Abdominal Pain and Vomiting in a Boy With Nephrotic Syndrome

Sabine D.M. Theuns-Valks, Joanna A.E. van Wijk, Marc van Heerde, Koert M. Dolman and Arend Bökenkamp

CLIN PEDIATR published online 19 August 2010
DOI: 10.1177/0009922810361366

Clinical Pediatrics
XX(X) 1–4

DOI: 10.1177/0009922810361366
http://clp.sagepub.com
SAGE

Abdominal Pain and Vomiting in a Boy With Nephrotic Syndrome

Sabine D. M. Theuns-Valks, MD[1], Joanna A. E. van Wijk, MD, PhD[1], Marc van Heerde, MD[1], Koert M. Dolman, MD, PhD[2], and Arend Bökenkamp, MD, PhD[1]

Abstract

Although nephrotic crisis, i.e. acute hypovolemia in the course of nephrotic syndrome, is not uncommon in children, this complication is seldom mentioned in literature. We report a 4-year old boy with a relapse of steroid-sensitive nephrotic syndrome precipitated by a viral respiratory infection, who presented with abdominal pain, vomiting, diarrhea and hypovolemic shock 15 hours after the initial hospital visit. Serum albumin had decreased from 1.5 to 0.6 g/dL, hemoglobin had risen from 16.1 to 19.5 g/dL and urine albumin concentration was 6.5 g/dL. He responded promptly to fluid resuscitation with normal saline and albumin infusion. A bacterial infection was excluded and a diagnosis of nephrotic crisis made based on the combination of a rapid drop in serum albumin and hemoconcentration. Acute loss of the colloid-osmotic pressure gradient at the capillary level caused fluid leakage into the interstitium. Together with fluid losses from intestinal ischemia, this led to acute hypovolemia.

Keywords

nephrotic crisis, nephrotic syndrome, hypovolemic shock

Patient Report

A 4-year-old boy with steroid sensitive nephrotic syndrome (SSNS) presented in shock at the emergency room. He had been coughing with signs of an upper airway infection for 5 days. He was seen at the outpatient clinic with fever, poor intake, and a 3+ positive dipstick for urine albumin (ie, >0.3 g/dL) since 1 day. Earlier, daily urine tests for albuminuria had been negative. Blood tests showed C-reactive protein 6 mg/L, hemoglobin 10.4 mmol/L (16.1 g/dL), urea 4.3 mmol/L (12.0 mg/dL), creatinine 18 μmol/L (0.20 mg/dL, enzymatic assay), and albumin 1.5 g/dL. Oral prednisone (60 mg/m^2/d) was started and extra fluid intake was advised as the hemoglobin was raised.

Later that day, he complained of abdominal pain, started vomiting, and developed diarrhea. Fifteen hours after the initial presentation, he presented with hypovolemic shock at the emergency department. We saw a pale boy with tachycardia (185 per minute), weak peripheral pulsations, peripheral cyanosis, and a capillary refill of 5 seconds. He was in respiratory distress with tachypnoea (45 per minute) and nasal flaring. Blood pressure and oxygen saturation were not measurable; temperature was 37.5°C (99.5°F). He was still alert and talking. Besides rales on pulmonary auscultation, no abnormalities were found on physical examination. There was no abdominal tenderness and peristalsis was normal. He had no edema. Laboratory tests revealed the following: hemoglobin 12.6 mmol/L (19.5 g/dL), hematocrit 60%, leucocytes 36.4 × 1,000 cells/mm^3, C-reactive protein 3 mg/L, sodium 140 mmol/L, potassium 4.4 mmol/L, blood urea nitrogen 12.3 mmol/L (34.5 mg/dL), creatinine 48 μmol/L (0.54 mg/dL), pH 7.37, bicarbonate 16.2 meq/L, base excess −7.6 mmol/L. Serum albumin had decreased to 0.6 g/dL. Quantitative urine analysis showed an albumin concentration of 6.5 g/dL (albumin/creatinine ratio 9430 mg/g). Renin and aldosteron were not measured. Urine sodium concentration was <10 mmol/L, urine potassium 27 mmol/L, resulting in a (K/K + Na) ratio well above 0.6. Together with a fractional

[1]VU University Medical Center, Amsterdam, The Netherlands
[2]Sint Lucas Andreas Hospital, Amsterdam, The Netherlands

Corresponding Author:
Sabine D. M. Theuns-Valks, Department of Pediatrics, VU Medical Center, De Boelelaan 1117, PO Box 7057, Amsterdam 1007 MB, The Netherlands
Email: sdm.theuns-valks@vumc.nl

excretion of sodium below 0.03% this reflected massive hyperaldosteronism.

The hypovolemic shock was treated with intravenous fluid resuscitation using 60 mL/kg of normal saline in the first half hour, followed by albumin infusion (human albumin 20%, 1 g/kg in 4 hours). Ceftriaxon was started intravenously after a blood culture was taken and corticosteroid therapy was switched to the intravenous route. On this therapy, the patient recovered promptly from hypovolemic shock. Blood cultures were negative and antibiotics were discontinued. Following fluid resuscitation he developed mild periorbital and pretibial edema. Serum albumin rose to 2.2 g/dL directly after infusion and remained above 1.2 g/dL thereafter. The nephrotic syndrome went into remission 5 days later. Of note, the boy had experienced a similar episode 8 months before.

Discussion

The differential diagnosis of abdominal pain, diarrhea, and vomiting in nephrotic syndrome includes peritonitis/sepsis and intestinal ischemia as a symptom of nephrotic crisis, that is, hypovolemic shock in the course of a nephrotic syndrome. In the case presented, clues to the latter were a history of gastroenteritis, hemoconcentration (rise in hemoglobin level from 10.4 to 12.6 mmol/L (16.1 to 19.5 g/dL), extremely low sodium excretion and a very rapid drop in serum albumin <1.0 g/dL. Infection was excluded by low C-reactive protein concentrations and a negative blood culture.

Nephrotic crisis is not uncommon but seldom mentioned in the literature.[1] Wang et al[1] identified 19 episodes (5.8%) of hypovolemic shock during 328 hospital admissions of children with nephrotic syndrome. Hypovolemic crises typically occurred early in the course of nephrotic syndrome (both de novo and during relapse), even before edema was evident.[1] Abdominal pain was mostly associated with other symptoms of hypovolemia.[1] Of note, 6 patients had more than 1 episode, which was also the case in our patient.

Van de Walle et al[2] studied 19 children aged 2.2 to 13 years with steroid-sensitive, minimal-change nephrotic syndrome (MCNS) during relapse. Of these, 9 children met the criteria of nephrotic crisis. Proteinuria and hypoalbuminemia were not different in patients with nephrotic crisis compared with the nonhypovolemic group. The hypovolemic children had increased renin, aldosterone, vasopressin, and noradrenalin resulting in a lower glomerular filtration rate (GFR) and sodium clearance and an increased distal-tubular Na/K-exchange ($U_{[K]}/(U_{[K]} + U_{[Na]}) > 0.6$). This is in line with data by Kapur et al[3] who identified nephrotic patients with hypovolemia using a cut-off of 0.2% for the fractional excretion of sodium ($100 \times U_{[Na]} \times S_{[creat]}/(S_{[Na]} \times U_{[creat]})$) reflecting avid sodium retention.

Patients with hypovolemia more commonly have a GFR >75% of normal, MCNS, and an acute onset of severe hypoalbuminemia <1.0 g/dL.[4,5] In contrast, patients with a GFR <50% of normal, albumin concentration >2.0 g/dL, and hypertension, were more likely to have normal or elevated intravascular volume. Tubulointerstitial inflammation, as occurs in membranous nephropathy and secondary focal glomerulosclerosis leads to sodium retention and lowers GFR,[6] which might explain why hypovolemia is observed mainly in MCNS where inflammation is absent.

Fluid handling across capillary walls is described by the Starling equation[7]:

$$J_v = L_p \times S \times \mathrm{EFP}, \quad (1)$$

where J_v denotes the transcapillary fluid flux, L_p the hydraulic conductance, S the filtration surface, and EFP the effective filtration pressure.[8]

The EFP is calculated as the difference between net hydrostatic and oncotic pressure gradients:

$$\mathrm{EFP} = (P_c - P_i) - (\Pi_c - \Pi_i), \quad (2)$$

where P represents the hydrostatic pressure (P_c = capillary, P_i = interstitial) and Π the oncotic pressure (Π_c = capillary, Π_i = interstitial).

The capillary oncotic pressure Π_c can be calculated using the formula of Landis and Pappenheimer.[9,10]

$$\Pi_c = 2.8A + 0.16A^2 + 0.12A^3 + 1.6G + 0.15G^2 + 0.006G^3, \quad (3)$$

with A representing serum albumin and G serum globulin, both in g/dL. A serum albumin concentration of 0.6 g/dL and globulin concentration of 2.5 g/dL, as observed in our patient, results in a Π_c of 7 mm Hg.

Fluid changes along the peripheral capillary in health and in compensated nephrotic syndrome are illustrated in Figures 1 and 2. In the normal situation (Figure 1), the hydrostatic pressure gradient at the arterial end exceeds the oncotic pressure gradient, favoring fluid extravasation. This is largely reversed at the venous end, where P_c has decreased and Π_c has stayed the same, leading to reabsorption of most of the filtrate. The remainder is reabsorbed via the lymphatic system.

Renal protein loss in nephrotic syndrome (Figure 2) leads to a decrease in Π_c causing an increase in EFP whereas the transcapillary hydrostatic pressure gradient remains largely unchanged, reflecting the high compliance

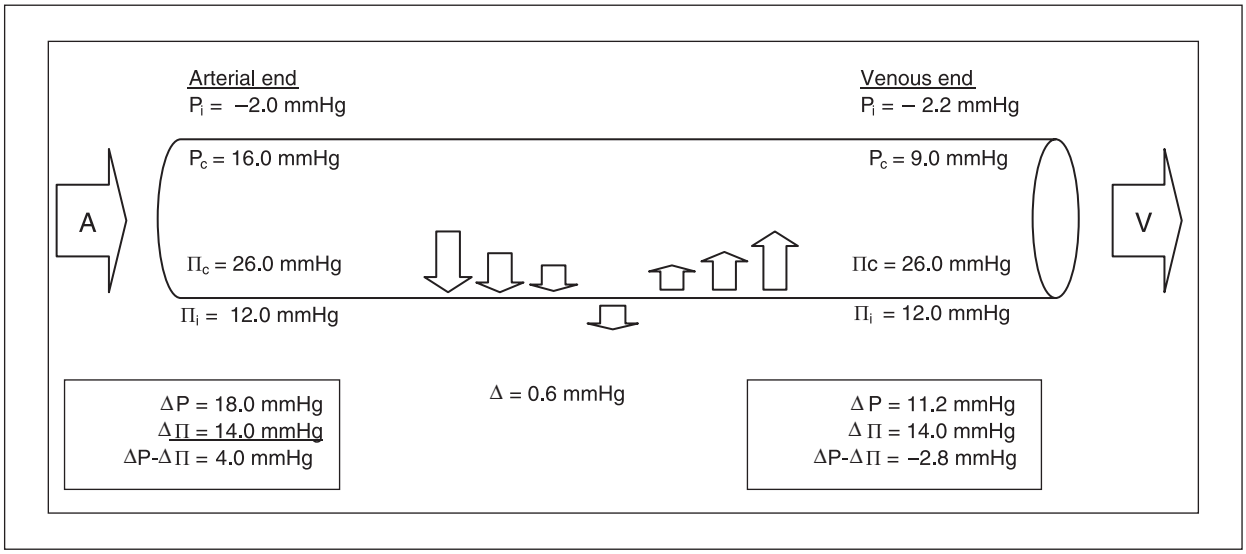

Figure 1. Model of the Starling forces along capillary wall (normal situation). Modified according to Vande Walle et al.[8]
Note: Starling equation: $J_v = K_f \times S \times$ EFP. Effective filtration pressure (EFP) = $\Delta P - \Delta\Pi$. Pressure gradient $\Delta P = P_c - P_i$, where P is the hydrostatic pressure and subscripts "c" and "i" stand for capillary and interstitial, respectively. Colloid osmotic gradient $\Delta\Pi = \Pi_c - \Pi_i$, where Π is the oncotic pressure and subscripts "c" and "i" stand for capillary and interstitial, respectively.

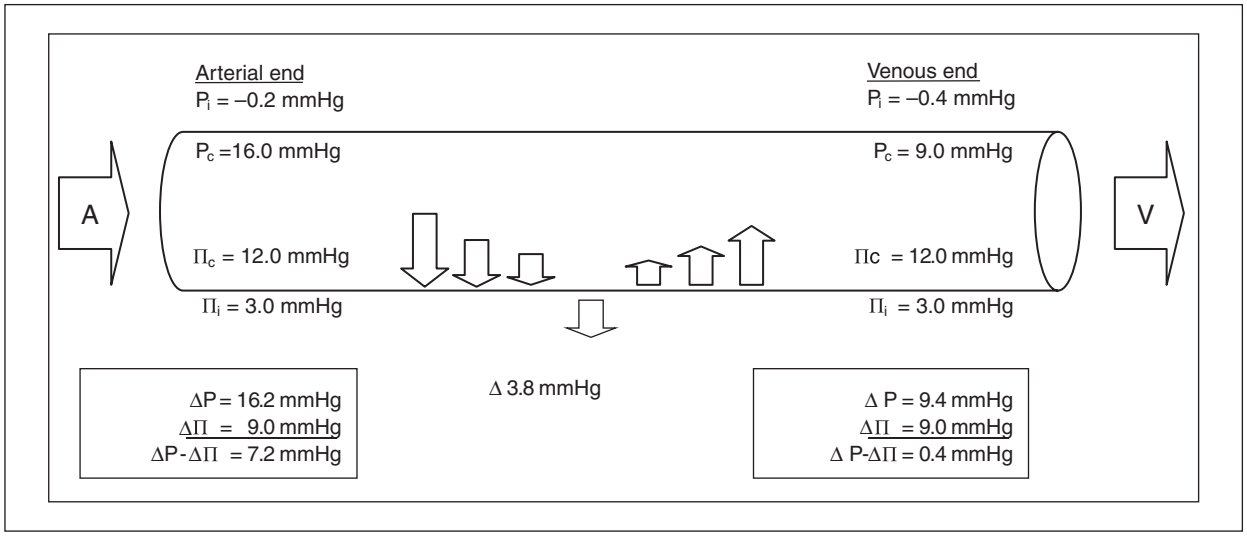

Figure 2. Model of the Starling forces along capillary wall (renal protein loss in nephrotic syndrome). Modified according to Vande Walle et al.[8]
Note: Starling equation: $J_v = K_f \times S \times$ EFP. Effective filtration pressure (EFP) = $\Delta P - \Delta\Pi$. Pressure gradient $\Delta P = P_c - P_i$, where P is the hydrostatic pressure and subscripts "c" and "I" stand for capillary and interstitial, respectively. Colloid osmotic gradient $\Delta\Pi = \Pi_c - \Pi_i$, where Π is the oncotic pressure and subscripts "c" and "i" stand for capillary and interstitial, respectively.

of the soft tissues.[11] Also, capillary permeability for fluid and macromolecules is increased in nephrotic syndrome favoring fluid extravasation.[11] During a slow decrease in plasma albumin concentration, washout of interstitial albumin limits fluid extravasation (so-called "osmotic buffering").[7] Therefore, in compensated nephrotic syndrome, there is little tendency to plasma volume depletion[8] and edema formation is for the most part due to sodium retention by stimulation of the ENaC sodium channel in the distal tubule.[12]

Nephrotic crisis is characterized by intravascular volume depletion with activation of the rennin–aldosteron system. In patients with nephrotic syndrome not due to MCNS, Van de Walle et al[5] found an inverse

relationship between plasma aldosteron and Π_c.[5] In the hypovolemic patients—most of them with congenital nephrotic syndrome—a Π_c <5 mm Hg was found. In this situation, hypovolemia results from failure to lower Π_i sufficiently to maintain the osmotic pressure gradient.[8] For this reason, children with congenital nephrotic syndrome require regular albumin infusions[13] and/or therapeutic interventions to limit renal albumin losses (angiotensin converting enzyme inhibition, nonsteroidal anti-inflammatory drugs, nephrectomy). In MCNS patients with relapse, by contrast, no clear relationship between Π_c, plasma aldosteron, and clinical signs of hypovolemia was found. As pointed out by the authors, this probably reflects different time points in the course of the relapse. A rapid onset of severe hypoalbuminemia, usually to concentrations <1.0 g/dL, may cause temporary disequilibrium between plasma and extravascular albumin stores.[5] This may lead to intravascular volume depletion until mobilization of interstitial albumin is accomplished and the osmotic gradient restored.[5] Intravascular fluid contraction causes intestinal ischemia, which further aggravates hypovolemia because of intestinal fluid losses as in our patient.

In the case presented, hypovolemia was treated with fluid resuscitation using normal saline (total 60 mL/kg) followed by 1 g/kg human albumin.[3] The latter is crucial to restore the oncotic gradient.[8] In the series by Wang et al,[1] this treatment was effective in 58 out of 61 episodes. In our patient, plasma albumin remained >1.2 g/dL on the following days, after a single albumin infusion. This reflects diminished albumin loss, mobilization of interstitial albumin stores and an increase in hepatic albumin synthesis.[14]

Conclusion

Nephrotic crisis presents with hypovolemic shock and abdominal symptoms reflecting gastrointestinal hypoperfusion. Hemoconcentration and albumin levels <1.0 g/dL are typical findings. Therapy includes intravenous fluid resuscitation and administration of intravenous albumin to restore normal adaptation mechanisms.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References

1. Wang SJ, Tsau YK, Lu FL, Chen CH. Hypovolemia and hypovolemic shock in children with nephrotic syndrome. *Acta Paediatr Taiwan*. 2000;41:179-183.
2. Van de Walle JG, Donckerwolcke RA, Greidanus TB, Joles JA, Koomans HA. Renal sodium handling in children with nephrotic relapse: relation to hypovolaemic symptoms. *Nephrol Dial Transplant*. 1996;11: 2202-2208.
3. Kapur G, Valentini RP, Imam AA, Mattoo TK. Treatment of severe edema in children with nephrotic syndrome with diuretics alone—a prospective study. *Clin J Am Soc Nephrol*. 2009;4:907-913.
4. Van de Walle JG, Donckerwolcke RA, van Isselt JW, Derkx FH, Joles JA, Koomans HA. Volume regulation in children with early relapse of minimal-change nephrosis with or without hypovolaemic symptoms. *Lancet*. 1995;346:148-152.
5. Van de Walle JG, Donckerwolcke RA, Koomans HA. Pathophysiology of edema formation in children with nephrotic syndrome not due to minimal change disease. *J Am Soc Nephrol*. 1999;10:323-331.
6. Rodriguez-Iturbe B, Herrera-Acosta J, Johnson RJ. Interstitial inflammation, sodium retention, and the pathogenesis of nephrotic edema: a unifying hypothesis. *Kidney Int*. 2002;62:1379-1384.
7. Levick JR. Capillary filtration-absorption balance reconsidered in light of dynamic extravascular factors. *Exp Physiol*. 1991;76:825-857.
8. Van de Walle JG, Donckerwolcke RA. Pathogenesis of edema formation in the nephrotic syndrome. *Pediatr Nephrol*. 2001;16:283-293.
9. Treskes M, Duijnhoven van JLP, Speelberg B. De waarde van de bepaling van de colloïd osmotische druk op de intensive care. *Ned Tijdschr Klin Chem*. 1996;21:68-70.
10. Hoefs JC. Globulin correction of the albumin gradient: correlation with measured serum to ascites colloid osmotic pressure gradients. *Hepatology*. 1992;16:396-403.
11. Doucet A, Favre G, Deschenes G. Molecular mechanism of edema formation in nephrotic syndrome: therapeutic implications. *Pediatr Nephrol*. 2007;22:1983-1990.
12. Svenningsen P, Bistrup C, Friis UG, et al. Plasmin in nephrotic urine activates the epithelial sodium channel. *J Am Soc Nephrol*. 2009;20:299-310.
13. Holmberg C, Antikainen M, Rönnholm K, Ala Houhala, M, Jalanko H. Management of congenital nephrotic syndrome of the Finnish type. *Pediatr Nephrol*. 1995;9:87-93.
14. Ballmer PE, Weber BK, Roy-Chaudhury P, et al. Elevation of albumin synthesis rates in nephrotic patients measured with [1-13C]leucine. *Kidney Int*. 1992;41:132-138.