave G, Gorbounova V, Gross D, Grossma A, Jense RT, *et al.* 2017 Enets consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. *Neuroendocrinology* **105** 196–200. (https://doi.org/10.1159/000457956)

Refardt J, Zandee WT, Brabander T, Feelders RA, Franssen GJH, Hofland LJ, Christ E, De Herder WW & Hofland J 2020 Inferior outcome of neuroendocrine tumor patients negative on somatostatin receptor imaging. *Endocrine-Related Cancer* **27** 615–624. (https://doi.org/10.1530/ERC-20-0340)

Riihimäki M, Hemminki A, Sundquist K, Sundquist J & Hemminki K 2016 The epidemiology of metastases in neuroendocrine tumors. *International Journal of Cancer* **139** 2679–2686. (https://doi.org/10.1002/ijc.30400)

Rose CF, Amodio P, Bajaj JS, Dhiman RK, Montagnese S, Taylor-Robinson SD, Vilstrup H & Jalan R 2020 Hepatic encephalopathy: novel insights into classification, pathophysiology and therapy. *Journal of Hepatology* **73** 1526–1547. (https://doi.org/10.1016/j.jhep.2020.07.013)

Sakusic A, Sabov M, Mccambridge AJ, Rabinstein AA, Singh TD, Mukesh K, Kashani KB, Cook D & Gajic O 2018 Features of adult hyperammonemia not due to liver failure in the ICU. *Critical Care Medicine* **46** e897–e903. (https://doi.org/10.1097/CCM.0000000000003278)

Shalimar, Rout G, Kumar R, Singh AD, Sharma S, Gunjan D, Saraya A, Nayak B & Acharya SK 2020 Persistent or incident hyperammonemia is associated with poor outcomes in acute decompensation and acute-on-chronic liver failure. *JGH Open* **4** 843–850. (https://doi.org/10.1002/jgh3.12314)

Shea YF, Chiu WY, Mok MY, Hung IF & Yau CC 2013 Sunitinib-induced hyperammonaemia in a patient with pancreatic neuroendocrine tumour. *Journal of Clinical Pharmacy and Therapeutics* **38** 327–329. (https://doi.org/10.1111/jcpt.12054)

Simonetto DA, Liu M & Kamath PS 2019 Portal hypertension and related complications: diagnosis and management. *Mayo Clinic Proceedings* **94** 714–726. (https://doi.org/10.1016/j.mayocp.2018.12.020)

Stepien KM, Geberhiwot T, Hendriksz CJ & Treacy EP 2019 Challenges in diagnosing and managing adult patients with urea cycle disorders. *Journal of Inherited Metabolic Disease* **42** 1136–1146. (https://doi.org/10.1002/jimd.12096)

Stergachis AB, Mogensen KM, Khoury CC, Lin AP, Peake RW, Baker JJ, Barkoudah E, Sahai I, Sweetser DA, Berry GT, *et al.* 2020 A retrospective study of adult patients with noncirrhotic hyperammonemia. *Journal of Inherited Metabolic Disease* **43** 1165–1172. (https://doi.org/10.1002/jimd.12292)

Turken O, Basekim C, Haholu A, Karagoz B, Bilgi O, Ozgun A, Kucukardali Y, Narin Y, Yazgan Y & Kandemir EG 2009 Hyperammonemic encephalopathy in a patient with primary hepatic neuroendocrine carcinoma. *Medical Oncology* **26** 309–313. (https://doi.org/10.1007/s12032-008-9121-8)

Vandamme T, Kunnen J & Simoens M 2012 Hyperammonemic encephalopathy in diffuse liver metastasis: is this the end stage? *Gastroenterology* **143** e9–e10. (https://doi.org/10.1053/j.gastro.2011.12.009)

Willson KJ, Nott LM, Broadbridge VT & Price T 2013 Hepatic encephalopathy associated with cancer or anticancer therapy. *Gastrointestinal Cancer Research* **6** 11–16.

Zandee WT, Kamp K, Van Adrichem RC, Feelders RA & De Herder WW 2017 Effect of hormone secretory syndromes on neuroendocrine tumor prognosis. *Endocrine-Related Cancer* **24** R261–R274. (https://doi.org/10.1530/ERC-16-0538)

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