Pediatr Nephrol (2013) 28:1153–1156
DOI 10.1007/s00467-013-2435-6

EDITORIAL COMMENTARY

Over- or underfill: not all nephrotic states are created equal

Detlef Bockenhauer

Received: 3 February 2013 / Revised: 4 February 2013 / Accepted: 6 February 2013 / Published online: 26 March 2013

Abstract Blessed were the days when it all made sense and the apparent mechanism for edema formation in nephrotic syndrome was straightforward: the kidneys lost protein in the urine, which lowered the plasma oncotic pressure. Thus, fluid leaked into the interstitium, depleting the intravascular volume with subsequent activation of renin/aldosterone and consequent avid renal sodium retention. As simple as that! Unfortunately, a number of clinical and laboratory observations have raised serious concerns about the accuracy of this "underfill" hypothesis. Instead, an "overfill" hypothesis was generated. Under this assumption, the nephrotic syndrome not only leads to urinary protein wasting, but also to primary sodium retention with consequent intravascular overfilling, with the excess fluid spilling into the flood plains of the interstitium, leading to edema. Recently, an attractive mechanism was proposed to explain this primary sodium retention: proteinuria includes plasma proteinases, such as plasmin, which activate the epithelial sodium channel in the collecting duct, ENaC. In this edition, further evidence for this hypothesis is being presented by confirming increased plasmin content in the urine of children with nephrotic syndrome and demonstrating ENaC activation. If correct, this hypothesis would provide a simple treatment for the edema: pharmacological blockade of ENaC, for instance, with amiloride. Yet, how come clinicians have not empirically discovered the presumed power of ENaC blockers in nephrotic syndrome? And why is it that some patients clearly show evidence of intravascular underfilling? The controversy of over- versus underfilling demonstrates how much we still have to learn about the pathophysiology of nephrotic syndrome.

Keywords Nephrotic syndrome · Overfill · Underfill · Sodium retention · ENaC · Plasmin · Blood volume

D. Bockenhauer (✉)
Great Ormond Street Hospital for Children NHS Foundation Trust and Institute of Child Health, University College London, 30 Guildford Street, London WC1N 1EH, UK
e-mail: d.bockenhauer@ucl.ac.uk

Introduction

Ideally, medical treatment is based on best evidence, which includes a thorough understanding of the pathophysiology of the respective disease [1]. Based on this knowledge of disease mechanisms we can then provide rational and sound treatments. Treatment of edema in nephrotic syndrome unfortunately does not fit this ideal. There are two opposing theories trying to explain the mechanism of edema formation: the under- and the overfill hypotheses and edema treatment is different depending on which one is applied.

The underfill hypothesis

We probably all learned the underfill hypothesis in medical school and it was formulated almost 100 years ago [2]: an unknown trigger leads to proteinuria; as the plasma protein level falls, the intravascular oncotic pressure decreases with consequent leakage of plasma water into the interstitium, thus generating edema. Owing to the extravasation of the fluid, the intravascular volume is decreased and neurohormonal markers of intravascular depletion are increased, such as vasopressin and aldosterone, resulting in highly concentrated urine with very low sodium content. Thus, renal sodium retention in this scenario is a secondary phenomenon, a physiological consequence of the underfilling [3]. The therapeutic consequences of this hypothesis for the treatment of edema are clear: expansion of intravascular volume and restoration of plasma oncotic pressure by administration of, for instance, albumin.

Problems with the underfill hypothesis

There are, however, a number of clinical observations that do not fit well with the underfill hypothesis, including:

1. Treatment of the edema of nephrotic syndrome by albumin alone reduces plasma renin activity, but is insufficient to induce diuresis [4, 5] and most clinicians will add a diuretic at some stage. In contrast, diuretic use alone can be successful in the treatment of edema in some patients [6].
2. Reducing activity of the renin–aldosterone axis by mineralocorticoid receptor antagonists, such as spironolactone or angiotensin-converting enzyme inhibitors does not result in a marked increase in sodium excretion in most patients with nephrotic syndrome [4, 7].
3. Once the patient goes into remission, the first symptom (besides the disappearance of proteinuria) is a large diuresis, well before plasma protein levels (and thus oncotic pressure) have normalized [8, 9]. Parents of a child with nephrotic syndrome sometimes first recognize the onset of remission by the sudden increase in urine output, subsequently confirmed by the disappearance of proteinuria on dipstix.
4. There are patients (and animal models) with analbuminemia and these typically do not suffer from edema [10–12].
5. Attempts at trying to measure blood volume and/or neurohumoral markers of volume depletion, such as renin/aldosterone, do not show a consistent picture, but suggest volume depletion in some, normal or excess volume in others [4, 5, 9, 13–17].
6. Administration of albumin in some patients is associated with evidence of volume overload, such as hypertension and pulmonary edema [18].

Strong experimental evidence against the underfill hypothesis was generated in an animal model of minimal change disease [19]: rats infused with puromycin aminoglycoside develop nephrotic-range proteinuria with minimal changes on histology [20]. The elegance of the experiments by Ichikawa et al. lay in the idea of perfusing only one kidney with PA and combining this approach with the then newly developed technique of nephron puncture. Hence, he was able to independently assess the effect of proteinuria in both the nephrotic, as well as the normal kidney. They noted that only the nephrotic kidney avidly conserved sodium. Indeed, in a separate study, the control kidney actually increased sodium excretion, as if sensing intravascular volume excess [21]. Moreover, Ichikawa et al. [19] controlled plasma protein levels within the normal range by infusion of homologous rat plasma to maintain euvolemia, suggesting that there might have been primary sodium retention in the nephrotic kidney, not mediated by volume depletion. With nephron puncture, they were further able to show that sodium delivery to the collecting duct was comparable in the nephrotic and the control kidney, whereas final sodium excretion was three-fold higher in the control kidney. Therefore, the collecting duct had to be the site of the avid sodium reabsorption in the nephrotic kidney.

The overfill hypothesis

Based on the above observations, an alternative explanation for the development of edema was put forward, the "overfill hypothesis": proteinuria, by some undefined mechanism causes primary sodium retention with consequent volume expansion and leakage of excess fluid in the interstitium [14]. But what mediates the primary sodium retention? The studies by Ichikawa et al. [19] had already identified the collecting duct as being the relevant segment, and the key molecular pathway for sodium reabsorption in this segment is the epithelial sodium channel, ENaC [22]. Studies in animal models did indeed show increased expression and apical targeting of ENaC in nephrotic syndrome [23–25], as well as enhanced Na-K-ATPase activity in this segment [26, 27]. Importantly, it was noted that modification of extracellular loops of ENaC by proteinases, such as plasmin, leads to activation of the channel [28, 29]. Thus, a clear explanation for primary sodium retention was at hand: the pathological filtration in nephrotic syndrome includes proteinases, which enhance sodium reabsorption in the collecting duct by modification of ENaC. Indeed, Svenningsen et al. recently showed that nephrotic urine activated ENaC channels expressed in cell culture and that this activation could be prevented by inhibitors of plasmin [30]. In the current study presented in this issue of *Pediatric Nephrology*, the group extends their findings by investigating a cohort of 20 children with idiopathic nephrotic syndrome [31]. They show that the urine of these children during relapse does indeed contain an increased amount of plasminogen/plasmin compared with urine collected during remission. And whereas the relapse urine did activate ENaC channels in a collecting duct cell line, remission urine did not.

So, is this now the final word in the under- vs overfill controversy? Are we all going to effectively treat edema in our nephrotic patients by sole administration of ENaC blockers, such as amiloride?

Probably not, as there clearly are some clinical observations that are difficult to reconcile with the overfill hypothesis.

Problems with the overfill hypothesis

1. Probably every pediatric nephrologist is familiar with nephrotic patients displaying obvious clinical signs of volume depletion: they are peripherally cool, typically have low blood pressure, tachycardia, and often abdominal pain, thought to reflect decreased intestinal

perfusion [32]. Blood tests in these patients show elevated hemoglobin levels, suggesting severe intravascular volume depletion [33]. Indeed, some of these patients develop spontaneous thrombosis of peripheral arteries [34, 35]. Whilst the latter is of course also promoted by the prothrombotic tendency of nephrotic syndrome, the hemoconcentration and resultant sluggish flow are likely contributory [36].

2. If ENaC blockers were indeed the effective treatment of edema, how come clinical practice has not empirically identified them as such? Whilst there is some evidence for the efficacy of amiloride in nephrotic syndrome [37], the effect is not as resounding as the logic of the overfill hypothesis would suggest. Certainly, in my own unscientific and unpublished experience, I have not been impressed. Is it because I have never dared to use amiloride as the sole diuretic, but always in combination with a loop diuretic? Amiloride is a competitive inhibitor of ENaC [38] and by co-administration of a loop diuretic, sodium delivery to the collecting duct will be enhanced and thus efficacy of amiloride may be diminished. Yet, in the study by Deschenes et al., amiloride was used in conjunction with furosemide [37].

Conclusions

The observations made with respect to primary sodium retention constitute an important contribution to our understanding of the formation of edema. They provide a welcome counterweight to the underfill hypothesis, which, by the resultant uncritical use of albumin can lead to dangerous complications such as pulmonary edema. However, uncritical acceptance of the overfill hypothesis with the consequent emphasis on diuresis is likely to be equally as dangerous, as it could lead to severe volume depletion with serious complications, such as thromboembolism. The problem is that not all nephrotic states are created equal. Even Meltzer and colleagues, when they proposed the overfill hypothesis in 1979, remarked that there were some patients who exhibited signs of under- and others of overfilling [14]. Probably, overall maintenance of volume homeostasis is severely impaired in nephrotic syndrome and patients can swiftly swing between over- and underfill states: some present with clinical signs of hypovolemia, yet develop pulmonary edema after repeated albumin infusions. Others present clinically euvolemic, yet develop vasoconstriction, abdominal pain, and tachycardia after aggressive diuresis. This apparent instability of intravascular volume highlights the need for close clinical observation of patients with nephrotic syndrome with rapid modification of the therapeutic measures based on the clinical findings. Thus, for now, the treatment of edema is likely to remain an art, rather than a science.

References

1. Bockenhauer D, Medlar AJ, Ashton E, Kleta R, Lench N (2012) Genetic testing in renal disease. Pediatr Nephrol 27:873–883
2. Epstein A (1917) Concerning the causation of edema in chronic parenchymatous nephritis: methods for its alteration. Am J Med Sci 154:638–647
3. Bockenhauer D, Aitkenhead H (2011) The kidney speaks: interpreting urinary sodium and osmolality. Arch Dis Child Educ Pract Ed 96:223–227
4. Usberti M, Gazzotti RM, Poiesi C, D'Avanzo L, Ghielmi S (1995) Considerations on the sodium retention in nephrotic syndrome. Am J Nephrol 15:38–47
5. Brown EA, Markandu ND, Sagnella GA, Squires M, Jones BE, MacGregor GA (1982) Evidence that some mechanism other than the renin system causes sodium retention in nephrotic syndrome. Lancet 2:1237–1240
6. Kapur G, Valentini RP, Imam AA, Mattoo TK (2009) Treatment of severe edema in children with nephrotic syndrome with diuretics alone–a prospective study. Clin J Am Soc Nephrol 4:907–913
7. Brown EA, Markandu ND, Sagnella GA, Jones BE, MacGregor GA (1984) Lack of effect of captopril on the sodium retention of the nephrotic syndrome. Nephron 37:43–48
8. Oliver W, Vadnay L, Sporynsk K (1963) Physiologic responses associated with steroid-induced diuresis in nephrotic syndrome. J Lab Clin Med 62:449–464
9. Brown EA, Markandu N, Sagnella GA, Jones BE, MacGregor GA (1985) Sodium retention in nephrotic syndrome is due to an intrarenal defect: evidence from steroid-induced remission. Nephron 39:290–295
10. Lecomte J, Juchmes J (1978) So-called absence of edema in analbuminemia. Rev Med Liege 33:766–770
11. Joles JA, Willekes-Koolschijn N, Braam B, Kortlandt W, Koomans HA, Dorhout Mees EJ (1989) Colloid osmotic pressure in young analbuminemic rats. Am J Physiol 257:F23–F28
12. Buehler BA (1978) Hereditary disorders of albumin synthesis. Ann Clin Lab Sci 8:283–286
13. Brown EA, Markandu ND, Roulston JE, Jones BE, Squires M, MacGregor GA (1982) Is the renin-angiotensin-aldosterone system involved in the sodium retention in the nephrotic syndrome? Nephron 32:102–107
14. Meltzer JI, Keim HJ, Laragh JH, Sealey JE, Jan KM, Chien S (1979) Nephrotic syndrome: vasoconstriction and hypervolemic types indicated by renin-sodium profiling. Ann Intern Med 91:688–696
15. Usberti M, Gazzotti RM (1998) Hyporeninemic hypoaldosteronism in patients with nephrotic syndrome. Am J Nephrol 18:251–255
16. Vande Walle JG, Donckerwolcke RA, van Isselt JW, Derkx FH, Joles JA, Koomans HA (1995) Volume regulation in children with early relapse of minimal-change nephrosis with or without hypovolaemic symptoms. Lancet 346:148–152
17. Koomans HA, Braam B, Geers AB, Roos JC, Dorhout Mees EJ (1986) The importance of plasma protein for blood volume and blood pressure homeostasis. Kidney Int 30:730–735
18. Reid CJ, Marsh MJ, Murdoch IM, Clark G (1996) Nephrotic syndrome in childhood complicated by life threatening pulmonary oedema. BMJ 312:36–38
19. Ichikawa I, Rennke HG, Hoyer JR, Badr KF, Schor N, Troy JL, Lechene CP, Brenner BM (1983) Role for intrarenal mechanisms in the impaired salt excretion of experimental nephrotic syndrome. J Clin Invest 71:91–103
20. Frenk S, Antonowicz I, Craig JM, Metcoff J (1955) Experimental nephrotic syndrome induced in rats by aminonucleoside; renal lesions and body electrolyte composition. Proc Swoc Exp Biol Med 89:424–427

21. Chandra M, Hoyer JR, Lewy JE (1981) Renal function in rats with unilateral proteinuria produced by renal perfusion with aminonucleoside. Pediatr Res 15:340–344
22. Kleta R, Bockenhauer D (2006) Bartter syndromes and other salt-losing tubulopathies. Nephron Physiol 104:73–80
23. Kim SW, Wang W, Nielsen J, Praetorius J, Kwon TH, Knepper MA, Frokiaer J, Nielsen S (2004) Increased expression and apical targeting of renal ENaC subunits in puromycin aminonucleoside-induced nephrotic syndrome in rats. Am J Physiol Renal Physiol 286:F922–F935
24. Kim SW, de Seigneux S, Sassen MC, Lee J, Kim J, Knepper MA, Frokiaer J, Nielsen S (2006) Increased apical targeting of renal ENaC subunits and decreased expression of 11betaHSD2 in HgCl2-induced nephrotic syndrome in rats. Am J Physiol Renal Physiol 290:F674–F687
25. de Seigneux S, Kim SW, Hemmingsen SC, Frokiaer J, Nielsen S (2006) Increased expression but not targeting of ENaC in adrenalectomized rats with PAN-induced nephrotic syndrome. Am J Physiol Renal Physiol 291:F208–F217
26. Feraille E, Mordasini D, Gonin S, Deschenes G, Vinciguerra M, Doucet A, Vandewalle A, Summa V, Verrey F, Martin PY (2003) Mechanism of control of Na, K-ATPase in principal cells of the mammalian collecting duct. Ann N Y Acad Sci 986:570–578
27. Deschenes G, Doucet A (2000) Collecting duct (Na+/K+)-ATPase activity is correlated with urinary sodium excretion in rat nephrotic syndromes. J Am Soc Nephrol 11:604–615
28. Kleyman TR, Myerburg MM, Hughey RP (2006) Regulation of ENaCs by proteases: an increasingly complex story. Kidney Int 70:1391–1392
29. Planes C, Caughey GH (2007) Regulation of the epithelial Na+ channel by peptidases. Curr Top Dev Biol 78:23–46
30. Svenningsen P, Bistrup C, Friis UG, Bertog M, Haerteis S, Krueger B, Stubbe J, Jensen ON, Thiesson HC, Uhrenholt TR, Jespersen B, Jensen BL, Korbmacher C, Skott O (2009) Plasmin in nephrotic urine activates the epithelial sodium channel. J Am Soc Nephrol 20:299–310
31. Andersen R, Buhl K, Jensen B, Svenningsen P, Friis U, Jespersen T (2013) Remission of nephrotic syndrome diminishes urinary plasmin content and abolishes activation of ENaC. Pediatr Nephrol. doi:10.1007/s00467-013-2439-2
32. Van de Walle JG, Donckerwolcke RA, Greidanus TB, Joles JA, Koomans HA (1996) Renal sodium handling in children with nephrotic relapse: relation to hypovolaemic symptoms. Nephrol Dial Transplant 11:2202–2208
33. Wang SJ, Tsau YK, Lu FL, Chen CH (2000) Hypovolemia and hypovolemic shock in children with nephrotic syndrome. Acta Paediatr Taiwan 41:179–183
34. Parrish RA, Scurry RB, Robertson AF 3rd (1976) Recurrent arterial thrombosis in nephrosis. Am J Dis Child 130:428–429
35. Citak A, Emre S, Sairin A, Bilge I, Nayir A (2000) Hemostatic problems and thromboembolic complications in nephrotic children. Pediatr Nephrol 14:138–142
36. Kerlin BA, Ayoob R, Smoyer WE (2012) Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol 7:513–520
37. Deschenes G, Guigonis V, Doucet A (2004) Molecular mechanism of edema formation in nephrotic syndrome. Arch Pediatr 11:1084–1094
38. Palmer LG, Andersen OS (1989) Interactions of amiloride and small monovalent cations with the epithelial sodium channel. Inferences about the nature of the channel pore. Biophys J 55:779–787