Hyperammonemia is an underdiagnosed prognostic complication in neuroendocrine neoplasm patients with liver metastases

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Background

- Neuroendocrine neoplasms (NEN) are rare usually slow-progressing tumors, often presenting with extensive liver metastases.
- Hyperammonemia due to insufficient hepatic clearance has been described in a few NEN cases
- No systematic evaluation of risk factors and outcomes of NEN-associated hyperammonemia exists so far.

Aim

- To describe the first cohort of NEN patients developing hyperammonemia
- To assess clinical characteristics and outcome of NEN patients
- To define prognostic factors in order to guide evaluation and management of these patients

Methods

Single center retrospective review of NEN patients developing hyperammonemia from the years 2000-2020

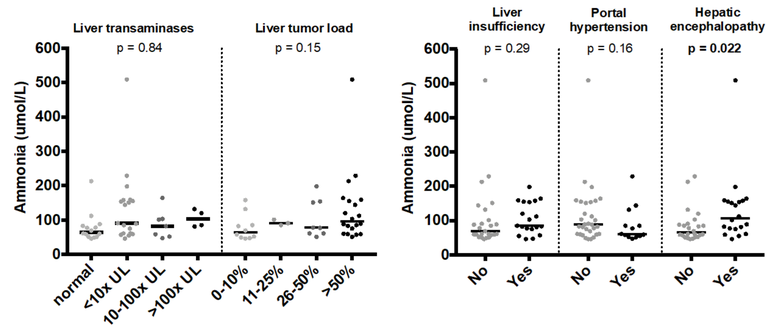
Results

Characteristics of the 44 NEN patients with hyperammonemia

Sex, male	28 (64)	n (%)
Age, years	65 (54-70)	median (IQR)
BMI, kg/m²	21.8 (18.5-25.6)	median (IQR)
NEN origin		
Gastro-duodenal	3 (6.7)	n (%)
Midgut	14 (31)	n (%)
Hindgut	0	n (%)
Pancreas	16 (35,6)	n (%)
Lung	3 (6.7)	n (%)
Unknown	8 (17.8)	n (%)
Grade		
NET grade 1	11 (25)	n (%)
NET grade 2	20 (45.5)	n (%)
NET grade 3	1 (2)	n (%)
NEC	2 (4.5)	
Unknown	10 (23)	n (%)
Metastases		
Liver	44 (100)	n (%)
Non-mesenteric lymph nodes	17 (39)	n (%)
Mesenteric lymph nodes	15 (34)	n (%)
Lung	5 (11)	n (%)
Bone	6 (14)	n (%)
Hormonal syndrome	19 (43)	n (%)
Laboratory		
Ammonia, maximum level (µmol/L)	83 (59-141)	median (IQR)
Chromogranin A, ng/L	3724 (293-56468)	median (IQR)
Follow up time, months	55 (31-105)	median (IQR)
Time diagnosis HA to death or loss of follow up, months	1.7 (0.1-22.7)	median (IQR)
Patients died	37 (84%)	n (%)

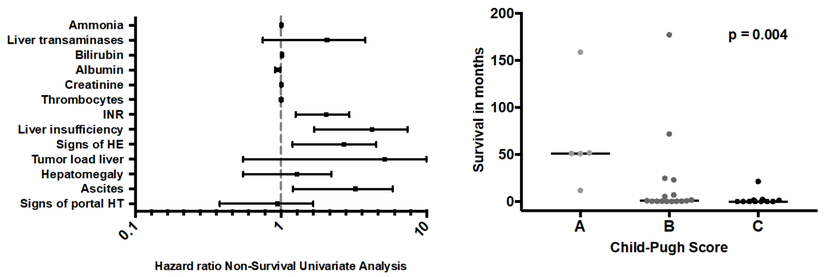
The main reasons for ammonia measurement were encephalopathy in 31%, general deterioration in 30% and post-interventional evaluation or evaluation due to acute triggers (e.g. sepsis) in 16%, respectively. The suspected underlying cause for hyperammonemia was tumor progression in the majority of patients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

Figure 1: Plasma ammonia levels in NEN patients according to different risk factors



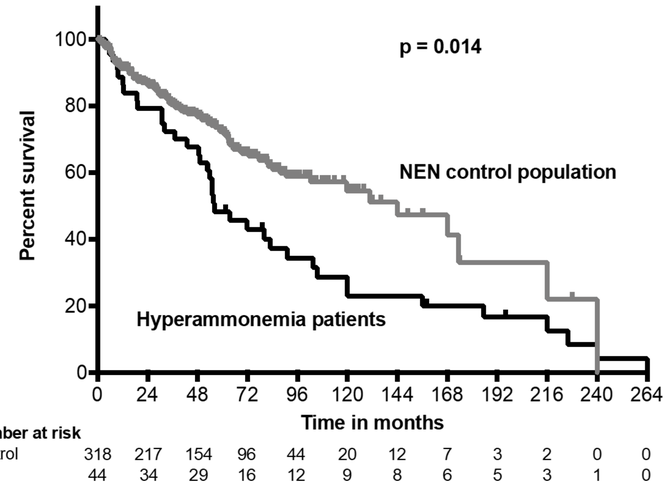
Data is shown as median with individual data points. The p-values depict the difference within the groups, bold writing indicating significance. UL = upper limit of normal

Figure 2: Prognostic factors associated with hyperammonemia in NEN patients



A) Forest plot showing the effect of the pre-defined risk factors on mortality risk according to the univariable regression analysis. The black squares reflect the hazard ratio, while the whiskers indicate the lower and upper limits of the 95% confidence interval. HE = encephalopathy; HT = Hypertension; INR = international normalized ratio of prothrombin time; B) Survival in relation to Child-Pugh scores. Data is shown as median with individual data points. The p-value depicts the difference within the groups, bold writing indicating significance.

Figure 3: Kaplan Meier analysis showing overall survival from time of diagnosis of NEN patients developing hyperammonemia, compared to a control population of stage IV NEN patients.



p-Value indicates difference in survival (Log Rank Test). Control = NEN control population, HA = hyperammonemia; NEN = neuroendocrine neoplasm;

Of the treated 18 patients, 83% received lactulose orally, in seven cases in combination with rifaximin.

Additional supportive medication with L-arginine and dexamethasone was given in three cases.

Two patients received SIRT with 90Yttrium-labelled microspheres.

PRRT with 177Lu-DOTATATE to lower the liver burden was given in one patient, while portal hypertension was treated by portal vein stent in another patient.

Conclusion

1. **Hyperammonemia comprises an underdiagnosed complication of NEN liver metastases and is associated with worse outcome.**
2. **Assessment of signs of encephalopathy and the Child-Pugh score could be helpful in selecting NEN patients for whom ammonia levels should be measured.**

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