

Proteinuria Selectivity in Childhood Nephrotic Syndrome

Mohamed Zaki, FRCPI*

Pady F Deasy, FRCPI**

Azhar S Daoud, MRCP***

Objective: To assess the value of proteinuria selectivity index (PSI) in predicting the response of children with nephrotic syndrome to corticosteroid therapy and its correlation with renal biopsy findings.

Setting: Paediatric Department, Our Lady's Hospital for Sick Children, Dublin, Ireland.

Design: Retrospective analysis of the records of 39 children admitted to the above hospital with nephrotic syndrome. PSI was performed for all children prior to therapy. All received corticosteroid therapy according to the protocol of International Study of Kidney disease in Children for initial attacks and relapses.

Results: Patients were divided into 3 groups according to their response to steroid; steroid responsive infrequent relapsers (n.15), steroid responsive frequent relapsers (10) and steroid resistant (8). PSI of < 0.01 was statistically significant in differentiation between the steroid responsive and resistant nephrotic syndrome. All children in the latter group had non-minimal change lesions on biopsy.

Conclusion: Protein selectivity index should continue to be one of the valuable initial tests in childhood nephrotic syndrome due to its useful additional predictive value on the response to steroid in those patients.

Bahrain Med Bull 1997;19(1):15-17

In health, urine contains very small amount of protein. However, in disease causing glomerular injury, protein loss in urine is much increased. Proteinuria selectivity index (PSI) is the comparison of the relative clearance of different plasma proteins in urine. This index has been advocated for identifying the nature of glomerular damage and this was based on the concept that more severe injury leads to higher functional pore size in the glomerular filter and thus to relatively higher clearance of larger protein molecules. If the ratio of a large molecular weight protein (eg. IgG) to a small molecular weight protein (eg. transferrin) is low (< 0.1) the proteinuria is called selective and if high it is called non-selective.

Many believe that proteinuria selectivity index (PSI) remains a useful discriminator for the response to treatment with steroid and prognosis in childhood nephrotic

syndrome (NS). Grupe showed that 96 % of children with PSI of less than 0.1 had minimal change disease and 97 % will respond completely to steroid therapy¹. Other investigators have confirmed these observations^{2,3,4}. A contrary opinion is expressed by Robson et al who stated that measuring PSI is of no real value⁵.

This study was undertaken to determine proteinuria selectivity in a group of children with primary nephrotic syndrome and its correlation with response to steroid treatment and renal biopsy findings.

METHODS

Thirty three Irish children (21 male and 12 female) with primary nephrotic syndrome in whom the PSI was estimated prior to therapy, were included in the study. All of them were admitted to our Lady's hospital for sick children, Dublin, Ireland. The diagnosis of NS was based on the presence of heavy proteinuria (> 40 mg/h/m³), hypoalbuminaemia (< 25 gm/L), hypercholesterolaemia and oedema.

Serum and urinary IgG and transferrin were measured according to the method described by Ellis and Buffone⁶. Selectivity of proteinuria was performed by Cameron method⁷. Blood pressure, haematuria, serum creatinine and C₃ were recorded for all patients. All children received corticosteroid therapy after initial diagnosis according to International Study of Kidney Disease in Children (ISKDC) protocol⁸. Statistical analysis was performed using Chi-square test.

* Consultant Paediatrician Farwania Hospital, Kuwait.
Formerly Research Fellow
Department of Paediatrics
University College
Dublin Ireland

** Consultant Paediatrician
Our Lady's Hospital for
Sick Children
Crumlin, Dublin
Ireland

*** Associate Professor
Jordan University of Science and Technology
Irbid, Jordan.
Formerly Consultant Paediatrician
Farwania Hospital, Kuwait.

RESULTS

Depending on their response to steroid therapy, patients were divided into 3 groups; steroid responsive infrequent relapsers (15), steroid responsive frequent relapsers (10) and steroid resistant (8) as shown in Table 1.

Table 1. Patient groups (steroid response, relapse) vs PSI and renal biopsy

Patient Data	Group 1 steroid responsive (Infrequent relapses)	Group 2 steroid responsive (Frequent relapses)	Group 3 steroid resistant
Age (years)			
Mean (range)	6.1 (2-12)	4.1 (2-7)	7.75 (5-13)
Sex (male/female)	8/7	7/3	6/2
Selectivity Index			
Mean (range)	0.057 (0.01-0.18)	0.095 (0.03-0.13)	0.176 (0.12-0.43)
Renal biopsy Performed (n)	2	6	8
Histology			
MC	2	6	0
MPG	0	0	4
FSG	0	0	3
MPGN	0	0	1

MC: minimal change lesion, MPG: membranoproliferative glomerulonephritis, FSG: Focal Segmental glomerulonephritis. MPGN: Mesangio proliferative glomerulonephritis

The mean age at diagnosis for the steroid responsive group was 6.1 years (range 2-12 years) and for the steroid resistant group was 7.75 years (range 5-13 years). In all three groups there were slight predominance of male children.

Renal biopsy were performed in 16 children. In all 8 children in the steroid responsive group, it disclosed minimal change lesions. In the steroid resistant group: there were focal glomerulosclerosis (FSG) in 4, membranoproliferative glomerulonephritis (MPG) in 3 and one with mesangioproliferative glomerulonephritis (MPGN). The distribution of patients according to steroid responsiveness and PSI is shown in figure 1. The PSI of 0.1 or less was found to be statistically significant ($P < 0.003$) in differentiating steroid responsive from non-responsive children. Ninety three percent of those who responded to steroids had a highly selective proteinuria (< 0.1). Only 60 % of patients with frequent relapses showed highly selective proteinuria. In the steroid resistant group there was only one child with selective proteinuria.

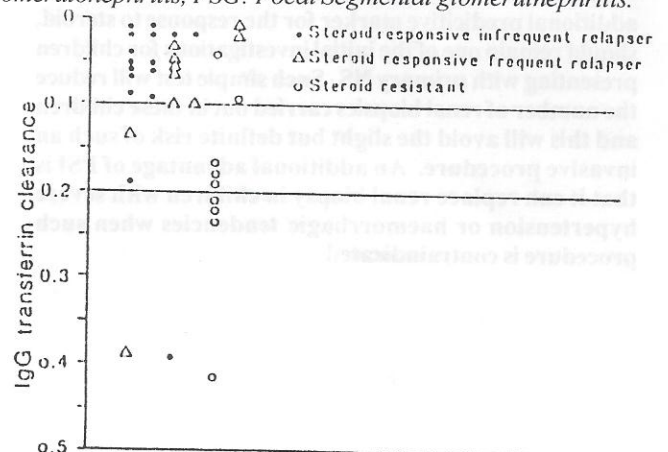


Figure 1. Correlation of proteinuria selectivity and response to steroids

Haematuria was found in 16 % of patients who were steroid responsive and in 75 % of steroid resistant group. Hypertension was detected in 24 % and 37 % in the two groups respectively. Serum creatinine and C_3 levels were within normal range in all children at diagnosis except with MPG who had low serum C_3 .

DISCUSSION

In NS the glomerular basement membrane (GBM) barrier is altered allowing the escape of plasma protein into urine. The mechanism for differential protein leakage is not exactly known. This may be due to loss of negative charges in GBM or development of population of large pores in GBM with escape of large protein molecules in urine⁷.

Our data showed that the majority of cases with high selectivity of proteinuria (PSI < 0.1) responded well to steroid therapy. Poor selectivity correlated with resistance to such therapy and with non-minimal lesion on histological examination. This was also the observation of other authors¹⁻⁴. Our study also showed that children with poor PSI are more likely to have other features indicating poor prognosis such as haematuria, hypertension and older age at presentation, though this was not statistically significant.

The argument against PSI as a valuable investigation in patients with NS was based on the fact that the magnitude of proteinuria does not always correlate with the histological findings. The excretion of protein does not depend entirely on the size of protein molecule but also on other factors such as glomerular filtration rate (GFR), transcapillary hydrostatic and oncotic pressures as well as the efficiency of tubular reabsorption of protein³. In addition, it is known that the state of hydration, degree of activity during urine collection will also influence protein excretion³. Practically it is possible to control GFR, position of the patient and degree of activity during urine collection.

CONCLUSION

From this work we can conclude that PSI, as an additional predictive marker for the response to steroid, should remain one of the initial investigations for children presenting with primary NS. Such simple test will reduce the number of renal biopsies carried out in these children and this will avoid the slight but definite risk of such an invasive procedure. An additional advantage of PSI is that it can replace renal biopsy in children with severe hypertension or haemorrhagic tendencies when such procedure is contraindicated.

REFERENCES

1. Grupe WE. Primary nephrotic syndrome in childhood. *Adv Pediatr* 1979;163:163-207.
2. Cameron JS, Blandford G. The simple assessment of selectivity in heavy proteinuria. *Lancet* 1966;ii:242-7.
3. Ellis D, Byffone G. Protein clearance and selectivity determination in childhood nephrosis: A reappraisal. *Clin Chem* 1981;27:1397-1400.
4. Laurent J, Philippon C, Lagrue G, et al. Proteinuria selectivity index- Prognostic value in lipid nephrosis and related diseases. *Nephron* 1993;65:185-9.
5. Robson AM, Vehaskari VM. Proteinuria. In: Postlethwaite (ed) *Clinical paediatric nephrology*. Bristol: Wright, 1993:20.
6. Ellis D, Buffone GJ. A new approach to the evaluation of proteinuric state. *Clin Chem* 1977;23:666-70.
7. International Study of Kidney Disease. Early identification of frequent relapser among children with minimal change nephrotic syndrome. *J Pediatr* 1982;101:514-8.
8. Brenner BM, Hostetter TH, Humes HD. Glomerular permselectivity barrier function based on discrimination of molecular size and charge. *Am J Physiol* 1978;234:455-60.