



Dialysis disequilibrium syndrome revisited: Feeling “Disequilibrated” due to inner ear dyshomeostasis?

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ABSTRACT

Dizziness is one of the most common hemodialysis-associated symptoms, and has been thought to be caused by cerebral edema or intravascular hypovolemia. However, the possibility of a peripheral vestibular disturbance due to hemodialysis has not been addressed as a cause of hemodialysis-associated dizziness. In the present study, we propose a new hypothesis accounting for hemodialysis-associated dizziness, i.e., the decrease in serum osmolality due to rapid removal of urea during dialysis causes inner ear fluid dyshomeostasis, leading to density difference between perilymph and endolymph.

Introduction/background

Dialysis disequilibrium syndrome (DDS) is characterized by the neurologic deterioration and cerebral edema that occurs after hemodialysis [1–8]. Clinical manifestations are similar to those that occur with increased intracranial pressure or acute hyponatremia, and include dizziness, nausea, vomiting, restlessness, and headache in mild forms, and seizures, obtundation, coma, and even death in severe forms. The main theory explaining the generation of these symptoms is the ‘reverse urea effect’, in which rapid clearing of urea during hemodialysis results in a reduction in serum osmolality, leading to an osmotic gradient between the extracellular and intracellular compartments that promotes water shift into cells and subsequent cerebral edema. Moreover, a decrease in serum osmolality due to urea losses induces intravascular fluids to flow into not only the cerebrospinal fluid but also the anterior chamber of the eye, which exacerbates cerebral edema and leads to increased intraocular pressure, respectively [1,9–12]. The blood-labyrinth barrier (BLB), which is essential for inner ear fluid homeostasis, possesses functional and structural similarity to the blood-cerebrospinal fluid (CSF) barrier or blood-aqueous humor barrier whereby tight junctions within the capillary serve as barriers to the movement of substances from the plasma [13–15]. Dizziness is one of the most common hemodialysis-associated symptoms [16,17], even in patients without DDS, and dizziness symptoms were found to be more severe in patients who received more frequent dialysis sessions per week and with longer single session durations [18]. While it has been speculated that the hemodialysis-associated dizziness is caused by

cerebral edema or intravascular hypovolemia, the possibility of a peripheral vestibular disturbance, which is the most common cause of dizziness in the general population, due to hemodialysis has not been addressed.

Hypothesis

In the present report, we present a patient complaining of hemodialysis-associated dizziness which was influenced by a change in head position, demonstrating characteristic positional nystagmus findings. We hypothesize that the mechanism by which the rapid reduction in plasma urea caused by hemodialysis can result in dyshomeostasis of the inner ear fluid causing dizziness in patients on hemodialysis.

Case presentation and evaluation of hypothesis

A 70-year-old woman with end-stage renal disease on hemodialysis visited our dizziness clinic. She had been suffering from diabetes mellitus, hypertension, and congestive heart failure, and started hemodialysis (three times a week) six months before her visit to our clinic complaining of dizziness. The patient began to experience dizziness after the first hemodialysis. She reported that her dizziness was aggravated by a change of head position, and became worse after every hemodialysis. She denied a previous history of dizziness of this kind and did not report any auditory symptoms, such as hearing loss. Neurologic examination revealed no focal neurologic deficits. The supine head-roll test showed persistent apogeotropic direction-changing positional

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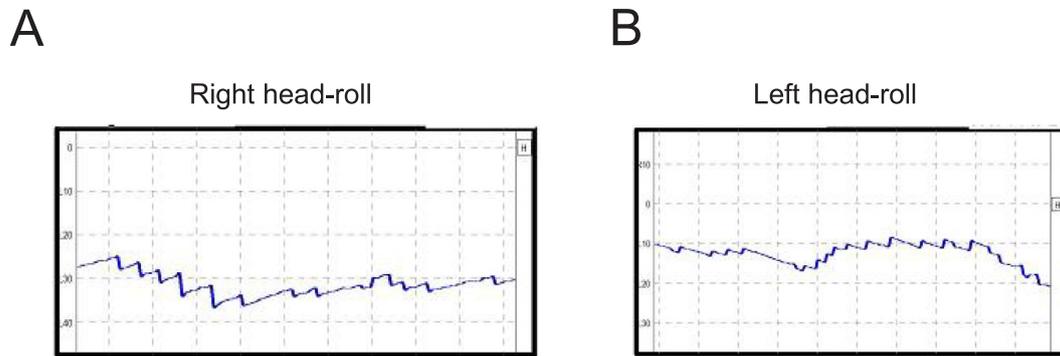


Fig. 1. Video nystagmography findings of persistent apogeotropic direction-changing positional nystagmus in a supine head-roll test. (A) In the right head-roll position, persistent left-beating nystagmus is observed. (B) In the left head-roll position, persistent right-beating nystagmus is observed.

nystagmus (PA DCPN), in which persistent left-beating nystagmus was observed when head-turning to the right in a supine position (Fig. 1A and supplemental video 1) and persistent right-beating nystagmus was observed when head-turning to the left in a supine position (Fig. 1B and supplemental video 2). The bithermal caloric test revealed no unilateral weakness, and brain magnetic resonance imaging showed no abnormality, except for mild chronic ischemic changes. The repetitive cupulolith repositioning maneuver (CRM) was not effective for the treatment of her dizziness.



video 1. Persistent left-beating nystagmus is observed in the right head-roll position.



video 2. Persistent right-beating nystagmus is observed in the left head-roll position.

The presence of PA DCPN indicates that the lateral semicircular canal (LSCC), which senses angular acceleration and is gravity-independent under normal conditions, is activated by the influence of gravity. It is generally accepted that PA DCPN is caused by LSCC cupulolithiasis, in which otoconial particles adhere to the LSCC cupula, and can be successfully treated by CRM. However, CRM was useless in our patient, and positional dizziness was aggravated after hemodialysis. Rapid removal of urea has been reported to reduce serum osmolality by an average of 26 mosmol/kg H₂O during routine hemodialysis in stable chronic patients [19], and the clinical signs of disequilibrium was reported to decline in parallel with the decline in serum osmolality changes [20]. The CSF-to-plasma and perilymph-to-plasma urea ratios increase significantly after hemodialysis. Although urea can pass through the BLB and blood-CSF barrier, its slow passage results in a significant time lag for redistribution [1,21], resulting in an osmotic gradient between blood and CSF, or blood and perilymph. Meanwhile, the removal of intravascular fluid during hemodialysis induces decreases in hydrostatic pressure. If the degree of decrease in the osmotic pressure is higher than the hydrostatic pressure in the inner ear capillaries, water moves from the capillaries into the perilymphatic space (Fig. 2, gray arrow), which consequently decreases the perilymph density (g/cm³). Moreover, water passage into the perilymph not only elevates the hydrostatic pressure but also reduces the osmotic pressure in the perilymph, which subsequently induces water transport from the perilymph to the endolymph (Fig. 2, blue arrow). Thus, a reduction in serum osmolality during hemodialysis can decrease the density of the perilymph, then the endolymph, in consecutive order.

Recently, it has been proposed that the density difference between the perilymph and the endolymph may elicit positional dizziness and

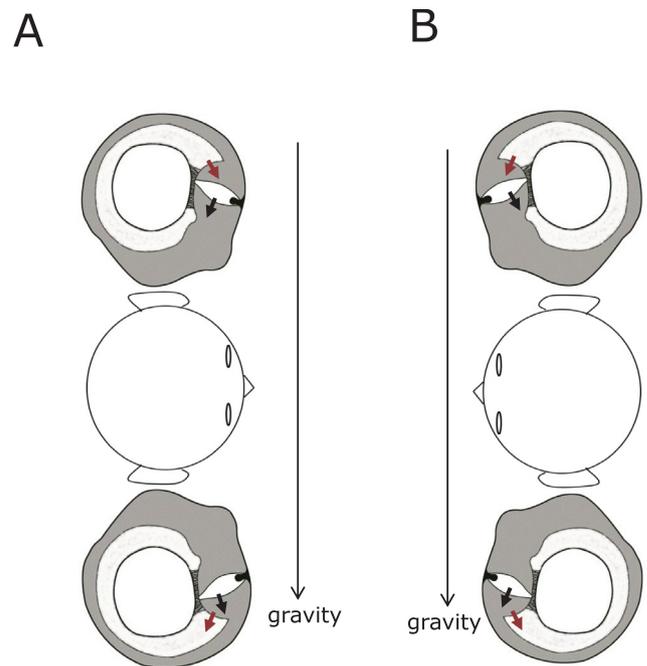


Fig. 2. The mechanism underlying persistent apogeotropic direction-changing positional nystagmus when perilymph density becomes lower than that of endolymph. The view from the top of the patient's head in a supine position is depicted in the second panels, and both lateral semicircular canals (LSCCs) are depicted in the first and third panels. When the perilymph density becomes lower than the endolymph density, the endolymphatic duct containing endolymph fluid will be influenced by gravity. (A) In a right head-roll position, the endolymphatic membrane in the ampulla is indented (brown arrows) ampullopetally and ampullofugally in the left (first panel) and right (third panel) LSCCs, respectively, which results in left-beating (apogeotropic) nystagmus in nystagmography. (B) In a left head-roll position, the endolymphatic membrane in the ampulla is indented (brown arrows) ampullopetally and ampullofugally in the right (first panel) and left (third panel) LSCCs, respectively, which results in right-beating (apogeotropic) nystagmus in nystagmography.

DCPN [22,23]. Endolymphatic fluid (gray space in Fig. 3A and B) is confined in the endolymphatic duct, which is completely immersed in the perilymphatic fluid (white space in Fig. 3A and B) and strictly separated from the perilymphatic space by the tight junctions in the endolymphatic membrane. The endolymphatic duct takes an eccentric position within the bony semicircular canal (SCC) and is attached to the crista ampullaris and to the opposing wall in the area of ampulla (Fig. 3A and B). Because adhesion between the cupula and the endolymphatic membrane at the ampulla separates the endolymphatic space medially and laterally to the cupula, endolymphatic fluid does not freely traverse through the cupula-membrane attachment, which

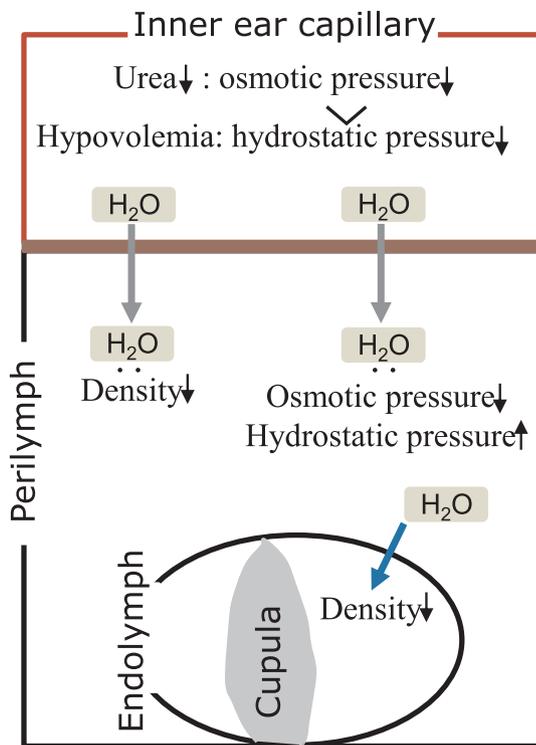


Fig. 3. Schematic illustration showing the hypothetical mechanism underlying persistent apogeotropic direction-changing positional nystagmus when rapid removal of blood urea causes reduction of serum osmolality in patients on hemodialysis. When the decrease in osmotic pressure is greater than the decrease in hydrostatic pressure after hemodialysis, water moves from the inner ear capillaries to the perilymph (gray arrows), lowering the density of the perilymphatic fluid. Subsequent water passage from the perilymph to the endolymph (blue arrow) lowers the density of the endolymph below that of the cupula.

enables the endolymphatic flow to cause deflection of the cupula. Moreover, because the endolymphatic membrane is very thin (approximately 0.02 mm) and easily deformable, mechanical indentation of the endolymphatic duct can drive endolymphatic flow, resulting in cupula deflection [24–26]. When the perilymph density becomes lower than the endolymph density after hemodialysis, as in our patient, gravity can induce indentation of the endolymphatic membrane of both ears at the ampulla area during a supine head-roll test. In the right head-roll position (Fig. 3A), the endolymphatic membrane is utriculopetally indented on the left LSCC (Fig. 3A, first panel, brown arrow) causing utriculopetal deflection of the cupula (Fig. 3A, first panel, black arrow) and utriculofugally indented on the right LSCC (Fig. 3A, third panel, brown arrow) causing utriculofugal deflection of the cupula (Fig. 3A, third panel, black arrow), which elicits left-beating (apogeotropic) nystagmus (Fig. 1A). In the left head-roll position (Fig. 3B), the endolymphatic membrane is utriculopetally indented on the right LSCC (Fig. 3B, first panel, brown arrow) causing utriculopetal deflection of the cupula (Fig. 3B, first panel, black arrow), and utriculofugally indented on the left LSCC (Fig. 3B, third panel, brown arrow) causing utriculofugal deflection of the cupula (Fig. 3B, third panel, black arrow), which elicits right-beating (apogeotropic) nystagmus (Fig. 1B). In addition to the density differences between the perilymph and the endolymph, subsequent water transport from the perilymph into the endolymph makes the density of the endolymph lower than that of the cupula (heavier cupula), resulting in additional PA DCPN in head-roll positions.

It has been reported that PA DCPN is observed in many inner ear disorders including Meniere's disease, sudden sensorineural hearing loss, Ramsay Hunt syndrome and acute otitis media complicated by

serous labyrinthitis, and the suggested mechanism of ageotropic nystagmus was the alteration of biochemical composition of inner ear fluids [27–34]. In normal conditions, the densities of the perilymph, endolymph, and cupula are thought to be the same because SCCs are gravity-independent. Due to the high sensitivity of receptors in the SCC, in which a density difference as small as $\sim 10^{-4}$ g/cm³ between the endolymph and the cupula is sufficient to make SCCs sensitive to gravity [35], even little differences in the density among them may elicit a significant SCC response. To the best of our knowledge, this study is the first report that addresses the possibility of inner ear fluid dyshomeostasis as a cause of hemodialysis-associated dizziness.

Conclusion

We propose inner ear fluid dyshomeostasis caused by hemodialysis as a possible hypothesis of hemodialysis-associated dizziness. Rapid removal of urea during hemodialysis reduces serum osmolality, which subsequently results in an osmotic gradient between the inner ear capillaries and the perilymph, moving water molecules from inner ear capillaries to the perilymph. Consequently, the perilymph density becomes lower than the endolymph density, eliciting positional dizziness and characteristic PA DCPN in a supine head-roll test.

Conflicts of interest

None.

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