December 30, 2019

PharmacologyOnLine

Newsletter • 2019 • vol.3 • 58-65

A DRAMATIC REPORT ON NEPHROTIC SYNDROME OF CHILDREN

Md. Harun-Or-Rashid[1], Sharif M. Shaheen[1], Dr. Tarek Muhammad Nurul Islam[2], Md. Mizanur Rahman[1], Md. Mamunur Rashid Munna[1] and Most. Nazmin Akter[1]

[1]Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Daffodil Tower (DT)-054/2 Sobahanbag, Mirpur Road, Dhanmondi, Dhaka-1207, Bangladesh.

[2]Sir Salimullah Medical College, Mitford Rd, Dhaka 1100

Email address: harun.1947.1952@gmail.com

Abstract

Nephrotic syndrome is a not unusual form of kidney ailment visible in youngsters. Historically, Roelans is credited with the first clinical description of nephrotic syndrome inside the past due fifteenth century, whereas Zuinger later supplied an in depth description of the scientific route of the disorder and its importance as a cause of persistent renal failure within the presteroid era. The nephrotic syndrome is characterised with the aid of accelerated permeability across the glomerular filtration barrier. Several mechanisms of glomerular injury are responsible for pathogenesis, consisting of circulating thing, circulating immune factors in immune-mediated disorders and mutations in podocyte or slit diaphragm proteins. Children with nephrotic syndrome are categorised as number one, secondary and congenital / childish nephrotic syndrome. Children with idiopathic nephrotic syndrome, the maximum commonplace shape, may be divided into those with steroid-resistant nephrotic syndrome, who're at increased chance for growing end-level renal sickness, and people with steroid-responsive nephrotic syndrome, representing the majority of cases. Treatment strategies include immunosuppressive and non-immunosuppressive measures. Congenital nephrotic syndrome is a nephrotic syndrome that offers at birth or in the course of the primary three months of existence whilst infantile nephrotic syndrome offers between 3 and 365 days of age. Research is being accomplished to similarly elucidate the disorder's molecular pathogenesis, become aware of new prognostic signs, and to develop higher processes to remedy.

Keywords: *Nephrotic syndrome, podocyte, Children, Steroid-resistance, Steroid-responsiveness, Genetics, Immunosuppressive, Treatment*

Introduction

Nephrotic Syndrome (NS) is the clinical manifestation of glomerular diseases. Nephrotic syndrome is a medical syndrome characterized by severe proteinuria (greater than 40 mg / m2 per hour) that causes hypoalbuminemia (less than 30 g / L), resulting in hyperlipidemia, oedema, and various complications. It is caused by increased permeability, particularly infectious or thrombo-embolic through the damaged basement membrane in the renal glomerulus. It is the culmination of a glomerular permeability abnormality that may be primary to congenital disorders, diabetes, systemic lupus erythematosus, neoplasia, or certain substance use with a disorder relevant to the kidneys [1][2][3]. That also increased risk of coronary heart disease associated with Nephrotic Syndrome. Patients with Nephrotic Syndrome (NS) are believed to be at increased risk of atherosclerosis and coronary heart disease (CHD). Nephrotic Syndrome can affect children of any age, from infancy to adolescence and is most commonly seen among school-aged children and adolescents. Nephrotic Syndrome affects 1-3 per 100,000 children <16 years of age. Males appear to be more affected than females at a ratio of 2:1 in children, but this predominance fails to persist in adolescence [4][5][6][7]

Cause of Nephrotic Syndrome (NS)

Genetic disorders: Nephrotic-syndrome typical Finnish-type congenital nephrotic syndrome, FSGS, Diffuse mesangial sclerosis, Denys-Drash syndrome, Schimke immuno-osseous dysplasia [8][9]

Proteinuria with or without nephrotic syndrome: Nail-patella syndrome, Alport's syndrome [10][11]

Multisystem syndromes with or without nephrotic syndrome: Galloway-Mowat syndrome, Charcot-Marie-Tooth disease, Jeune's syndrome, Cockayne's syndrome, Laurence-Moon-Biedl-Bardet syndrome Metabolic disorders with or without nephrotic syndrome: Alagille syndrome, Alpha-1 antitrypsin deficiency, Fabry disease, Glutaric acidaemia, Glycogen storage disease, Hurler's syndrome, Lipoprotein disorders , Mitochondrial cytopathies, Sickle-cell disease[12][13][14]

Idiopathic nephrotic syndrome: MCNS, FSGS, Membranous nephropathy

Secondary causes: Infections Hepatitis B, C, HIV-1, Malaria, Syphilis, Toxoplasmosis

Drugs: Penicillamine, Gold, Non-steroidal anti-inflammatory drugs, Pamidronate, Interferon, Mercury, Heroin, Lithium[15]

Immunological or allergic disorders: Castleman's disease, Kimura's disease, Bee sting, Food allergens [16]

Associated with malignant disease: Lymphoma, Leukaemia

Glomerular hyperfiltration : Oligomeganephronia, Morbid obesity, Adaptation to nephron reduction [17].Most children of Nephrotic Syndrome are in the form of primary or idiopathic. Nephrotic Syndrome may also be secondary to systemic diseases such as systemic lupus erythematosus, Henoch-Schönlein purpura, malignancy, and infections. The underlying

abnormality in Nephrotic Syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. In idiopathic, hereditary, and secondary forms of Nephrotic Syndrome, there are immune and nonimmune insults to the podocyte that lead to foot process effacement of the podocyte, a decrease in number of functional podocytes, and altered slit diaphragm integrity. The end result is increased protein "leakiness" across the glomerular capillary wall.[18]

Complication of Nephrotic Syndrome (NS)

Edema is the most common presenting symptom of children with Nephrotic Syndrome. There are several alterations in the lipid profile in children with Nephrotic Syndrome, Children with nephrotic syndrome are especially susceptible to infections such as cellulitis, spontaneous bacterial peritonitis. This occurs as a result of many factors, particularly hypoglobulinemia as a result of the urinary losses of immunoglobulin (Ig)G. Nephrotic Syndrome is a hypercoagulable state resulting from multiple factors. [19-25

Diagnosis of patients with Nephrotic Syndrome (NS)

The diagnosis of Nephrotic Syndrome is confirmed by urinalysis with first morning urine protein: creatinine ratio and serum albumin, and cholesterol levels; evaluation to rule out secondary forms of nephrotic syndrome (children ≥10 yr): complement C3 level, antinuclear antibody, double-stranded DNA and hepatitis B and C, and HIV in high-risk populations; and kidney biopsy (for children ≥12 yr, who are less likely to have MCNS). A spot urine protein: creatinine ratio should be >2.0. The serum albumin level is <2.5 g/dL, and serum cholesterol and triglyceride levels are elevated. Serum complement levels are normal. Children with their first episode of nephrotic syndrome is admitted for successful education of the family regarding all aspects of the condition. [26][27][28]

Treatment of patients with Nephrotic Syndrome (NS)

Corticosteroids are the mainstay of therapy for MCNS (Minimal Change Nephrotic Syndrome). Prednisone or prednisolone should be administered as a single daily dose of 60 mg/m2/day or 2 mg/kg/day to a maximum of 60 mg daily for 4-6 weeks followed by alternate-day prednisone for a period ranging from 8 weeks to 5 months, with tapering of the dose. Approximately 80-90% of children respond to steroid therapy. Response is defined as the attainment of remission within the initial 4 weeks of corticosteroid therapy. In case of severe symptomatic edema, including large pleural effusions, ascites, or severe genital edema, should be hospitalized managed by salt restriction and diuretics. Dyslipidemia should be managed with a low-fat diet. If there is suspicion of infection, a blood culture should be drawn prior to starting empiric antibiotic therapy [29][30][31][32]

Relapse of Nephrotic Syndrome (NS)

Relapse of nephrotic syndrome is defined as a urine protein: creatinine ratio of >2 or ≥3+ protein on urine

dipstick testing for 3 consecutive days. Relapses are usually treated in a manner similar to the initial episode, except that daily prednisone courses are shortened. Steroid-dependent patients, frequent relapse's, and steroid-resistant patients are candidates for alternative therapies. Calcineurin inhibitors (cyclosporine or tacrolimus) are recommended as initial therapy for children with steroid-resistant nephrotic syndrome. Mycophenolate, Levamisole, Rituximab are another options.

Pneumococcal vaccination and influenza vaccination annually to the child and their household contacts; defer vaccination with live vaccines until the prednisone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days. Live virus vaccines are contraindicated in children receiving corticosteroid sparing agents such as cyclophosphamide or cyclosporine [33][34][35]

Conclusion:

Most children with steroid-responsive Nephrotic Syndrome have repeated relapses, which generally decrease in frequency as the child grows older. Children with steroid-resistant Nephrotic Syndrome, most often caused by FSGS (Focal Segmental glomerulosclerosis), generally have a poor prognosis. These children develop progressive renal insufficiency, ultimately leading to end stage renal disease.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgments

The authors are grateful to Sharif M. Shaheen , Md. Mizanur Rahman, Md. Mamunur Rashid Munna and Most. Nazmin Akter for concept, design, and approval of paper. The authors are also grateful to Dr. Tarek Muhammad Nurul Islam for the data collection from the different articles and also critical revision of paper.

References

1. Hill AJ, Stone DE, Elliott JP, Gerkin RD, Ingersoll M, Cook CR. Management of Nephrotic Syndrome in the Pregnant Patient. J Reprod Med. 2016 Nov-Dec;61(11-12):557-61
2. Raina R, Krishnappa V. An update on LDL apheresis for nephrotic syndrome. Pediatr. Nephrol. 2018 Sep 14
3. Dumas De La Roque C, Prezelin-Reydit M, Vermorel A, Lepreux S, Deminière C, Combe C, Rigothier C. Idiopathic Nephrotic Syndrome: Characteristics and Identification of Prognostic Factors. J Clin Med. 2018 Sep 09;7(9)
4. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, Wigfall D, Miles P, Powell L, Lin JJ, Trachtman H, Greenbaum LA. Management of childhood onset nephrotic syndrome. Pediatrics. 2009; 124(2): 747-757. Epub 2009 Jul 27
5. Srivastava T, Simon SD, Alon US: High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood, Pediatr Nephrol 13 (1):13-18, 1999.

6. Bonilla-Felix M et al: Changing patterns in the histopathology of idiopathic nephrotic syndrome in children, Kidney Int 55 (5):188590, 1999.
7. Filler G et al: Is there really an increase in non-minimal change nephrotic syndrome in children? Am J Kidney Dis 42 (6):1107-13, 2003.
8. Hinkes B et al: Genetic causes of nephrotic syndrome in the fi rst year of life. American Pediatric Nephrology Meeting, 2006. Marburg.
9. Lenkkeri U et al: Structure of the gene for congenital nephrotic syndrome of the Finnish type (NPHS1) and characterization of mutations, Am J Hum Genet 64 (1):51-61, 1999.
10. ISKDC: The primary nephrotic syndrome in children. Identifi cation of patients with minimal change nephrotic syndrome from initial response to prednisone, J Pediatr 98 (4):561-64, 1981.
11. Niaudet P: Steroid-resistant idiopathic nephrotic syndrome in children. In Avner ED, Harmon WE, Niaudet P, editors: Pediatric nephrology, Philadelphia, 2004, Lippincott Williams & Wilkins.
12. Caridi G, Bertelli R, Carrea A, et al. Prevalence, genetics, and clinicalfeatures of patients carrying podocin mutations in steroid-resistantnonfamilial focal segmental glomerulosclerosis. J Am Soc Nephrol2001; 12:2742–46.
13. Karle SM, Uetz B, Ronner V, Glaeser L, Hildebrandt F, Fuchshuber A. Novel mutations in NPHS2 detected in both familialand sporadic steroid-resistant nephrotic syndrome. J Am Soc Nephrol2002; 13:388–93
14. Frishberg Y, Rinat C, Megged O, Shapira E, Feinstein S, Raas-Rothschild A. Mutations in NPHS2 encoding podocin are aprevalent cause of steroid-resistant nephrotic syndrome amongIsraeli-Arab children. J Am Soc Nephrol2002; 13:400–05
15. Ito S, Ikeda M, Takata A, Kikuchi H, Hata J, Honda M. Nephroticsyndrome and end-stage renal disease with WT1 mutation detectedat 3 years. Pediatr Nephrol1999; 13:790–91.
16. Denamur E, Bocquet N, Baudouin V, et al. WT1 splice-sitemutations are rarely associated with primary steroid-resistant focaland segmental glomerulosclerosis. Kidney Int2000; 57:1868–72.2
17. Fuchshuber A, Gribouval O, Ronner V, et al. Clinical and geneticevaluation of familial steroid-responsive nephrotic syndrome inchildhood. J Am Soc Nephrol2001; 12:374–78.
18. Garin EH. Circulating mediators of proteinuria in idiopathic minimallesion nephrotic syndrome. Pediatr Nephrol2000; 14:872–78.
19. Ulinski T, Aoun B. Pediatric idiopathic nephrotic syndrome: treatment strategies in

20. steroid dependent and steroid resistant forms. Curr Med Chem. 2010;17:847–853.
21. Schrier RW, Gottschalk CW. Diseases of the Kidney. 4th ed. Boston: Little, Brown; 1988. p. 1749.p. 1899.
22. Davison AM, Cameron JS, Grunfeld JP, Ponticelli C, Ritz E, Winearls CG, et al. Oxford textbook of clinical nephrology. 3rd ed. New York: Oxford University Press; 2005. p. 421.
23. Gulati S, Kher V, Gulati K, Arora P, Gujral R. Tuberculosis in childhood nephrotic syndrome in India. Pediatr Nephrol. 1997;11:695–698.
24. Gorensek MJ, Lebel MH, Nelson JD. Peritonitis in children with nephrotic syndrome. Pediatrics. 1988;81:849–856.
25. Latta K, von Schnakenburg C, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol. 2001;16:271–282.
26. Tain YL, Lin G, Cher TW. Microbiological spectrum of septicemia and peritonitis in nephrotic children. Pediatr Nephrol. 1999;13:835–837.
27. Tain YL, Lin G, Cher TW. Microbiological spectrum of septicemia and peritonitis in nephrotic children. Pediatr Nephrol. 1999;13:835–837.
28. Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Nelson textbook of pediatrics. 18th ed. Philadelphia: Saunders; 2007. pp. 2193–2194.
29. Tejani A, Fikrig S, Schiffman G, Gurumurthy K. Persistence of protective pneumococcal antibody following vaccination in patients with the nephrotic syndrome. Am J Nephrol. 1984;4:32–37.
30. Alpay H, Yildiz N, Onar A, Temizer H, Ozçay S. Varicella vaccination in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2002;17:181–183.
31. Kato S, Chernyavsky S, Tokita JE, Shimada YJ, Homel P, Rosen H, et al. Relationship between proteinuria and venous thromboembolism. J Thromb Thrombolysis. 2010;30:281–285.
32. Ulinski T, Guigonis V, Baudet-Bonneville V, Auber F, Garcette K, Bensman A. Mesenteric thrombosis causing short bowel syndrome in nephrotic syndrome. Pediatr Nephrol. 2003;18:1295–1297.
33. Cade R, Spooner G, Juncos L, Fuller T, Tarrant D, Raulerson D, et al. Chronic renal vein thrombosis. Am J Med. 1977;63:387–397.
34. Rabelink TJ, Zwaginga JJ, Koomans HA, Sixma JJ. Thrombosis and hemostasis in renal disease. Kidney Int. 1994;46:287–296.
35. Llach F. Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. Kidney Int. 1985;28:429–439.
36. Lau SO, Tkachuck JY, Hasegawa DK, Edson JR. Plasminogen and antithrombin III deficiencies in the childhood nephrotic

37. syndrome associated with plasminogenuria and antithrombinuria. J Pediatr. 1980;96(3 Pt 1):390–392.

Fig-1: Nephrotic Syndrome of the children

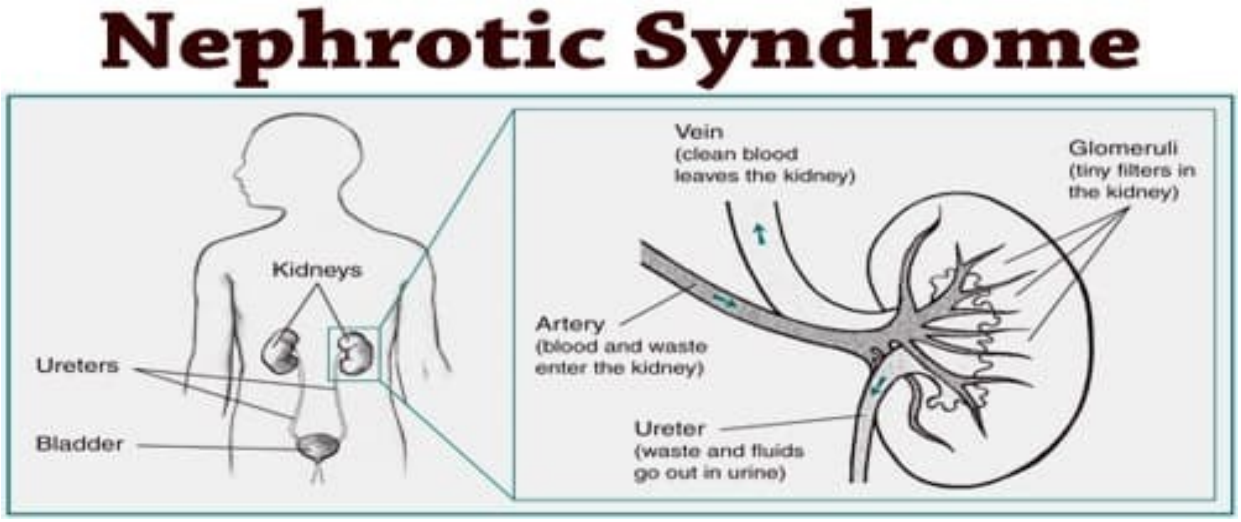
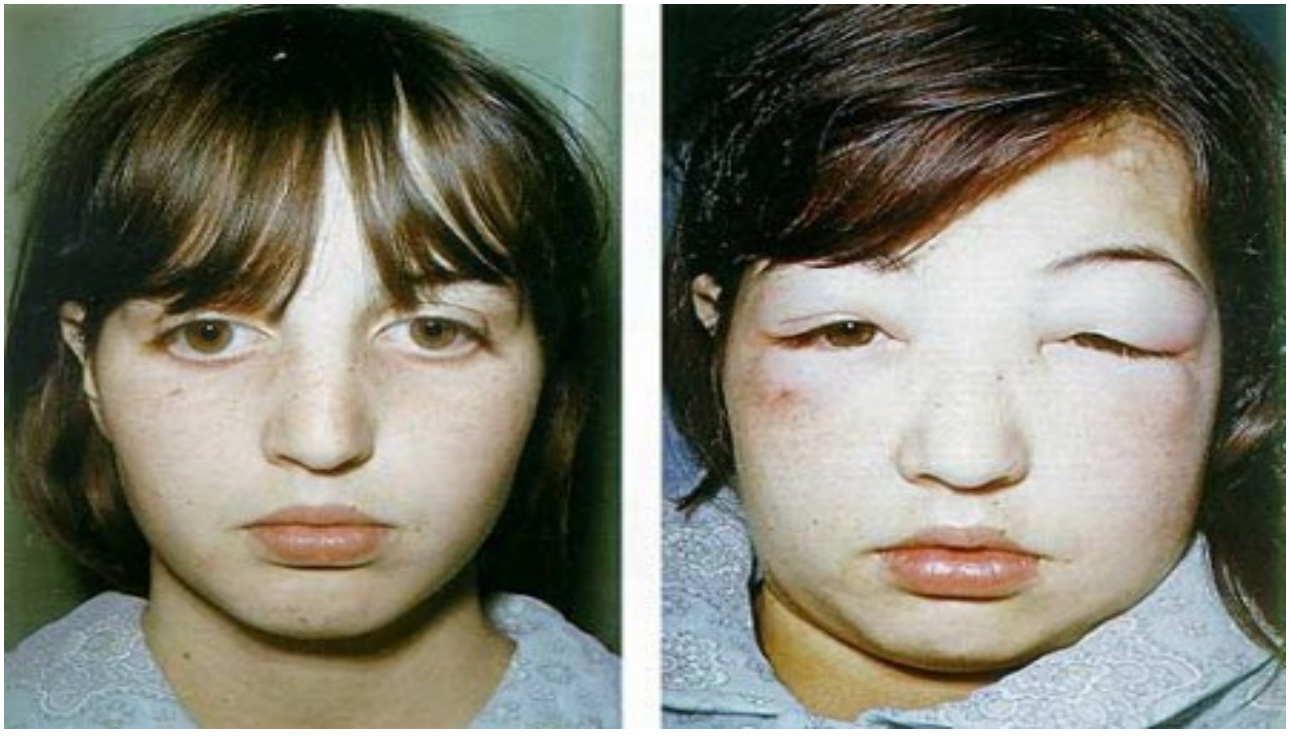


Fig-2: Edematic patients with Nephrotic Syndrome (NS)



Before **After (Nephrotic syndrome)**