PLASMATIC OSMOLALITY AND HEPATIC ENCEPHALOPATHY: A NEW PLAYER ON THE FIELD?

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EDITORIAL

The blood-brain barrier (BBB), the interface between the blood and the brain, is a highly regulated assembly of cells. As a result, osmotic gradients exist across the BBB which dictates the direction of water diffusion. Cerebral oedema is a result of brain hypertonicity and increasing non-permeable molecules in the blood can help draw water from the brain. However, this will theoretically only occur when the BBB is intact, non-impaired. Clinically, identifying BBB breakdown remains very challenging. Plasmatic osmolarity is defined as the concentration of osmotic compounds per litre of plasma, expressed as milliosmoles per litre (mOsm/L). Whereas plasmatic osmolality (POosm) corresponds to the concentration of osmotic compounds per kg of plasmatic water, quantified as milliosmoles per kilogram (mOsm/kg). Even though osmolarity vs osmolality in clinical practice is insignificant, Posm is most commonly used and is calculated using the formula POsm (mOsm/kg) = (Na+ (mmol/L) × 2) + glucose (mmol/L) + urea (mmol/L). POsm corresponds to the sum of all osmotic compounds (active ones which draw water across membranes and inactive ones which do not influence transmembrane water movement). Under physiological conditions, normal plasma POsm lies between 280 and 295 mmol/kg. Inactive compounds are represented mainly by urea, whereas active compounds primarily include Na+ , K+ and glucose. Thus, it is possible to calculate active POsm which takes into account only the active compounds: POsmact (mOsm/kg) = (Na+ (mmol/L) × 2) + glucose (mmol/L) which ranges between 275 and 290 mmol/kg under healthy conditions. Ultimately, the most accurate and precise method to measure serum osmolality is by determining the cryoscopic delta at plasmatic congelation point, or by measuring the plasmatic resistivity (POsmmes). Both techniques consider all plasmatic osmotic compounds; active, inactive; beyond those measured by clinical routine biochemistry. Osmotic gap (OsmGap) is calculated by POsmmes − POsm and is below 10 mOsm/kg during physiological conditions. An OsmGap higher than 10 mOsm/kg indicates the presence of osmoles in the plasma that are not measured and found in electrolyte blood test; the main causes are accumulation of alcohols (ethanol, methanol, ethylene-glycol), sugars (mannitol, sorbitol), lipids and proteins.

In the brain, as in other organs, osmolality is closely regulated. Thus, chronic changes in osmolality are frequently well tolerated. However, on the contrary, acute variation in osmolality is less well tolerated and frequently symptomatic since compensatory mechanisms have insufficient time to initiate. This explains why the acute onset of hyponatraemia or hyperammonaemia influences the clinical presentation and management of the patient. Thus, in hepatic encephalopathy (HE), a rapid increase in blood ammonia as observed in acute liver failure, leads to the swelling of astrocytes where detoxification of ammonia via glutamine synthetase generates glutamine in the cytosol. In turn, hypertonicity arises since the cell is unable to compensate and rapidly extrude other active osmoles.1 Brain oedema persists and intracranial hypertension develops. In cirrhosis, where a more progressive increase in ammonia develops, active osmoles (including myoinositol and taurine), are extruded outside the astrocyte and the brain. As a result, low-grade oedema develops which does not lead to intracranial hypertension.2,3 Extrusion of active osmoles have been described to counteract brain swelling in several other acute brain injuries.4

In this issue of the journal, Liotta et al 5 present an original study suggesting that plasmatic hyperosmolality could be implicated in the pathophysiology of HE. In this study, the authors retrospectively included patients with either acute (ALF) or acute-on-chronic liver failure (ACLF) with overt HE admitted to the ICU that underwent determination of POsmmes, serial Glasgow Coma Scale (GCS) evaluations and CT scans within the first 24 hours. Patients with focal brain lesions, those that received hyperosmolar therapy (mannitol, hypertonic saline), albumin or needed renal replacement therapy prior to POsmmes determination or GCS assessment, were excluded. Patients underwent hourly neurological examinations, including GCS assessments and repeated cerebral CT-scans. The CT scan allowed them to determine the specific gravity of cerebrospinal fluid (CSF) via attenuation using a quantitative measurement software which was previously described by the same group.6

Among 140 patients with liver failure and overt HE, 73 patients (52%) (39 ALF, 34 ACLF) were included, of whom 28 (38%) had grade 4 coma. Sixty-seven patients had a brain CT-scan. Blood ammonia levels were at 182.5 µg/dL [108.8-305.0]. The authors found that POsmmes at admission was elevated (303.9 ± 15.4 mOsm/kg) despite normal serum sodium levels (136.6 ± 6.3 mEq/L) and that the osmolality was correlated with GCS ($r=-0.49$, $P < .001$). CSF attenuation was also found to be correlated with both POsmmes ($r=-0.37$, $P = .002$) and GCS ($r = 0.27$, $P = .027$). In adjusted multivariate models, increased osmolality was independently associated with more severe HE (ordinal adjusted OR 0.26 [95% CI 0.22, 0.31] for GCS per standard deviation increase in osmolality) and lower CSF attenuation (linear adjusted $\beta = -0.039$ [95% CI − 0.069, −0.009] Hounsfield unit per 1mOsm/kg). Taken together these results suggest that plasma of ALF/ACLF patients contains osmotic compounds that are not accounted for in clinical routine blood biochemistry. With no change in serum sodium levels, POsmmes is higher than POsm and indeed, serum OsmGap was 9.1 (± 8.2 SD) with some patients who had an OsmGap above 10 mOsm/kg.

In the neuro-ICU setting, the use of osmotic agents as salvage therapy has been extensively studied in traumatic brain injury, subarachnoid haemorrhage and stroke. Classically, the administration of those agents, mannitol or hypertonic saline (30% saline), is in attempt to alleviate brain oedema and hence prevent fatal brain herniation.7 Hypertonic saline administration increases POsm while mannitol increases only POsmmes. Therefore, most intensivists associate increase POsm with a decrease in brain water content and therefore the results presented by Liotta et al are unforeseen. However, using quantitative cerebral CT-scan, Lescot et al 8 could demonstrate a differential effect of the osmotic agents in traumatic brain injury according to whether the brain tissue was contused or not. These results clearly demonstrate that hypertonic saline induces swelling of the contused lesion where the anatomical properties of the blood-brain barrier (BBB) are impaired, whereas hypertonic solution induces a reduction in brain water tissue in areas where the BBB is intact. This could explain the findings of the presented study5 and those reported by the same group in another study where a decrease in POsm was associated with neurological worsening and brain oedema,6 which would suggest BBB breakdown. Taken together, these results suggest that osmotic agents should only be used to reduce brain water content if the BBB is unimpaired. BBB permeability has been demonstrated to be altered in both animal models and in patients with liver failure.9-11 Patients in this study had decreased blood-CSF barrier permeability, a classical surrogate marker of BBB permeability, as attested by CSF attenuation. An increase in BBB permeability may be a result of hyperammonaemia or

systemic inflammation.12 Unfortunately, at present, compounds in the blood responsible for the increase in POsmmes cannot be identified, a limitation of the CT-scan technique. We previously encountered the same limitation in patients with cirrhosis with impaired BBB permeability.10 However, other techniques are able to identify these compounds. Metabolomics is a method to help identify compounds in CSF which normally do not cross the blood-CSF barrier.9 However, this study was conducted in patients with cirrhosis whereas access to CSF in patients with ALF is potentially dangerous since the lumbar puncture is invasive and potentially harmful with low platelets and increased prothrombin time. Recently, a study using MR-spectroscopy with a high field (9.4 Tesla) was able to detect a large number of individual compounds in brains of rats with chronic liver disease.13 In the near future, such non-invasive techniques will probably be able to identify the composition of the CSF by putting a specific voxel in the lateral ventricles. Unfortunately, presently, it is not possible to evaluate the BBB or the blood-CSF barrier permeability at bedside.

To conclude, this study demonstrates once again that CT scan, with certain limitations, remains a valuable tool to study pathophysiology in unstable ICU patients. The authors of the study suggest to measure POsmmes in ICU patients with liver failure, however, further validation is required. Despite the authors suggestion that hyperosmolality may be a unique therapeutic target, without any clear pathophysiological explanation, modulation of POsm in order to reverse severe HE seems premature and could be potentially harmful.

CONFLICT OF INTEREST

Christopher F. Rose: Research collaborations with Synlogic and Mallinckrodt Pharma and is an advisor for Thoeris, Axcella, Morphocell Technologies, Sana Biotechnologies, Horizon Therapeutics and Lupin Pharma Canada.

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