Selectivity of Proteinuria in Childhood Nephrotic Syndrome

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In 1960, Blainey *et al.* introduced the concept that in proteinuria the glomerulus retained a filtering action. They showed that the clearance of a particular protein was inversely proportional to its molecular weight. Thus, small molecular weight proteins were cleared more readily than the large ones. This property they called 'selectivity'. They further showed that if this selectivity was of a high order, the prognosis and response to steroids in the nephrotic syndrome were good.

Other workers have now established that selectivity of proteinuria is of use in predicting the response to corticosteroids in the nephrotic syndrome (Joachim *et al.*, 1964; Cameron and White, 1965). Selectivity may be defined as the slope of the regression line relating the logarithm of renal clearance of proteins relative to that of transferrin, to the logarithm of their molecular weights. If such a regression is steep, the proteinuria is said to be highly selective, and response to corticosteroids is likely to be good.

The nephrotic syndrome is a frequent disorder in childhood, but only one previous report (Cameron and White, 1965) has dealt with selectivity of proteinuria in childhood nephrotic syndrome.

Material and Methods

Studies were made on 26 patients, between 2 and 14 years, admitted with the nephrotic syndrome to the Adelaide Children's Hospital between April 1966 and April 1968. The criteria of 'nephrotic syndrome' were: gross proteinuria, hypoproteinaemia, and oedema.

The urinary concentration of 5 proteins, orosomucoid (mol. weight 40,000), albumin (mol. weight 67,000), transferrin (mol. weight 88,000), IgG (mol. weight 150,000), and α_2 -macroglobulin (mol. weight 840,000), were measured by immunodiffusion. The technique was the Soothill modification of the Ouchterlony method; commercial antisera placed in wells in 'home-made' agar plates or commercially prepared immunodiffusion plates (Hoechst) were used. The values so

obtained for the urinary concentration of each protein were divided by the plasma concentration of the same protein to give the appropriate U/P value; the U/P value for the individual proteins was compared with that for transferrin and expressed as a percentage. These percentages were then plotted on logarithmic paper, against the molecular weight. The slope of the resultant regression line was obtained by the method of least squares. This value (θ) was used as a measure of the selectivity of the proteinuria. Typical examples are shown in Fig. 1 and 2.

All patients in the trial were treated with initial high-dose (40 mg. prednisolone per day or equivalent) corticosteroids and bed-rest. Most were also given penicillin and a high-protein diet. Salt and water restriction was dependent on the clinic to which they were admitted.

The patient was considered to have responded to corticosteroid administration if there was a disappearance of clinical signs and symptoms, and the 24-hour urinary protein fell below 50 mg. All patients who thus responded had at least one period of remission of greater than 3 months. Failure of response was defined as persistence of clinical signs and symptoms, with a 24-hour urinary protein of greater than 500 mg.

The histological diagnosis was made from percutaneous renal biopsy samples. These samples were examined by light microscopy only. The stains used were haematoxylin and eosin, Mallory's trichromate, and periodic acid silver. The diagnoses in Table I were taken from the routine reports on such samples, which were provided without knowledge of the selectivity studies. It can be seen from Table II that not all points fall exactly on a straight line. This is to be expected when there is a coefficient of variation in measuring protein level in serum by the immunodiffusion technique. Soothill (1962) showed an average coefficient of variation from 14 to 25 depending on the protein estimated. The coefficient of variation for transferrin was found to be 15 by the technique used in this experiment.

That the relation is a linear one is strongly suggested by the correlation coefficient determined in each patient so that the line could be plotted by the methods of least squares. This correlation coefficient was greater than -0.85 in all but 5 cases.

Received January 6, 1969.

FIG. 1.—Case 4. Protein clearance expressed as a percentage of transferrin clearance is plotted on a logarithmic scale on the ordinate. Molecular weight divided by 10,000 is plotted on the abscissa.

The regression line makes an angle of 74° with the horizontal and the proteinuria is said to be highly selective.

FIG. 3.—Selectivity angles of 17 children with the nephrotic syndrome which responded to corticosteroids, compared with 5 children whose nephrotic syndrome did not respond.

FIG. 2.—Case 25. Protein clearance is plotted against molecular weight as in Fig. 1. The angle of selectivity is 31.5° . This child deteriorated when given prednisolone.

FIG. 4.—Selectivity angles of children with the nephrotic syndrome, in which renal biopsy revealed 'minimal lesion', are compared with those of children with nephrotic syndrome, in association with glomerulonephritis found in renal biopsy.

Because of this variation in repeated readings a line through 4 or 5 points is preferred to a ratio between two proteins, as used by Cameron and Blandford (1966) and MacLean and Robson (1967).

Results

The results are summarized in Table I. It can be seen that all patients with a selectivity regression angle of greater than 50° responded to corticosteroids, while those at or below 50° did not. The mean angle for the steroid-responsive group was 66.6° , SD 6.1° . In the non-responsive group, the mean angle was 36.6° , SD 6.2° .

A correlation with the histological diagnosis can be noted, those patients with minimal changes by light microscopy having higher selectivity of proteinuria than those who had obvious pathology. These results are expressed in graphical form in Fig. 3 and 4.

50° is chosen as an arbitrary dividing line because it falls below the mean of the responsive group less 2 SD and above the mean of the non-responsive group plus 2 SD.

Discussion

This study shows that measuring the selectivity of proteinuria is of value in childhood nephrotic syndrome. Cases with high selectivity responded well

to steroid therapy, and high selectivity correlated with a minimal change in histological appearance. The test outlined thus provides a useful guide to management, and potentially could reduce the number of renal biopsies carried out in these children. This avoids the slight but definite risk of the procedure, and in addition the selectivity test can be carried out in those children who have severe hypertension or a haemorrhagic tendency (Handley and Lawrence, 1967) in whom renal biopsy is contraindicated. It has been claimed (Joachim *et al.*, 1964) that, in adults, protein selectivity provides a better guide to the steroid response than renal biopsy; the present study suggests that, for children, these two techniques are at least of equal value in assessing the likelihood of steroid response.

Summary

Studies of selectivity of proteinuria in childhood nephrotic syndrome in 26 patients are presented. A good correlation between high selectivity, expressed as a regression angle of greater than 50° , and steroid response, is demonstrated.

Thanks are due to the Honorary Staff, the Adelaide Children's Hospital, for their co-operation in this study, and to Dr. M. Fowler and Dr. R. Carter, Pathology

TABLE I

Correlation of Selectivity of Proteinuria with Response to Corticosteroids and Histological Diagnosis

Case No.	Age (yr.)	Selectivity Angle (degrees)	Renal Histology	Response to Steroid
1	7	77	Minimal change	Yes
2	10	77	Minimal change and ureteric reflux	Yes
3	4	75	Minimal change	Yes
4	7	74	Minimal change	Yes
5	14	74	Minimal change	Yes
6	6	74	Not available	Yes
7	4	74	Minimal change	Yes
8	9	72	Minimal change	Yes
9	8	70	Minimal change	Yes
10	5	70	Minimal change	Yes
11	6	70	Minimal change	Yes
12	7	69	Minimal change and nephroblastoma	Yes
13	3	69	Minimal change	Yes
14	14	69	Minimal change	Yes
15	11	69	Minimal change	Not used
16	6	68	Minimal change	Yes
17	12	64	Minimal change	Yes
18	8	57	Minimal change	Yes
19	11	50	Membranous glomerulonephritis and ureteric reflux	No
20	12	40	Proliferative glomerulonephritis	No
21	10	40	Polyarteritis nodosa, severe glomerulitis	No
22	14	37	Disseminated lupus, severe glomerulitis	No
23	13	33	Proliferative glomerulonephritis	Not used
24	7	32	Membranous glomerulonephritis	Not used
25	8	31	Proliferative glomerulonephritis	No
26	11	30	Proliferative glomerulonephritis	Not used

TABLE II

Urine to Plasma (U/P) Ratio for Individual Proteins and this U/P Ratio as Percentage of Transferrin U/P

Patient	α_1 -Acid Glyco-protein	% of Transferrin U/P	Albumin	% of Transferrin U/P	Transferrin	% of Transferrin U/P	Ig G	% of Transferrin U/P	α_2 -Macro-globulin	% of Transferrin U/P
1	5.024	993	0.513	101	0.506	100	0.031	6	Unobtainable	
2	3.479	347	1.096	109	1.002	100	0.038	4	Unobtainable	
3	3.270	981	0.340	102	0.333	100	0.067	20	Unobtainable	
4	2.619	504	0.728	140	0.520	100	0.033	6	Unobtainable	
5	1.209	252	0.368	77	0.480	100	0.012	2.5	Unobtainable	
6	105.098	696	15.876	106	15.001	100	0.525	3.5	0.001	0.06
7	0.701	1593	0.132	300	0.044	100	0.006	14	Unobtainable	
8	1.206	215	0.589	105	0.561	100	0.015	3	Unobtainable	
9	3.803	190	0.889	44	1.998	100	0.061	3	0.002	0.1
10	10.044	201	5.100	102	4.986	100	0.661	13	0.009	0.2
11	1.943	524	0.518	140	0.371	100	0.066	18	Unobtainable	
12	1.604	350	0.469	102	0.458	100	0.059	13	0.003	0.7
13	14.049	747	3.762	198	1.880	100	0.471	25	0.002	1
14	0.766	153	0.531	106	0.501	100	0.063	13	Unobtainable	
15	6.031	186	1.756	54	3.248	100	0.097	3	0.003	0.1
16	8.097	299	1.981	73	2.705	100	0.240	9	0.011	0.04
17	2.566	265	1.281	132	0.968	100	0.381	39	0.049	5
18	16.104	350	5.523	120	4.602	100	2.286	50	0.143	3
19	0.342	170	0.162	81	0.201	100	0.050	25	0.009	4
20	1.683	201	1.009	120	0.838	100	0.377	45	0.176	21
21	1.523	199	0.927	121	0.764	100	0.455	60	0.152	20
22	0.251	202	0.126	102	0.124	100	0.083	67	0.023	19
23	0.972	120	0.817	101	0.812	100	0.431	53	0.130	17
24	1.998	123	1.629	100	1.620	100	0.860	54	0.264	16
25	0.353	140	0.256	100	0.255	100	0.151	59	(IgA) 0.298	59
26	0.247	130	0.194	101	0.192	100	0.096	50	(α_2) 0.038	20

Department of the Adelaide Children's Hospital, for their reports on renal biopsies; and to Dr. J. R. Lawrence and Professor G. M. Maxwell for their help and encouragement throughout the past 2 years. The research was supported by a grant from the Adelaide Children's Hospital Research Trust. Antisera and partigen immunodiffusion plates were supplied by Australian Hoechst.

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