

Proteinuria in Children with Febrile Illnesses

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Marks, M. I., McLaine, P. N., and Drummond, K. N. (1970). *Archives of Disease in Childhood*, 45, 250. **Proteinuria in children with febrile illnesses.** Transient proteinuria in the absence of underlying renal disease was detected in 11 of 198 children (5.6%) admitted to hospital with an acute febrile illness. Proteinuria was noted only in children whose fever was higher than 38.4 °C. Selectivity studies on the protein excreted showed patterns ranging from poorly to highly selective. Initial screening for proteinuria using a dipstick method revealed a high incidence of false positives, of which only about 30% could be confirmed by the sulphosalicylic acid method.

The pathophysiology of transient proteinuria in febrile patients is not understood; a number of mechanisms are probably involved. Since fever was the only detected feature common to each of the patients with proteinuria, it seems unlikely that the specific aetiology of the fever is a factor of importance in the pathogenesis of the proteinuria.

The association of proteinuria with fever was first described in the 19th century (Gerhardt, 1869). Though its significance and pathogenesis are not understood, it is generally considered to be a benign and transient phenomenon (Schwartz and Kassirer, 1963).

It was once thought possible to predict the seriousness of a given renal disease on the basis of the quantity of protein excreted (King and Gronbeck, 1952). It is now recognized, however, that in certain serious renal disorders the degree of proteinuria may be minimal (Hardwicke and Soothill, 1967; Pollak *et al.*, 1958). Conversely, as in certain forms of the nephrotic syndrome, a good prognosis may be seen even with massive proteinuria (*Canadian Medical Association Journal*, 1967; Arneil, 1967).

The purpose of this study was to determine the incidence and clinical significance of proteinuria in febrile children. An attempt was made to characterize the selectivity pattern of the urinary proteins by means of differential protein clearances.

Materials and Methods

Included in the study were 198 febrile children admitted to the Montreal Children's and Alexandra

Hospitals from January to March 1968. Fever was defined as a temperature rise above 37.2 °C. orally or 37.8 °C. rectally. Renal disease was excluded on the basis of the physical examination and normal urinalyses, either at the time of the fever or subsequently.

Using a dipstick* method an initial screening test for proteinuria was done on all febrile children upon admission to hospital and at 4-hourly intervals during the febrile period. If a reading of 30 mg./100 ml. or more was obtained, a sulphosalicylic acid method (Cipriani and Brophy, 1943) was then used to exclude any false positives detected by the dipstick method and to quantitate the proteinuria. The quantitative sulphosalicylic acid method for urine protein measurement was done in the following manner. 0.5 ml. 3% sulphosalicylic acid was added to an equal volume of urine. Using the same volumes of urine and distilled water as a blank, the turbidity of the sulphosalicylic acid precipitate was measured at 540 μ in a Coleman Junior Spectrophotometer. The protein concentration was determined by using a standardized curve prepared with solutions of known protein concentration. All measurements were done by the same person; no patient received any drug or radiopaque dye known to give false positives by this method. The accuracy of this method has been shown to compare favourably with a micro-Kjeldahl method (Cipriani and Brophy, 1943; Looney and Walsh, 1939), with immunoassay methods (Rennie and Keen, 1967), and is similar to that used by Harrison *et al.* (1968). Urines with a protein concentration of 30 mg./100 ml. or more as determined by the sulphosalicylic acid method were concentrated 10–20 times in

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dialysis tubing* by osmotic activity against a sucrose medium for use in the selectivity studies of the protein excreted (McFarlane, 1964). Blood was taken within 24 hours of urine sampling and the serum removed.

The serum protein concentration was measured by the biuret method (Gornall, Bardawill, and David, 1949). Using a modification of the methods of Cameron and White (1965) and MacLean and Robson (1967) selectivity studies were done on the protein excreted. Immunodiffusion plates† containing antibodies to human transferrin (MW 88,000), immunoglobulin G (IgG, MW 150,000), and α_2 -macroglobulin (MW 840,000) were used to determine the urine: serum (U/S) ratios for each of these proteins. To calculate the relative clearances of these proteins the U/S ratios of both IgG and α_2 -macroglobulin were expressed as a percentage of the U/S ratio of transferrin (100%) and plotted on a logarithmic scale against the respective molecular weights of these proteins. From the slope of the line obtained the angle theta (θ) was measured (Joachim *et al.*, 1964). This angle reflects the degree of selectivity of the proteinuria; values in excess of 67° are indicative of high selectivity whereas those less than 54° represent poor selectivity (Joachim *et al.*, 1964).

To determine whether the proteinuria was persistent, a 24-hour urine collection was obtained on all patients with proteinuria within two weeks of the febrile episode.

Results

The clinical diagnoses included bacterial and viral respiratory infections (30%), viral exanthemata (14%), gastro-enteritis (8%), infectious hepatitis (5%), and viral stomatitis (4%). Miscellaneous causes including patients with the Riley Day syndrome, leukaemia, septicaemia, osteomyelitis mumps, cervical adenitis, and mastoiditis accounted for 27% of cases. The cause of the fever was unknown in 12%.

*Dialyzer Tubing, Seamless Cellulose—Fisher Scientific Co. Ltd., Montreal, Quebec.

†Immunoplate—Hyland Division Travenol Laboratories Inc., Los Angeles, California.

TABLE I

Sex Distribution, Ages, and Incidence of Proteinuria by Dipstick and Sulphosalicylic Acid Tests in 198 Patients

	No. of Patients	No. of Tests	Dipstick Positive	Confirmed* Positive (30 mg./100 ml. or more)	Ages
Male	102	142	17	5	2 mth.-16 yr.
Female	96	133	20	6	4 mth.-17 yr.
Total	198	275	37	11	Mean = 4.5 yr.

*By sulphosalicylic acid method.

As shown in Table I, 275 urines from 198 patients were tested. 37 urine samples were positive by the dipstick method; these specimens were from different subjects. Proteinuria was confirmed by the sulphosalicylic acid method in 11 patients. Thus, the incidence of proteinuria in febrile children was 11 out of 198, or 5.6%. The incidence was similar in both sexes. The majority of false positives detected by the dipstick method contained less than 10 mg. protein per 100 ml. by the sulphosalicylic acid technique.

Proteinuria was not detected in 96 urines tested from patients whose temperatures ranged from $37.2-38.3^\circ\text{C}$. (see Table II). The 24-hour urine specimens obtained from the 11 patients with proteinuria within two weeks of the initial febrile episode each contained less than 40 mg. protein.

TABLE II

Incidence of Proteinuria in Relation to Temperature Range

Temperature ($^\circ\text{C}$.)	No. Patients Tested	Proteinuria Confirmed
37.2-38.3	62	0
38.4 or greater	136	11
Total	198	11

Table III provides data on the 11 patients with proteinuria. Fever was due to a variety of causes. Ages ranged from 7 months to 16 years and the temperature from $38.4-40.0^\circ\text{C}$. Urine protein concentration was from 30-91 mg./100 ml., with a mean of 48.5. A detailed microbiological study was not performed on these patients nor was a consistent treatment schedule followed.

Differential protein clearances were performed on 10 of the 11 patients (Table IV). The θ angle in 6 patients (over 60°) suggested a highly selective proteinuria; in 4 patients it was less than 54° , indicating a poor selectivity (Joachim *et al.*, 1964).

In 3 of the 4 patients with poorly selective proteinuria α_2 -macroglobulin was detected in the urine. An abnormal rise of both serum (1700 mg./100 ml.) and urine IgG was seen in the fourth patient (Case 7). Two patients (Cases 8 and 9) with α_2 -macroglobulin in the urine had pyuria (8-10 and 15-20 WBC/h.p.f. on a centrifuged specimen). Urine cultures failed to confirm a urinary tract infection in these children.

Of the 11 patients with proteinuria, 4 were retested during subsequent febrile periods a few days to a week after the episode in which proteinuria was detected. The temperature increase was as

TABLE III
Clinical and Laboratory Data on Patients with Febrile Proteinuria

Case No.	Diagnosis	Age	Sex	Temperature (°C.)	Urine Protein Concentration* (mg./100 ml.)	Urine Volume† (ml.)	Total Serum Protein (g./100 ml.)
1	Pneumonia	16 yr.	M	38.5	91	150	7.55
2	Otitis media	5½ yr.	M	39.0	30	60	7.24
3	Convulsion and vitamin D deficiency	7 mth.	F	39.1	39	40	6.94
4	Upper respiratory infection	3½ yr.	F	39.5	64	54	7.20
5	Otitis media	22 mth.	M	40.0	80	58	6.64
6	Measles	4 yr.	F	39.6	32	110/4 hr.	6.42
7	Asthma	6½ yr.	F	39.5	49	85	8.40
8	CNS sarcoma and flu-like illness	11 yr.	F	38.4	46	60	7.30
9	Measles	4 yr.	F	38.4	45	40	6.34
10	Pneumonia	9½ yr.	M	39.6	47	55	7.41
11	Septicaemia	3½ yr.	M	39.7	40	51	—

*Sulphosalicylic acid method.

†Single voided specimens except Case 6.

TABLE IV
Urine Protein Selectivity in Patients with Febrile Proteinuria

Case No.	IgG*	α_2 -macroglobulin*	θ Angle
1	21	0	72°
2	24	0	70°
3	22	0	71.5°
4	22	0	71.5°
5	32	0	66°
6	41	0	60°
7	234	0	1°
8	92	109	10°
9	183	96	2°
10	94	95	8°

* $\frac{\text{U/S ratio of IgG (or } \alpha_2\text{-macroglobulin)}}{\text{U/S ratio of transferrin}} \times 100$.

high as or higher than the initial fever in 3 of 4 patients. Proteinuria was absent at this time.

Discussion

The amount of urinary protein normally excreted is variable. In adults reported values reflect the sensitivity and accuracy of the methods used, with averages from 39–118 mg./24 hours per 1.73 sq.m. (Rigas and Heller, 1951; Berggård, 1961). The upper limit of normal for children is considered to be 75–100 mg./24 hours (Garrett, 1967).

Randolph and Greenfield (1967), using a dipstick method, reported a transient proteinuria in 6.3% of pre-adolescent children tested over a 6-year period. Some of their patients had an acute illness when proteinuria was detected, however many were apparently well. In our study only 30% of the urines considered positive by the dipstick method were confirmed to have 30 mg./100 ml. or more of protein by the sulphosalicylic

acid method. Thus, though the dipstick method is satisfactory as a screening test (Rennie and Keen, 1967), a considerable number of false positives may be encountered (*Medical Letter on Drugs and Therapeutics*, 1966).

Normal urine contains proteins of varying molecular weight, in amounts that reflect the relative concentration of these proteins in the serum (Rowe and Soothill, 1961a). The mechanism of normal proteinuria is not understood but probably depends on the relative rates of protein filtration at the capillary basement membrane and the rate of proximal tubular reabsorption (Sellers, 1956). Proteinuria has been observed in a number of situations in which there is no known renal disease. These include exercise (Poortmans and Jeanloz, 1968; Rowe and Soothill, 1961b), changes in posture (Slater, O'Doherty, and DeWolfe, 1960), exposure to cold (Sargent and Johnson, 1956), emotional stress (Starr, 1926; Ahronheim, 1944), adrenaline administration (King and Baldwin, 1955), abdominal operations (Macbeth and Pope, 1968), and fever (Gerhardt, 1869; Schwartz and Kassirer, 1963; Welty, 1937; Ehrström, 1941). Several theories have been proposed to explain the proteinuria which may be seen with fever. One theory is that an inflammatory response in the kidney resulting from an infectious agent may lead to proteinuria (Schreiner, 1957; Jensen, 1967; Burch and Sun, 1968). However, Welty (1937) showed that even in the absence of demonstrable infection, fever induced by hyperthermia treatment could lead to an increased protein excretion. King and Baldwin (1955) showed that the injection of adrenal medullary hormones might cause transient proteinuria in humans. The effect of these hormones, released as a result of stress induced by the fever, may be an

important factor in the development of febrile proteinuria. It is of interest that proteinuria was not detected during a subsequent febrile episode in 4 of the 11 patients with proteinuria during the initial study period. While an explanation for this phenomenon is not at hand, it may reflect the need for a certain specific set of circumstances to obtain in order that the urine protein concentration be high enough to detect (e.g. state of hydration, plasma volume, epinephrine release, renal blood flow). It may also be related to the specific cause of the fever (e.g. one or more particular viral agents), a parameter which was not possible to assess accurately in our study.

The protein excretion pattern is poorly selective in normal subjects (Rowe and Soothill, 1961a), postural proteinuria (Rowe and Soothill, 1961b), and certain forms of renal disease (Soothill, 1962). A more selective pattern is seen in exercise proteinuria (Rowe and Soothill, 1961b), multiple myeloma (Harrison *et al.*, 1966), and the minimal lesion type of the nephrotic syndrome (Soothill, 1962). The 4 patients with poorly selective proteinuria had extremely low θ angles. A satisfactory explanation for the high IgG/transferrin U/S ratios is not at hand; it is possible that with the techniques employed both intact (MW 150,000) and light chain (MW 20,000) urinary IgG molecules were measured in these patients. This might account for the unusual values of the θ angle observed.

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