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Original Article

Quantitative CT-scan to evaluate cerebral edema secondary to hyperammonemia in ICU: A proof-of-concept study

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ABSTRACT

Background: Hyperammonemia is a critical condition sometimes associated with severe neurological symptoms and cerebral edema. Quantitative CT-scan may help directly assess the impact of ammonia levels on brain structures, offering the potential to improve patient management.

Methods: We conducted a retrospective, proof-of-concept study on patients admitted to the ICU with ammonemia >100 μmol/L who underwent one or more brain CT-scans. Weight, volume, and specific gravity of brain structures were assessed using BrainView software (Institut National des Télécommunications).

Results: Seven patients and 14 CT-scans were evaluated. Ammonia levels were positively correlated with whole brain weight (ρ = 0.64 and P=0.014) and volume (ρ = 0.64 and P=0.014), but no association was found with specific gravity. Similar results were found for hemispheres (ρ = 0.62, P=0.018 for weight and ρ = 0.62, P=0.019 for volume), whereas no significant correlations were noted for cerebellum, brainstem, and cerebrospinal fluid. No significant correlation could be found between variations in weight, volume, specific gravity, and variations in ammonemia.

Conclusions: Our findings suggest that total brain weight and volume correlate with ammonia levels, with varying impacts on different brain structures, yet our study could not find any significant association between the variations of ammonemia and the variations of CT measures. Quantitative CT scan could be of interest for evaluating cerebral edema in patients with severe hyperammonemia, paving the way for more targeted therapeutic interventions.

Introduction

Hepatic encephalopathy can result from acute or chronic liver failure and/or portosystemic shunts, but also inborn errors of metabolism, or drug side effects, with liver cirrhosis being the leading cause.[1–4] Hyperammonemia is at the center of its pathophysiology, even if its precise effect on the brain is still debated.[3,5] Indeed, hyperammonemia is responsible for cerebral edema, but whether this edema is responsible for the clinical symptoms outside herniation is debated.[5] In neurocritical care, computed tomography (CT) is routinely used to investigate neurological deterioration and can reveal cerebral edema in acute settings. However, conventional CT interpretation is primarily qualitative and may be less sensitive to mild or early diffuse edema, and changes may be difficult to quantify and track over time. MRI with diffusion weighted sequences and diffusion tensor imaging can provide more sensitive tissue-level information, but is often impractical in unstable intensive

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care unit (ICU) patients. Quantitative CT analysis could therefore offer objective metrics to monitor brain changes and assess the cerebral impact of ammonia fluctuations.[5] Importantly, several ammonia-lowering strategies such as lactulose, rifaximin, renal replacement therapy, and more recently ammonia scavengers[6] can reduce plasma ammonia. Yet, clinicians lack a practical quantitative marker to assess whether lowering ammonemia induces meaningful changes in cerebral edema. In ICU patients, neurological examination is often confounded by sedation and critical illness, and routine CT interpretation remains largely qualitative and may be insensitive to subtle changes over time. A readily available quantitative imaging marker could therefore support treatment monitoring, help interpret ammonia trajectories in relation to brain edema, and serve as a surrogate endpoint in future interventional studies. Quantitative CT analysis provides objective measurements (weight, volume, and specific gravity) of brain compartments and could complement routine imaging by enabling longitudinal tracking of edema dynamics in response to ammonia-lowering therapies.

Quantitative CT-scan is a technique that is easily available, even if it is not commonly used in the clinical routine of hepatic encephalopathy, except to rule out differential diagnoses such as intracranial bleeding.[7] It enables the measurement of the weight, volume, and specific gravity (defined as the weight of the volume of an object) of the different cerebral structures. It has previously been used in patients with liver disease with or without hepatic encephalopathy.[7–9] Unfortunately, the data were not correlated to ammonemia levels. The purpose of this study was to evaluate the capacity of quantitative CT-scan to measure modification of cerebral edema secondary to ammonemia variations.

Methods

Study Design

This is a retrospective, monocentric study on patients admitted to the medical neuro-ICU of the Pitié-Salpêtrière University hospital, a tertiary care center in Paris, France, between January 2010 and December 2024.

Inclusion Criteria

The inclusion criteria were defined as follows: (1) hyperammonemia >100 μmol/L[10]; (2) CT-scan with contiguous slices without interspaces; (3) no previous neurological history; and (4) no history of contrast medium injection within the last 2 weeks before CT scanning. The following data were collected: age, sex, etiology of hyperammonemia, and ammonemia value at the day of each CT-scan.

Ethics

Data were acquired in routine care. The retrospective use of routine care data for research purposes was authorized through the non-opposition procedure, which waived the requirement for ethics committee approval under French law. Anonymized data were managed in accordance with the STROBE checklist for observational studies (https://www.strobe-statement.org/checklists/).

CT-scan Analysis

All CT-scans were acquired on the same Siemens scanner (Germany) that is monthly calibrated by manufacturer technicians. Additionally, the absence of drifts is assessed weekly with an internal routine procedure. CT-scan images consisted of 1.25 mm-thick non-overlapping, contiguous slices, yielding an approximate number of 200 slices per patient. Quantitative brain CT analysis was performed using the BrainView software (Institut National des Télécommunications).[11] Briefly, BrainView is designed to analyze DICOM images acquired from brain CT scans by performing automatic segmentation, excluding extracranial compartments on each slice. Interactive slice-by-slice segmentation allows the delineation of different anatomical regions. The software, previously validated and extensively used, provides weight, volume, and specific gravity (see Degos et al.[12] for detailed formulas estimating the measurements and references[11,13] for previous validations of the software). Specific gravity corresponds to the weight of the compartment (in grams) divided by the volume of the compartment in mL, with a normative value of 1.0331 ± 0.0012 in healthy parenchyma.[14] These measurements were estimated for the whole brain and each individual region (right and left hemispheres, brainstem, cerebellum, and intraventricular cerebrospinal fluid [CSF]). We defined the total brain as the sum of hemispheres, brainstem, and cerebellum, excluding CSF. Measurements of the effect of variation in ammonemia were made in patients who had more than one CT-scan: the difference between the first and second measures of ammonemia, and between the first and second CT-scan measures of weight, volume, and specific gravity of brain structures were made. One patient had a third CT-scan assessment, and the differences between the second and third CT-scan assessments were also calculated.

Statistical Analysis

Results are expressed as counts and frequencies for categorical variables and medians (interquartile range [IQR]) for quantitative variables. Correlations were performed using Spearman correlation. All tests were two-sided, and a P value <0.05 was considered statistically significant. Analyses were performed using R Statistical Software version 4.4.2 (R Project for statistical computing, Vienna, Austria).

Results

A total of seven patients who had ammonemia above 100 μmol/L and underwent one or more brain CT scans during their ICU stay were included. There was no patient with hyperammonemia above 100 μmol/L who did not benefit from a CT scan and/or was excluded during the considered period. Baseline characteristics of the patients, including hyperammonemia etiologies, biological and clinical data at the time of the CT-scan are shown in Table 1, and detailed data per patient are shown in Supplementary Table S1. Patients had a median age of 45 (IQR: 31–48) years, four (57.1%) patients were female. Three (42.8%) patients had hyperammonemia due to inborn errors of metabolism (ornithine carbamoyltransferase deficiency), two (28.6%) due to bypass surgery (with possible metabolic dysfunction-associated steatotic liver disease, not previously di-

Table 1
Baseline characteristics of the patients (n = 7).

Characteristics	Data
Age (years)	45 (31–48)
Sex (male/female)	3/4
Etiology of hyperammonemia	
Inborn error of metabolism	3 (42.9)
Bypass surgery (with not previously diagnosed MASLD)	2 (28.6)
Ureterosigmoidostomy	1 (14.3)
Acute alcoholic hepatitis	1 (14.3)
Number of CT-scan assessments	14
1	1 (14.3)
2	5 (71.4)
3	1 (14.3)
Per CT-scan assessments (n = 14)	
Clinical data	
Mean arterial pressure (mmHg)	79 (69–97)
Temperature (°C)	37.0 (36.3–37.6)
SpO_2 (%)	98 (98–99)
Glasgow coma scale	3 (3–9)
FOUR score	9 (8–13)
Richmond agitation-sedation scale	−5 (−5 to −2)
Treatment for hyperammonemia*	
Renal-replacement therapy	3 (21.4)
Sodium benzoate	2 (14.2)
Sodium phenylbutyrate	1 (7.1)
Arginine	2 (14.2)
Levocarnyl	1 (7.1)
Lactulose	1 (7.1)
Biological data	
Ammonemia (μmol/L)	184 (136–258)
ALT (UI/L)	57 (45–329)
AST (UI/L)	67 (34–1477)
Bilirubin (μmol/L)	91 (22–171)
Creatinine (μmol/L)	96 (77–153)
Potassium (mmol/L)	4.1 (3.7–4.4)
Sodium (mmol/L)	139.5 (136.2–141.5)
Leukocytes (G/L)	13.1 (10.3–15.1)
Platelets (G/L)	140 (103–169)
Hemoglobin (g/dL)	9.2 (8.3–10.9)
Prothrombin ratio	88 (81–93)

Data are presented as n(%) or median (interquartile range).
ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CT: Computed tomography; FOUR: Full Outline of UnResponsiveness; MASLD: Metabolic dysfunction-associated steatotic liver disease; SpO_2: Peripheral oxygen saturation.
* Some patients can have several drugs.

agnosed), one (14.2%) due to acute alcoholic hepatitis, and one (14.2%) due to ureterosigmoidostomy. All the patients were mechanically ventilated. One patient (14.2%) had a single CT-scan, five (71.4%) patients had two CT-scans, and one (14.2%) patient had three CT scans, for a total of 14 CT-scan assessments. The median delay between ICU admission and CT-scan/ammonemia assessment was 1.5 (IQR: −1 to 4) days, and the median time interval between paired CT-scans for patients with repeated imaging was 11 (IQR: 4–22) days. The median ammonia level was 194 (IQR: 181–251) μmol/L at the first CT scan and 184 (IQR: 136–258) μmol/L for all CT-scans. In the follow-up, four out of the seven patients (57.1%) died, whereas the three others (42.8%) improved.

The median brain weight was 1297.8 (IQR: 1182.0–1359.4) g (Table 2) and was positively correlated with ammonemia (ρ = 0.64, P=0.014), as was volume (ρ = 0.64, P=0.014) but not specific gravity (ρ = 0.29, P=0.318, Figure 1). Very similar results were found for the hemispheres, with a correlation trend between ammonemia and weight (ρ = 0.62, P=0.018) and volume (ρ = 0.62, P=0.019). No correlations were found for cerebellum, brainstem, and CSF (Supplementary Figure S1).

Measurements of the effect of variation in ammonemia were made in patients who had more than one CT-scan, resulting in a total of seven "delta" measures for the entire cohort. The variation in ammonemia between two CT-scan assessments was −158 (IQR: −201 to 10) μmol/L. The median variation in brain weight was 29.45 (IQR: −1.55 to 49.53) g, in volume 23.41 (IQR: −1.70 to 46.56) mL and in specific gravity 7.671 (IQR: −28.9 to 26.6) × 10^{-4}g/mL (Figure 1), but no significant correlations were found between the variations in ammonemia levels and the variation of CT measures (Supplementary Figure S2).

According to the normative value of 1.0331 (IQR: 1.0307–1.0355) (mean ± 2 standard deviations) in healthy individuals for whole-brain specific gravity,[14] we found four (28.6%) CT-scans with normal specific gravity, six (42.9%) with low specific gravity, and four (28.6%) with high specific gravity. Of the four (57.1%) patients who died, one had normal whole brain specific gravity on one CT-scan assessment, one had low specific gravity on two CT-scan assessments, one had normal specific gravity on two CT-scan assessments and high specific gravity on one CT-scan assessment, and one had high specific gravity on two CT-scan assessments.

Discussion

In this proof-of-concept study, we evaluated 14 CT scans from seven ICU patients with hyperammonemia. We found that total brain weight and volume were associated with ammonia levels, but that different brain regions were not equally affected. We found no significant correlations between the variations in ammonemia and the variation of brain structures measures. The kinetics of hyperammonemia-related brain edema are time-dependent and potentially biphasic; therefore, heterogeneity in imaging timing relative to ammonia peak and therapeutic interventions may have attenuated correlations, particularly for specific gravity. Even when ammonemia decreases, changes in water content and protein extravasation may follow a delayed trajectory, which may uncouple volume/weight from specific gravity.

Acute hyperammonemia rapidly induces cerebral glutamine accumulation. In rat models, hyperammonemia is associated with an increase in cerebral glutamine levels and a decrease in specific gravity, showing an increase in brain water content and thus the presence of vasogenic edema in the first hour.[15] Our data did not show a significant change in specific gravity in our small number of patients, but we did confirm swelling of all brain structures with weight and volume increase. The fact that the CT-scans were performed >24 h after the onset of the disease may contribute to these discrepancies in the change in specific gravity. In fact, animal models of traumatic brain injury have shown a biphasic development of brain edema, with minimal specific gravity on day 2, followed by an increase to normal levels on day 4, and then a further decrease to its lower level on day 6.[16]

The correlations between weight/volume and ammonemia were not equally distributed over the different brain regions as previously described in animal models.[17] In addition, variations in ammonemia were correlated with variations in quantitative CT-scan measurements only in the hemispheres. The density of neurons and thus the importance of extracellular space could partially explain those results. Another explanation might be

Table 2
Quantitative CT-based measurements of brain regional weight, volume, and specific gravity of the brain, hemispheres, cerebellum, brainstem, and CSF.

Brain regions	Weight (g)	Volume (mL)	Specific gravity (g/mL)	Δ Weight (g)	Δ Volume (mL)	Δ Specific gravity (10^{-4} g/mL)
Brain	1297.8 (1182.0–1359.4)	1253.1 (1149.5–1324.1)	1.032 (1.029–1.036)	29.45 (−1.55 to 49.53)	23.41 (−1.70 to 46.56)	7.7 (−28.9 to 26.6)
Hemispheres	1116.5 (1000.5–1165.8)	1081.7 (969.2–1136.1)	1.031 (1.029–1.035)	30.06 (13.23–41.85)	24.74 (12.75–44.07)	5.2 (−27.5 to 26.7)
Right hemisphere	553.5 (504.7–590.2)	536.0 (489.0–572.7)	1.031 (1.028–1.036)	15.20 (2.00–20.95)	15.01 (2.03–20.92)	2.0 (−28.2 to 21.7)
Left hemisphere	563.1 (495.8–577.0)	545.6 (480.2–561.5)	1.031 (1.029–1.035)	13.19 (10.91–21.75)	12.28 (9.45–22.34)	8.4 (−26.8 to 28.7)
Cerebellum	141.7 (126.4–174.5)	136.9 (121.7–167.8)	1.037 (1.031–1.041)	0.02 (−26.73 to 6.10)	−0.04 (−26.23 to 5.44)	5.4 (−29.8 to 32.7)
Brainstem	29.0 (25.5–46.8)	28.3 (24.8–45.7)	1.026 (1.023–1.029)	−1.49 (−3.57 to 1.69)	−1.38 (−3.50 to 1.66)	20.6 (−29.5 to 26.3)
CSF	21.8 (12.4–36.4)	21.5 (12.2–36.2)	1.012 (1.011–1.014)	0.14 (−3.40 to 3.69)	0.13 (−3.35 to 3.66)	−3.6 (−29.7 to 3.6)

Data are presented as median (interquartile range).
CSF: Cerebrospinal fluid; CT: Computed tomography.

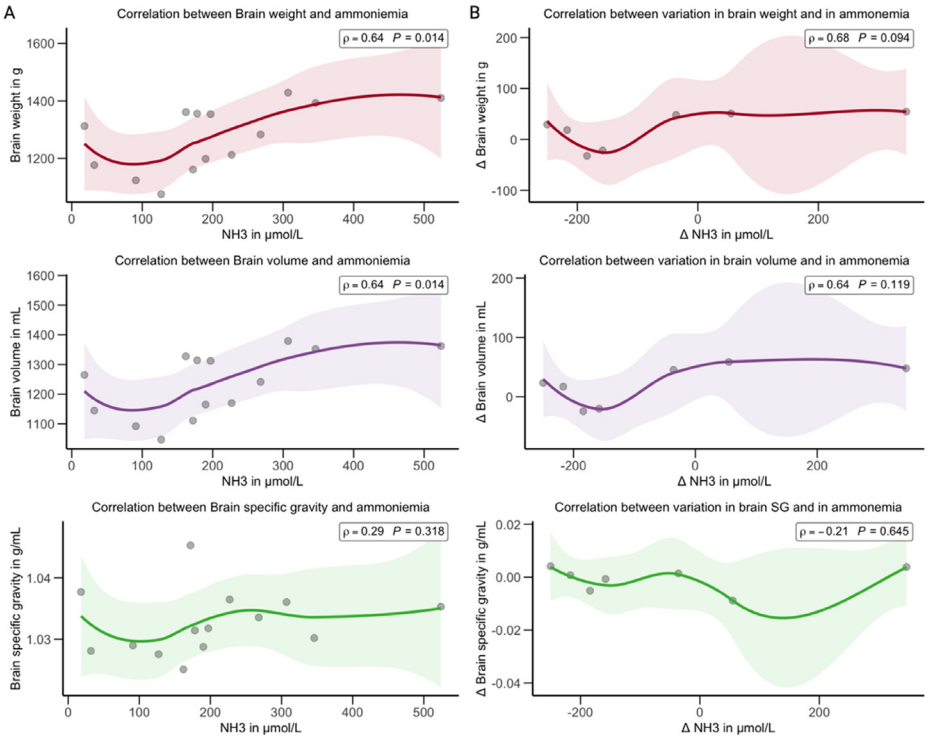

Figure 1. Correlations between ammonemia and brain weight, volume, and specific gravity, and correlation between the variation of measures and ammonemia levels. A: Correlations between ammonemia and brain weight, volume, and specific gravity. B: Correlations between the variation of ammonemia and the variation of brain weight, volume, and specific gravity. NH3: Ammonia.

the delay in the resolution of cytotoxic/vasogenic edema mechanisms after ammonemia modification. The decrease in ammonemia levels induced volumetric changes, but non-significant changes in specific gravity. Hyperammonemia induces astrocytic glutamine accumulation and cytotoxic swelling; loss of osmolytes such as taurine or myo-inositol, and water transfer through aquaporin 4–NKCC1 can lag during recovery, uncoupling volume from specific gravity.[18] In addition, transition to vasogenic edema and blood–brain barrier permeability may allow protein extravasation and raise specific gravity even after normalization of water content (since specific gravity can be biased by protein content).[19] In support of this hypothesis in liver failure contexts, a prior quantitative CT study using BrainView in acutely decompensated cirrhosis reported altered CSF specific gravity and differences according to acute liver failure status,[7] consistent with blood–brain barrier involvement. Importantly, that study did not find regional differences in parenchymal specific gravity by acute liver failure or encephalopathy status. Since liver failure accounted for only one patient in our series and etiologies were heterogeneous, these findings cannot be directly extrapolated to our cohort. It is also possible that the limited number of patients preclude to detect differences in other brain regions due to a lack of statistical power.

The mortality was rather high in our patients, but their numbers are too limited to draw any conclusion. Overall, three out of four patients who died had normal and/or high whole-brain specific gravity. This could suggest a tendency of higher mortality with normal and/or high whole brain specific gravity, although our data is underpowered to allow proper correlation computations. Indeed, our preliminary study is limited by its retrospective design and the inclusion of a small number of patients. Not all patients had the same number of scans, and not all scans were performed at the same time points relative to the beginning of hyperammonemia management. Etiologies of hyperammonemia were heterogeneous in this proof-of-concept cohort, which can influence edema mechanisms and CT-based measurements. Acute liver-related hyperammonemia may combine ammonia toxicity with systemic inflammation and blood–brain barrier dysfunction, potentially increasing vasogenic components, whereas urea cycle disorders may produce rapid ammonia changes with predominant cytotoxic astrocytic swelling. Ureterosigmoidostomy and post-bypass etiologies may involve intermittent ammonia peaks and additional metabolic or catabolic factors. These differences could uncouple volume/weight changes from specific gravity and contribute to variability between patients and brain regions. Our study

is underpowered to perform stratified or multivariable analyses; larger prospective studies are needed to evaluate whether quantitative CT metrics change differently according to hyperammonemia etiology.

Regarding clinical implications, quantitative CT could offer objective markers of brain swelling to complement routine CT interpretation, especially when neurological examination is confounded by sedation. In practice, repeating CT may be most informative in cases of severe or rapidly changing hyperammonemia, lack of neurological improvement after ammonia lowering, or clinical concern for intracranial hypertension. These potential use cases should be evaluated prospectively, balancing expected benefit against performing CT-scans in potentially unstable patients and radiation exposure. In future multicenter studies, this approach could be integrated through standardized CT acquisition parameters and centralized (and/or automated) quantitative analysis, enabling harmonized longitudinal measurements across sites and evaluation of clinically meaningful endpoints.

Conclusion

In conclusion, our study suggests that quantitative CT-scan might be a valuable tool to study cerebral edema in patients with hyperammonemia event if they are severe and hospitalized in the ICU, to help to better understand the pathophysiology.

CRediT Authorship Contribution Statement

Lina Jeantin: Writing – review & editing, Formal analysis, Data curation. **Mathilde Piljan:** Writing – review & editing, Investigation, Data curation. **Damien Galanaud:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Clémence Marois:** Writing – review & editing, Formal analysis, Data curation. **Charlotte Bouzbib:** Writing – review & editing, Data curation. **Louis Puybasset:** Writing – review & editing, Software, Methodology, Formal analysis. **Dominique Thabut:** Writing – review & editing, Validation, Supervision, Conceptualization. **Nicolas Weiss:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

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Ethics Statement

The data used in this study were obtained during routine clinical care. Under French law, the retrospective use of routinely collected clinical data for research purposes is permitted through the non-opposition procedure. Consequently, formal approval from an ethics committee and informed consent were not required.

Conflict of Interest

Given his role as editorial board member, Nicolas Weiss had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor. The other authors have nothing to disclosure.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2026.01.004.

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