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CASE REPORT

Treatment of extreme overhydration in an adolescent boy with idiopathic nephrotic syndrome

Andrzej Szydłowski[1], Anna Szydłowska[1], Agata Masłocha[1], Aurelia Morawiec-Knysak[2], Katarzyna Broll-Waśka[2], Agnieszka Jędzura[2], Maria Szczepańska[2]

[1]Student at the Department of Paediatrics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[2]Department of Paediatrics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

ABSTRACT

The key factors in the diagnosis of nephrotic syndrome (NS) in children are as follows: proteinuria > 50 mg/kg/day and serum albumin level ≤ 30 g/l (prevalence: 16/100,000; incidence: 2–7/100,000 cases per year). Glucocorticoids are preferred to obtain remission. Diuretics and albumin infusions are used in oedema reduction. In cases of extreme overhydration, renal replacement therapy (RRT) is advised.

A 16-year-old boy with no past medical history was admitted in critical condition due to massive oedema and anuria. Standard NS treatment was introduced on admission. The patient underwent continuous RRT combined with loop diuretics and albumin administration. Thirty-six litres of ultrafiltrate was achieved. No relapse was observed within 6 months of discharge.

The presented case is unusual due to the enormous oedema, reaching approximately 30% of the initial body weight, which led to a vital clinical problem. The use of continuous RRT combined with steroid therapy allowed for a safe evacuation of the oedema and remission.

KEY WORDS:

renal replacement therapy, nephrotic syndrome, oedema, nephrology.

INTRODUCTION

Nephrotic syndrome (NS) develops due to urinary protein loss, mainly albumins, exceeding compensatory mechanisms. Increased proteinuria is caused by pathological permeability of the glomerular filtration barrier. Diagnosis of nephrotic syndrome in children is considered when proteinuria increases above 50 mg/kg/day and albumin concentration in blood decreases by ≤ 30 g/l. As the final effect of described abnormalities, patients manifest oedema, hyperlipidaemia, and other complications [1–4].

In most paediatric cases, the morphologic background of idiopathic NS (INS) is minimal change nephropathy. It constitutes 90% of NS cases in children aged 1–10 years and 50% >10 years. The incidence of INS oscillates around 2–7/100,000, whereas the prevalence (including recurrent cases) is 16/100,000. Idiopathic nephrotic syndrome is diagnosed twice as often in boys than in girls. Incidence peaks at between 2 and 6 years of age, and the frequency halves at over 12 years of age [1, 2].

The basic treatment of first acute-onset INS consists of glucocorticosteroids (GCS), causing remission of the disease in 80% of treated children. The response to steroid defines clinical types of NS, such as: steroid sensitive, steroid dependent, frequently recurrent NS, primarily and secondarily steroid resistant NS [2].

The symptomatic treatment of NS is focused mainly on oedema evacuation and prevention of NS complications. To reduce oedema during an acute onset, diuretics

ADDRESS FOR CORRESPONDENCE:

Andrzej Szydłowski, Department of Paediatrics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland, e-mail: andrzej.szydlowsky@gmail.com

in combination with oncotic fluid infusions (e.g. 20% albumin) are used. In the case of oliguria and extreme overhydration, it may be useful or even necessary to introduce extracorporeal water evacuation using renal replacement therapy methods (RRT) [1].

The authors present the management of an NS outbreak in an adolescent boy with an enormous oedema.

CASE REPORT

A 16-year-old boy with generalized oedema and anuria was admitted to the Children's Nephrology Ward for further diagnostics and treatment. The symptoms increased during the 3 weeks prior to admission. Initially the oedema was situated in the lower extremities, spreading to the abdomen, face, and upper extremities with an exceptional intensification during the week prior to hospitalization. The boy developed anuria a day before admission. An estimated increase in body weight of 25 kg was reported (33% of body weight).

Because of the patient's refusal to be hospitalized, he was administered a "dehydrating" dietary supplement by his mother.

The patient neglected previous chronic conditions and any medicine administration, reporting only nicotinism. On admission, a significant dyspnoea and tachypnoea was reported (RR 30/min, BP 142/104 mm Hg, HR 122/min, $SatO_2$ – 99% obtained with passive oxygen therapy). The patient's body weight and height were 95.2 kg and 178 cm, respectively. According to collected medical history, the patient was not overweight or obese. Physical examination revealed the following: significant generalized oedema, mostly intensified in lower extremities, scrotum, and penile area, bilaterally muted alveolar murmur in the pulmonary area, and muted percussion below the 4th intercostal space. Laboratory test results revealed characteristics typical for NS (Table 1).

Abdominal ultrasonography showed the following: a large volume of pleural fluid causing atelectasis of lower lung segments; peritoneal fluid (2 cm in perihepatic area, 1–2 cm within interloop spaces; 7 cm within recto-vesical pouch; 6 cm around right paracolic recess); hepatosplenomegaly with hyperechogenic liver parenchyma; bilaterally enlarged hyperechogenic kidneys with diminished corticomedullary differentiation (right kidney 13.2 × 5.2 cm; left kidney 13.0 × 6.0 cm), without signs of calyces and pelvis dilation; and echo-negative urinary bladder. Moreover, a thickened (< 9 mm), swollen, blurry intestinal wall was shown.

A chest X-ray picture showed the presence of bilateral intrapleural fluid, reaching the 4th right and 5th left anterior rib sections, along with symptoms of atelectasis. Due to persistent anuria (lasting > 24 h), intense dyspnoea, and increasing oedema, despite loop diuretics treatment, an urgent RRT in the form of continuous isolated ultrafiltration (SCUF) and, subsequently, haemofiltration were introduced. An acute two-lumen catheter was placed in the right internal jugular vein. A Prismaflex System machine, Baxter (Healthcare Corporation, One Baxter Parkway, Deerfield, IL, USA) was used with low-molecular-weight heparin anticoagulation. Intermittent haemofiltration was continued from day 4 using Fresenius Medical Care 4008 S machines (Fresenius Medical Care AG and Co. KGaA, Bad Homburg, Germany).

Intravenous GCS treatment (methylprednisolone 60 mg/24 h) and empirical antibiotics were introduced consecutively. During SCUF, due to critical hyponatraemia and hypoalbuminaemia with coexisting coagulopathy, the patient received infusion of plasma and 20% albumin. Symptomatic treatment consisted of nadroparin calcium, proton pump inhibitor, calcium and vitamin D_3 supplementation, and oxygen therapy. Patient's body weight and fluid balance was controlled regularly (Figure 1).

On the 4th day of treatment echocardiography was performed, revealing 3 cm of pericardial fluid (cardiac tamponade excluded). Left ventricle (LV) size was within the upper limit, with maintained correct contractibility of the cavities. To exclude connective tissue diseases, an antibody profiling was ordered (RNPSm, Sm, Ro-52, SS-B, Scl-70, Jo-1, Centromere B, PCNA, dsDNA, nucle-

TABLE 1. Laboratory test results showing the characteristics typical for nephrotic syndrome, changing over time

Variable	Day 1	Day 13	DAY 27	Reference range
Total protein [g/l]	32.2 ↓	46.20 ↓	61.70	60–80
Albumin [g/l]	12.35 ↓↓	29.56 ↓	43..67	35–50
Cholesterol [mmol/l]	12.34 ↑↑	9.75 ↑	9.14 ↑	3.60–5.20
Creatinine [µmol/l]	107	95	77	53–115
D-dimers [µg/l]	3290 ↑↑	2340 ↑	–	< 500
Proteinuria [g/l]	45.90 ↑↑	45.20 ↑↑	Trace	0.00
HB [g/dl]	17.90 ↑	13.10	12.50	12.50–16.10
PLT [103/µl]	415	303	256	150–450
WBC [103/µl]	13.34 ↑	13.47 ↑	18.90 ↑	4.00–10.50

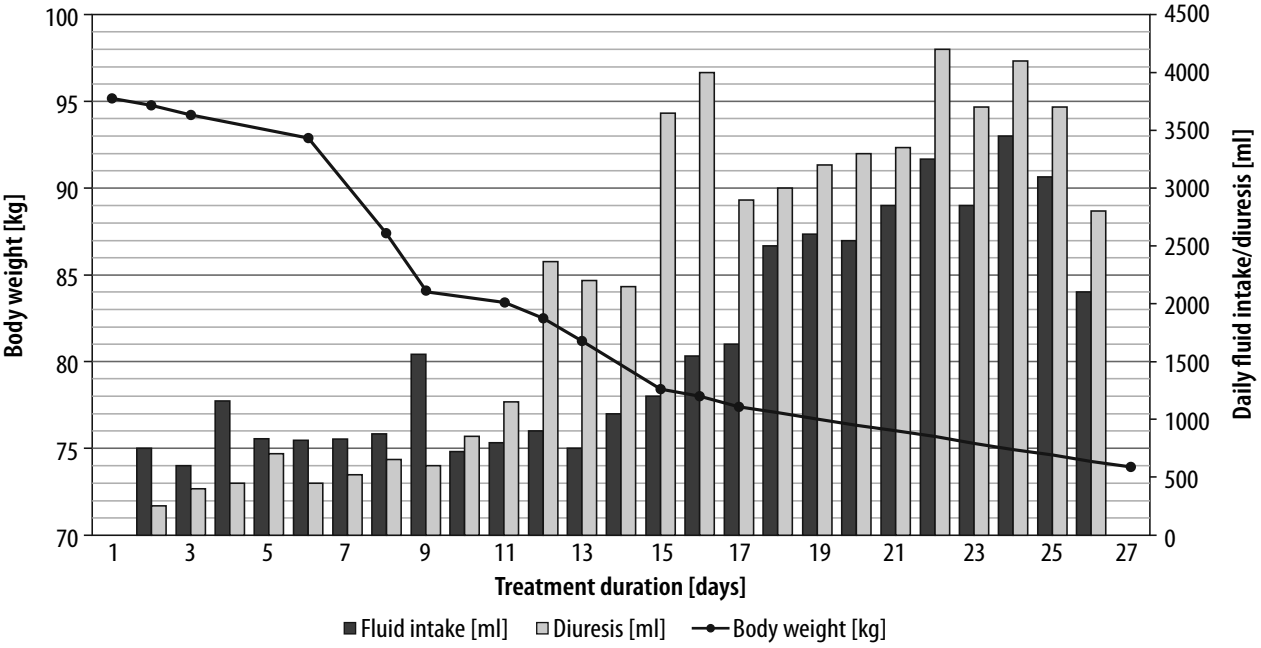

FIGURE 1. Patient's body weight to fluid balance, presented over the time of treatment

osomes, histones, ribosomal-P-protein, AMA-MM2, anti-MPO and anti-PR2), all of which were negative.

Extracorporeal dehydration was finished on the 14th day, after normalisation of diuresis, improved laboratory tests results, and after reaching euvolaemia. During the hospitalisation a total of 19 RRT sessions were performed (at the beginning as constant ultrafiltration, then, in order to avoid long-term immobility of the boy, as "classic" paused haemodialysis) with a total of 36 l of ultrafiltrate (Figure 1).

The patient was discharged on the 25th day of hospitalization, in good general condition, with body weight of 73.9 kg, BP 143/87 mm Hg, and eGFR 90.2 ml/min/1.73 m^2 (Schwartz method). The combination of pharmacological therapy and RRT allowed a controlled and safe dehydration, with consecutive gradual elimination of accumulated oedema and a 21 kg body weight reduction over 4 weeks. Outpatient care consisted of continuation of GCS treatment, according to the recommended dosing. Due to arterial hypertension, angiotensin-converting-enzyme inhibitors and supplementation of vitamins and electrolytes (magnesium 900 mg 2 × per day; calcium 400 mg 2 × per day; potassium 391 mg 1 × per day cholecalciferol 2500 IU 1 × per day) were added. Anticoagulation prophylaxis was continued (Figure 2). The presented case was eventually classified as steroid-sensitive INS.

DISCUSSION

The cause of NS is damage of glomerular microstructure and loss of negative electric potential of the glomerular filtration barrier. Leaking of the glomerular microstructure in NS results in a significant urinary protein loss. Albumin production in liver is increased but in most cases to a level not satisfactory to compensate the loss. Hypoalbuminaemia decreases oncotic pressure of blood, leading to disequilibrium in Starling forces, resulting in diffusion of fluid into the interstitium. An additional mechanism affecting the formation of oedema is an increased absorption of sodium in the renal collecting duct, leading

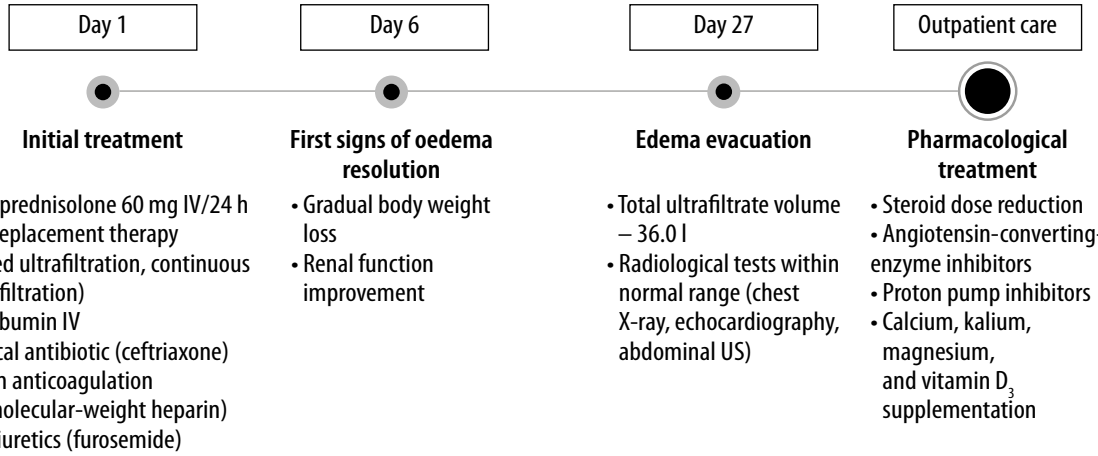

FIGURE 2. The initial pharmacological and renal replacement therapy treatment and its modifications over time of hospitalization

to retention of sodium and water [5–8]. Ichikawa *et al*. observed that the concentration of sodium in the urine of patients affected by NS was 3 times lower than in a healthy control group. This formed the basis of the theory claiming that sodium reabsorption in NS depends on dysfunction of the nephron's collecting duct [9]. Animal-model-based research conducted by Svenningsen *et al*. explained the pathomechanism of this phenomenon. Plasminogen is filtrated by a damaged filtration barrier in patients with NS, and is then converted into plasmin by urokinase present in collecting tubules. Plasmin then activates ENaC (amiloride-sensitive sodium channel), which results in sodium resorption, retention, and accumulation of oedema [10]. Moreover, in NS sodium-potassium ATP-ase is activated on the basolateral area of cells located in the cortical segment of distal tubule, independently of aldosterone and vasopressin. An additional mechanism of sodium retention is resistance of the medullar segment of distal tubule to atrial natriuretic peptide. All the mechanisms of increased sodium retention in nephron in the course of NS are additionally stimulated by angiotensin II [6–10].

Oedemas appear due to diffusion of water from blood vessels into the extracellular matrix; they can be local or generalized. Extremely intense oedema may have multiple consequences including immobilization, skin lesions, and stretch marks, as well as complications leading to infections [5]. An obstruction in venal outflow due to intensified oedema, along with significant abnormalities in serum composition, additionally increases risk of thrombosis. The knowledge of oedema pathogenesis in NS allows the optimal treatment to be applied, depending on the intensiveness of this symptom.

It is not recommended to reduce oedema quickly, because dehydrating the patient too rapidly may result in hypovolaemia and glomerular filtration rate (GFR) impairment in the pre-renal acute kidney injury (AKI) mechanism. Rapidly developing NS in children results in hypovolaemia, leading to reduced GFR even before dehydrating therapy [11–14]. In the case described, it was necessary to pay simultaneous attention to the massive peripheral oedema and to AKI symptoms.

During the acute onset of an active phase of NS, the patient requires albumins with loop diuretics to reduce the oedema, combined with albumin infusion and sodium intake reduction. In the case of anuria and extreme overhydration, it is necessary to apply continuous veno-venous ultrafiltration [1, 5]. An advantage of such a procedure is a controlled regulation of patient dehydration. Sutherland *et al*. revealed that accumulated overhydration < 20% in the beginning of RTT has a more favourable prognosis, compared to patients with overhydration percentage (%FO) > 20% (46% vs. 68%, $p < 0.01$). During the state of accumulated overhydration equal to > 10 %FO RRT should be considered, whereas in a situation where overhydration exceeds 20% FO the patient should unquestionably begin RRT or renal supportive therapy [15]. Placement of an intravenous central catheter for RRT is the indication for anticoagulant application as the thromboembolism prophylaxis. In our patient the risk of thromboembolism was very high due to the enormous oedema, massive proteinuria, immobilization, and extremely low serum albumin level, which is consistent with current guidelines on the treatment of INS [2].

It is necessary to remember that all steroids are removed by continuous RRT, so their dose should be increased. Honoré *et al*. summarized that the daily doses of methylprednisolone and prednisone need to be higher by 70–100% during continuous RRT, but they do not explain in detail the doses depending on the RRT method used [16]. Dubinsky *et al*. in their manuscript point out the pharmacokinetics of frequently used drugs in children treated with RRT and provide wide evidence on how to adjust the doses [17].

First-line medical staff should constantly be educated in terms of differential diagnosis of life-threatening illnesses manifested by mild symptoms. Recognition of initial symptoms of nephrotic syndrome's acute onset and the potential results of chronic treatment allow for quick admission to the hospital, as well as application of less invasive treatment methods, resulting in more favourable prognosis. Moreover, financial expenses of a prolonged hospitalization and treatment of an extremely overhydrated patient greatly surpass the cost of an early-stage diagnosis. Finally, the use of media-advertised dietary supplements may delay the diagnostic process and lead to severe consequences.

CONCLUSIONS

Treatment of every case of NS should be planned with thorough knowledge and criticism. It is especially vital in the group of non-compliant adolescent patients. The treatment algorithm should be adjusted, sometimes resulting in unconventional methods not applied to paediatric patients on a daily basis.

DISCLOSURE

The authors declare no conflict of interest.

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