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Pediatrics. 2016 July ; 138(1): . doi:10.1542/peds.2015-4528.**The Effect of a Gluten-Free Diet in Children With Difficult-to-Manage Nephrotic Syndrome****Kevin V. Lemley, MD, PhD^a, Christian Faul, PhD^b, Karla Schramm, BA^b, Kevin Meyers, MD^c, Frederick Kaskel, MD, PhD^d, Katherine M. Dell, MD^e, Debbie S. Gipson, MD^f, Keisha Gibson, MD^g, and Howard Trachtman, MD^h**^aDivision of Nephrology, Children's Hospital Los Angeles, Department of Pediatrics, University of Southern California Keck School of Medicine, Los Angeles, California^bDivision of Nephrology and Hypertension, Department of Medicine and Department of Cell Biology and Anatomy, University of Miami Leonard M. Miller School of Medicine, Miami, Florida^cDivision of Nephrology, Department of Pediatrics, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania^dDivision of Nephrology, Department of Pediatrics, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, New York^eCenter for Pediatric Nephrology, Department of Pediatrics, Cleveland Clinic Children's, Case Western Reserve University, Cleveland, Ohio^fDivision of Nephrology, Department of Pediatrics, CS Mott Children's Hospital, University of Michigan, Ann Arbor, Michigan^gDivision of Nephrology, Department of Medicine and Pediatrics, University of North Carolina, Chapel Hill, North Carolina^hDivision of Nephrology, Department of Pediatrics, NYU Langone Medical Center, NYU School of Medicine, New York, New York**Abstract**

Case reports have linked childhood nephrotic syndrome to food sensitivity, including gluten. We report our experience with 8 children (6 boys, 2 girls; age at implementation of special diet 2–14 years) with difficult-to-manage nephrotic syndrome who were placed on a gluten-free diet for 3.4 ± 4.3 years (range, 0.6–14 years) and who had clinical improvement enabling reduction or discontinuation in steroid dosage.

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Drs Lemley and Trachtman conceptualized and designed the study, identified patients and compiled case reports, and drafted the initial manuscript; Dr Faul and Ms Schramm conceptualized the study; Drs Meyers, Kaskel, Dell, and Gibson identified the patients and compiled the case reports; Dr Gipson conceptualized and designed the study, identified the patients, and compiled the case reports; and all authors approved the final manuscript as submitted.

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Nephrotic syndrome (NS) is a rare condition in childhood that presents with proteinuria, hypoalbuminemia, and edema. Kidney function is usually normal. Most children (>90%) respond to an initial course of oral steroids and are designated as having steroid-sensitive NS. These children are presumed to have minimal change disease and typically do not undergo a confirmatory kidney biopsy.¹ However, ~30% to 50% of patients have difficult-to-manage disease characterized by steroid dependence or frequent relapses. A smaller percentage will fail to respond to an initial course of steroids and are considered to have steroid-resistant NS. Patients with difficult-to-manage NS are often treated with immunosuppressive medications to alleviate debilitating side effects due to prolonged steroid therapy or sequelae of uncontrolled NS such as infection.² However, these second-line agents also have significant side effects and/or are nephrotoxic. There is an urgent need to develop novel therapeutic approaches to frequently relapsing, steroid-dependent, or steroid-resistant NS that are safe and well tolerated and which can achieve extended remission of proteinuria.

Over the last 40 years, case reports and patient series have been published that describe the impact of food sensitivity and alterations in the diet to control NS in pediatric and adult patients.³⁻⁷ Most patients were presumed to have sensitivity to cow's milk, and intervention focused on implementation of a milk-free or otherwise restricted diet. Removal of these dietary antigens resulted in resolution of NS. Lagrue et al⁵ reported the largest experience comprising 42 subjects with difficult-to-manage NS. Use of an oligoantigenic diet, which seems to have excluded gliadin, in 13 patients resulted in >50% reduction (median decrease, 90%) in proteinuria in the majority of cases and complete remission in 5 cases. The response was rapid (within 1 week in most cases), and proteinuria recurred immediately in most responsive patients when the restricted diet was stopped. In a subset of patients with NS, long-term steroid-free remissions were achieved by more specific dietary elimination, including elimination of gluten.⁵ These observations suggest that gluten sensitivity may contribute to disease in select cases of childhood NS.

A group of pediatric nephrologists compiled their experience with difficult-to-manage NS in a nonrandom cohort of patients whose clinical behavior was ameliorated after starting a gluten-free diet. This series is the largest to date documenting the efficacy of this nonpharmacologic approach to treating NS in children or adults.

METHODS

Patients with steroid-sensitive NS with a steroid-dependent or frequently relapsing pattern or steroid-resistant NS who were treated with a gluten-free diet were identified at the participating pediatric nephrology centers. The patients received medical care at several medical centers, and the treatment of NS was not standardized. In general, patients did not undergo a kidney biopsy at presentation and were initially treated with daily steroids followed by alternate-day steroids, based on the protocol implemented at each site to manage the first presentation of NS. Relapses were treated with daily prednisone until the patients achieved remission followed by an interval of alternate-day therapy with or without taper, as per the local treatment regimen. Both steroid-dependent and steroid-resistant disease were treated with a variety of immunosuppressive agents. Remission was defined as

a dipstick test result of negative or trace in a first morning urine sample for 3 consecutive days. Relapse was defined as a dipstick test result of 3+ or more or a protein/creatinine ratio >2.0 mg/mg in a first morning urine sample in children with edema or 2+ or more for 3 consecutive days in children without edema. The definitions of the International Study of Kidney Diseases in Children regarding steroid dependence (relapse of proteinuria while receiving alternate-day steroids or within 2 weeks of discontinuation of the drug), frequently relapsing NS (2 relapses in the initial 6 months of disease or 4 relapses in any 12-month period), or steroid resistance (failure to respond to an initial 4- to 6-week course of steroids) were generally applied to the characterization of the study patients.⁸

The gluten-free diet was selected as a course of therapy by the medical team or the family and patient. Initial education about a gluten-free diet was conducted in consultation with a nutritionist in select cases. The gluten-free diet was implemented by the family in the home setting with no in-home supervision from medical staff or a renal nutritionist. Adherence to the diet was voluntary and was not assessed in a systematic manner.

The study was reviewed and determined not to be subject to regulation by participating center institutional review boards.

CASE REPORT

An 11-year-old boy (case no. 2) had onset of NS at age 7 years. Although he was responsive to oral corticosteroids, he relapsed during the initial course of therapy and was eventually treated with oral cyclophosphamide (total cumulative dose, 168 mg/kg). A kidney biopsy was performed 10 months into his course of treatment and demonstrated minimal change disease, immunoglobulin (Ig) M variant. There was no histopathologic evidence of focal segmental glomerulosclerosis. At that time, he was being maintained on alternate-day oral steroids to prevent persistent relapses. Shortly after his biopsy, his parents elected to start him on a gluten-free diet. With the exception of a brief, self-limited relapse (precipitated by ingestion of a cupcake), the patient has been without any relapses and off all therapy, and he continues to follow the gluten-free diet over 4 years later.

The clinical features of this patient and the remaining 7 cases are summarized in Table 1.

DISCUSSION

To the best of our knowledge, this case series represents the largest cohort of patients, pediatric or adult, with frequently relapsing, steroid-dependent, or steroid-resistant NS who have been treated with a gluten-free diet and demonstrates a favorable impact on the course of their NS. All patients experienced a significant reduction in the relapse rate from the year before the change in diet compared with the period when they were maintained on the gluten-free diet. Moreover, in each case, the attending nephrologist was able to lower the dose or discontinue steroid use and other immunosuppressive medications. The beneficial impact of the gluten-free diet was reinforced by the relapses and recurrence of a steroid-dependent course that occurred in some cases in association with documented re-exposure to gluten. None of the patients reported any significant side effects while on the gluten-free diet.

Celiac disease (CD), the classic gastrointestinal manifestation of gluten sensitivity, occurs in 1% of the population.⁹ Renal disease, including mesangial IgA deposition without clinically overt IgA nephropathy, has been described in patients with CD.¹⁰ In patients with IgA nephropathy, gluten induces alterations in intestinal immunity and barrier function.¹¹ Withdrawal of gluten from the diet of some individuals with glomerular disease such as IgA nephropathy with NS is reportedly associated with resolution of both CD and renal manifestations.¹²

We are unable to elucidate the mechanism of action of the gluten-free diet in the children with difficult-to-manage NS. However, gluten restriction could affect NS in several ways. First, there may be an alteration in the intestinal microbiome leading to changes in the release of inflammatory mediators that are responsible for increasing glomerular permeability to protein.³ Second, there may be a direct effect of the gluten-free diet on podocyte structure. Primary childhood NS, which is predominantly due to either minimal change disease or focal segmental glomerulosclerosis, represents a podocytopathy, in which abnormalities in the glomerular visceral epithelial cell result in increased permeability to protein.¹³ CD is characterized by loss of the intestinal epithelial barrier function.¹⁴ Circulating levels of zonulin, a protein that is implicated in the pathogenesis of CD, are elevated in CD and reduced upon instituting a gluten-free diet.^{15, 16} Mechanistically, zonulin activates protease-activated receptor 2 (PAR2), a member of the G-protein-coupled receptor family, and induces signaling events that lead to changes in the actin cytoskeleton and cell-cell junctions.¹⁷ PAR2 is expressed on podocytes, and the gluten-induced elevation in serum zonulin levels may influence the interaction between PAR2 and protease-activated receptor 3, which has been implicated in cell signaling and podocyte structure and function.^{18, 19} We propose that implementation of a gluten-free diet may stabilize the podocyte actin cytoskeleton and have a favorable impact on the clinical course of children with difficult-to-manage NS through its effects on the zonulin-PAR2 axis.

Our study has several important limitations, including its retrospective design. The patients were self-selected on the basis of their willingness to implement the dietary change. Thus, the case series may have a bias toward reporting responders and not patients in whom the intervention failed. The gluten-free diet was self-administered, and we were thus unable to ascertain adherence to the diet. There was no consistent laboratory monitoring of serologic markers of CD, although how informative these data might be in this particular manifestation of gluten sensitivity is currently unknown. Information is unavailable to fully assess the impact of this change on growth, weight, blood pressure, or quality of life. However, gluten-free diets are followed in patients with CD with a normal growth pattern. Finally, children with frequently relapsing NS can achieve a spontaneous remission at any time and, therefore, we cannot draw definitive conclusions about the efficacy of the gluten-free diet in the study patients without a controlled clinical trial.

CONCLUSIONS

This case series suggests that in a subset of children with difficult-to-manage NS, a relatively simple and safe intervention namely, elimination of gluten from the diet, may reduce the need for potentially toxic immunosuppressant therapies. Prospective studies are

needed to confirm the efficacy of a gluten-free diet in childhood NS, to investigate biomarkers that could identify those patients who are most likely to benefit from this novel therapy, and to clarify the mechanism of action. The growing use of and greater access to gluten-free food items underscore the feasibility of this approach.

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ABBREVIATIONS

CD	celiac disease
Ig	immunoglobulin
NS	nephrotic syndrome
PAR2	protease-activated receptor 2

REFERENCES

1. Metz DK, Kausman JY. Childhood nephrotic syndrome in the 21st century: what's new? *J Paediatr Child Health.* 2014; 51:497–504.
2. Gipson DS, Massengill SF, Yao L, et al. Management of childhood onset nephrotic syndrome. *Pediatrics.* 2009; 124(2):747–757. [PubMed: 19651590]
3. Uy N, Graf L, Lemley KV, Kaskel F. Effects of gluten-free, dairy-free diet on childhood nephrotic syndrome and gut microbiota. *Pediatr Res.* 2015; 77(1–2):252–255. [PubMed: 25310757]
4. Sandberg DH, Bernstein CW, McIntosh RM, Carr R, Strauss J. Severe steroid-responsive nephrosis associated with hypersensitivity. *Lancet.* 1977; 1(8008):388–391. [PubMed: 65510]
5. Lagrue G, Laurent J, Rostoker G. Food allergy and idiopathic nephrotic syndrome. *Kidney Int Suppl.* 1989; 27(suppl):S147–S151. [PubMed: 2484004]
6. Laurent J, Lagrue G. Dietary manipulation for idiopathic nephrotic syndrome. A new approach to therapy. *Allergy.* 1989; 44(8):599–603. [PubMed: 2610334]
7. Laurent J, Rostoker G, Robeva R, Bruneau C, Lagrue G. Is adult idiopathic nephrotic syndrome food allergy? Value of oligoantigenic diets. *Nephron.* 1987; 47(1):7–11. [PubMed: 3627337]
8. Nakanishi K, Iijima K, Ishikura K, et al. Japanese Study Group of Renal Disease in Children. Two-year outcome of the ISKDC regimen and frequent-relapsing risk in children with idiopathic nephrotic syndrome. *Clin J Am Soc Nephrol.* 2013; 8(5):756–762. [PubMed: 23371961]
9. Guandalini S, Assiri A. Celiac disease: a review. *JAMA Pediatr.* 2014; 168(3):272–278. [PubMed: 24395055]
10. Rostoker G, Chaumette MT, Wirquin E, et al. IgA mesangial nephritis, IgA antigliadin antibodies, and coeliac disease. *Lancet.* 1990; 336(8718):824–825. [PubMed: 1976192]
11. Coppo R. The intestine-renal connection in IgA nephropathy. *Nephrol Dial Transplant.* 2015; 30(3):360–366. [PubMed: 25387475]
12. Woodrow G, Innes A, Boyd SM, Burden RP. A case of IgA nephropathy with coeliac disease responding to a gluten-free diet. *Nephrol Dial Transplant.* 1993; 8(12):1382–1383. [PubMed: 8159309]
13. Somlo S, Mundel P. Getting a foothold in nephrotic syndrome. *Nat Genet.* 2000; 24(4):333–335. [PubMed: 10742089]
14. Diamanti A, Capriati T, Bizzarri C, et al. Celiac disease and endocrine autoimmune disorders in children: an update. *Expert Rev Clin Immunol.* 2013; 9(12):1289–1301. [PubMed: 24215416]
15. Fasano A, Not T, Wang W, et al. Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. *Lancet.* 2000; 355(9214):1518–1519. [PubMed: 10801176]

16. Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity, and cancer. *Physiol Rev.* 2011; 91(1):151–175. [PubMed: 21248165]
17. Tripathi A, Lammers KM, Goldblum S, et al. Identification of human zonulin, a physiological modulator of tight junctions, as prehaptoglobin-2. *Proc Natl Acad Sci USA.* 2009; 106(39):16799–16804. [PubMed: 19805376]
18. Madhusudhan T, Wang H, Straub BK, et al. Cytoprotective signaling by activated protein C requires protease-activated receptor-3 in podocytes. *Blood.* 2012; 119(3):874–883. [PubMed: 22117049]
19. Schramm, K.; Walter, B.; Sloan, A., et al. Abstract Supplement for the American Society of Nephrology (ASN). Philadelphia, PA: 2014 Nov 11–16. Zonulin, a circulating factor that regulates podocyte function and glomerular permeability. Abstract SA-PO435

TABLE 1

Summary of the Clinical Features of the Study Patient and the Other 7 Cases

Case No.	Age (y) at Start of Gluten-Free Diet	Current Age (y)	Sex	NS Type (Pathology if Available)	Previous Immunosuppressive Therapy	Immunosuppressive Therapy on Gluten-free Diet	Relapse Rate (No./Year) Prior/Post	Duration of Follow-up (mo)
1	14	16	M	SD	Prednisone, tacrolimus, mycophenolate mofetil	Tacrolimus	4/1.5	27
2	8	12	M	SD (MCD, IgM variant)	Prednisone, cyclophosphamide	None	4/0	48
3	12	15	M	SD	Prednisone, cyclophosphamide, mycophenolate mofetil, cyclosporine, tacrolimus, galactose, rituximab	None while on the diet for 7 mo	2/0 Relapse rate rose to 3 per year when diet was stopped	7
4	8.5	12	M	SD	Prednisone, cyclophosphamide	None	4/<1	20
5	6	7	M	FR	Prednisone	None	4/<1	18
6	12	26	F	SD	Prednisone, cyclophosphamide, methylprednisolone IV	None	3/<1	14 y off medication
7	7.5	9	F	SR (FSGS)	Prednisone, tacrolimus for 6 mo	Prednisone, low dose every other day, tacrolimus	Persistent proteinuria/0 with complete normalization of proteinuria	24
8	2	3.5	M	Partial response to steroids	Prednisone, cyclosporine	None	1/1	18

F, female; FR, frequent relapse; FSGS, focal segmental glomerulosclerosis; IgM, immunoglobulin M; IV, intravenous; M, male; MCD, minimal change disease; SR, steroid resistant; SD, steroid dependent.