Disorders of Plasma Sodium – Causes, Complications, and Correction

Supplemental Appendix

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Pathogenesis of Osmotic Demyelination

It is well accepted that rapid changes in the plasma sodium concentration can result in brain demyelination, but the precise mechanism underlying this injury is still under investigation. The discovery of bile pigment in the brains of jaundiced patients who died of central pontine myelinolysis led Norenberg to the idea that osmotically-induced disruption of the blood brain barrier might be the cause of the disorder. [1] This was an attractive hypothesis because it had been shown that a rapid rise in plasma osmolality opens the blood brain barrier (BBB), possibly by shrinking endothelial cells and altering their tight junctions.[2,3]

Norenberg's hypothesis was supported by studies by Baker and co-workers which found that development of demyelination in the rat was associated with magnetic resonance indices of BBB disruption and that IgG and C3d were found after rapid correction of hyponatremia in areas of the brain undergoing osmotic demyelination.[4] Because complement is toxic to oligodendrocytes (the cells in the central nervous system involved in synthesizing, organizing and wrapping myelin around nerves), these findings suggested that a rapid increase in plasma sodium leads to BBB disruption, followed by an influx of complement into the brain, which then results in demyelination.

More recently, Gangkam-Kengne and co-workers found that under some conditions, osmotic opening of the blood brain barrier could be dissociated from subsequent

demyelination and suggested that injury to astrocytes was the primary lesion in osmotic demyelination.[5] Studying the temporal relationship between astrocyte loss and myelin loss in a rat model of osmotic demyelination, these investigators found that astrocyte death precedes demyelination. Astrocytes, the most abundant cell type in the nervous system, regulate water homeostasis in the brain; these cells become depleted of organic osmolytes during the adaptation to hyponatremia, and loss of osmolytes make them more vulnerable to injury from osmotic stress. The foot processes of astrocytes encircle brain capillaries and interact with endothelial cells, oligodendrocytes, and microglia.[6] There is evidence that alterations in astrocyte proteins, such as aquaporins, which regulate water and ion flux, directly affect the ability of oligodendrocytes to maintain myelin structure and integrity.[7] Connexins connect astrocytes to each other and to oligodendrocytes in a network whose integrity is crucial for myelination and remyelination after demyelinative injury.[5,7] In addition, astrocytes play an important role in inducing endothelial cells to form the tight junctions characteristic of the BBB[8] and signaling between astrocytes and endothelial cells can lead to rapid and transient opening of the BBB. [6] Therefore, shrinkage and subsequent apoptosis of astrocytes could explain many of the phenomena that occur after rapid correction of chronic hyponatremia: transient opening of the blood brain barrier, loss of myelin-producing oligodendroytes and proliferation of microglia.

Supplemental References

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Case Examples

Case 1

A 57 year old woman with a 20 year history of bipolar disorder treated with lithium undergoes abdominal surgery and is given nothing by mouth beginning at midnight the night before her operation. Two days after surgery she becomes unresponsive. Perioperative input is 6250 ml 5% dextrose in lactated Ringer's solution (sodium concentration 130 mmol per liter), and urine output is 5870 ml. Pre-operative plasma sodium was normal and 24 hours after surgery it is 168 mmol per liter. She is treated with 5% dextrose in 0.45% saline (sodium concentration 77 mmol per liter) at 100 ml per hr and plasma sodium increases to 175 mmol per liter over 8 hours. Urine osmolality is 159 mOsm per kilogram, urine sodium is 36 mmol per liter and urine potassium is 9 mmol per liter.

The patient has nephrogenic diabetes insipidus caused by long-term lithium therapy. Pre-operative plasma sodium was normal because thirst prompted her to replace urinary water losses. Perioperative fluids were nearly isotonic, providing her with almost no electrolyte-free water. Therefore, excretion of dilute urine without water replacement resulted in a rapid onset of severe hypernatremia with neurological symptoms. Treatment with 0.45% saline at 100 ml per hr was inadequate, because only 50 ml per hr of electrolyte-free water was provided, less than half the rate of urinary water losses. A rapid onset of severe hypernatremia risks osmotic demyelination and the plasma sodium should be rapidly re-lowered

with a rapid infusion of 5% dextrose in water, combined with furosemide to eliminate the excess sodium given to her in the intravenous fluids.

Case 2

A 50 year old man is admitted with subarachnoid hemorrhage. He is treated with intravenous 0.9% sodium chloride (sodium concentration 154 mmol per liter) at 200 ml per hr, and plasma sodium gradually falls from normal to 125 mmol per liter. He is then treated with 4.5 liters of intravenous fluid having an average sodium concentration of 300 mmol per liter, and is given nothing by mouth. Despite therapy with hypertonic fluids, plasma sodium does not change. The 24 hour urine output is 4.8 liters, urine osmolality is 625 mOsm per kilogram, urine sodium 263 mmol per liter and urine potassium 24 mmol per liter.

This patient has the syndrome of inappropriate antidiuretic hormone secretion (SIADH) caused by subarachnoid hemorrhage. Vasopressin secreted in response to his acute neurological injury caused the urine to be concentrated (urine osmolality 625 mOsm per kilogram) despite the presence of hypotonic hyponatremia and large amounts of sodium were excreted in the urine because of volume expansion with isotonic saline. The plasma sodium concentration fell because the urine was hypertonic (urine sodium plus potassium concentration equals 287 mmol per liter). The sodium contained in two liters of isotonic saline can be excreted in just over one liter of hypertonic urine; the net effect is positive electrolyte-free water balance, weight gain and hyponatremia. Intravenous fluid with a sodium concentration of

300 mmol per liter was ineffective because the sodium plus potassium concentration of the infusate and its rate of input was nearly matched by the sodium plus potassium concentration of the urine and its rate of output. If urine output continues at its current rate and composition, infusion of 3% saline (sodium concentration 513 mmol per liter) at 100 ml per hour would approximately replace urinary sodium losses, allowing net electrolyte-free water loss which would increase the plasma sodium.

Case 3

A 30 year old woman with von Willebrand's disease is treated with desmopressin before and after cholecystectomy to prevent bleeding. On the third hospital day, she has a major motor seizure. Plasma sodium concentration is 109 mmol per liter, urine osmolality is 325 millisomoles per kg, urine sodium is 114 mmol per liter and urine potassium is 9 mmol per liter. She is treated with 3% saline (sodium concentration 513 mmol per liter) at 100 ml per hour (2 ml per kg body weight per hour) for 5 hours and plasma sodium increases to 119 mmol per liter. During the next eight hours all fluid intake is withheld, the plasma sodium increases to 127 mmol per liter and she becomes fully alert and oriented. A repeat urine osmolality is 100 mOsm per kilogram and urine output is 600 ml per hr. The next day, plasma sodium is 139 mmol per liter. A day later she becomes unresponsive. Spastic quadriparesis and pseudobulbar palsy develops and, after two weeks, magnetic resonance imaging of the brain confirms the diagnosis of osmotic demyelination syndrome. The patient survives, with permanent, severe disabilities.

The patient developed symptomatic hyponatremia due to exogenous antidiuretic hormone (desmopressin). Because of severe symptoms, administration of 3% saline was indicated to increase plasma sodium by 4 to 6 mmol per liter. Absent urinary water losses, an increase of 10 mmol per liter would be expected, because 1 ml of 3% saline per kg body weight should increase the plasma sodium by approximately 1 mmol per liter and she was given 10 ml per kg. However, as the effect of desmopressin wore off and plasma hypotonicity suppressed endogenous vasopressin secretion, the urine became maximally dilute, and the plasma sodium continued to increase owing to urinary water losses. Three days of hyponatremia was sufficient time for brain cells to adapt; the large, rapid increase in plasma sodium (30 mmol per liter in 28 hours) caused osmotic demyelination, with a typical biphasic clinical course, and this resulted in permanent brain damage.

Case 4

A 60 year old man with a history of heavy beer drinking presents with confusion, weakness and falls 10 days after being started on hydrochlorthiazide for the treatment of hypertension. Serum sodium is 104 mmol per liter and serum potassium is 2.5 mmol per liter. Urine osmolality is 650 mOsm per kilogram and urine sodium is 10 mmol per liter. Hydrochlorthiazide is discontinued and he is treated with potassium supplements and 2 micrograms of desmopressin subcutaneously. Over the next six days, repeat doses of desmopressin are given every eight hours and he is also treated with an infusion of 3% saline that is adjusted to achieve a 4 mmol per liter daily increase in plasma sodium. When the

plasma sodium concentration reaches 128 mmol per liter, desmopressin and 3% saline are discontinued. The patient's symptoms resolve and his plasma sodium eventually returns to normal.

The patient has thiazide-induced hyponatremia with several risk factors for developing osmotic demyelination: plasma sodium less than 105 mmol per liter, hypokalemia, and alcoholism. Once the thiazide is discontinued, he is also at risk of developing a spontaneous water diuresis that could result in unintentional rapid correction of hyponatremia. Because of these risks, he was given desmopressin to prevent urinary water losses from developing. Repeated administration of desmopressin creates a state of iatrogenic SIADH and the plasma sodium is increased by administering hypertonic potassium chloride and sodium chloride. The goal of therapy for all patients with severe hyponatremia is a daily increase of 4 to 6 mmol per liter. Because of this patient's added risk factors for developing osmotic demyelination syndrome, a 4 mmol per liter daily target was chosen.