Investigating the child with unexpected proteinuria

About 5% of well children will be found to have proteinuria on dipstick examination. Although most instances will be benign, clinically significant renal disease occurs in a few cases. The urinary protein to creatinine ratio is the key investigation.

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The hazard of proteinuria has long been recognised. Hippocrates knew it as 'frothy urine'. In the 17th century, coagulation of urine by heat was used as a method of detection (Figure 1). Today, semiquantitative dipstick urinalysis complemented by laboratory measurement has removed much of the uncertainty as to the significance of the finding of proteinuria in an individual child (Figure 2).

This review will address the problem of a child aged from one month to 15 years with an unexpected finding of proteinuria. It is assumed that the child is of normal growth and development, is not oedematous and has normal blood pressure, and that there is no family history of renal disease. The child may have presented with a nonspecific febrile illness, nocturnal or diurnal wetting, abdominal pain or dysuria where urinary tract infection is suspected, and a dipstick urinalysis is performed. (When the presentation suggests disease of the urinary tract, investigations relevant to the presentation and differential diagnosis will be required.)

In screening studies, approximately 5% of well children will be found to have proteinuria by dipstick examination.[1]

Initial investigation

Dipstick urinalysis

The total amount of protein normally excreted in 24 hours is less than 150 mg and the urinary protein to creatinine ratio is less than 20 mg protein/mmol creatinine,[2] which is enough to cause a trace reaction on standard dipsticks.

False positives may occur on semiquantitative dipstick analysis if the urine is contaminated with certain antiseptics or is highly alkaline.

Urinary protein:creatinine ratio

Errors occur in the collection of timed urine specimens and for most purposes the urinary protein to creatinine ratio is a satisfactory method for estimating the protein excretion rate.

No special preparation is required and urine collected into a clean container is satisfactory. Spontaneously voided urine collected deliberately

IN SUMMARY

- **About 5% of children will be found to have proteinuria on dipstick examination.**
- **The urinary protein to creatinine ratio is the key investigation when a finding of proteinuria is unexpected; normally this ratio will be less than 20 mg protein/mmol creatinine; a higher, fixed ratio is associated with a high incidence of clinically significant disease and warrants further investigation.**
- **Most instances of unexpected proteinuria are due to (benign) transient proteinuria, which is found in association with fever and following exercise.**
- **Other types of proteinuria are postural proteinuria (benign) and fixed proteinuria (associated with disease).**

from a child with bladder control or opportunistically or into an adhesive bag for younger children is suitable. Refrigeration would be wise if there is to be a delay of more than 12 hours before submission to a laboratory.

Types of proteinuria

Normal urine

Normal urine contains a small amount of protein. A range of protein species is present.

As stated above, the urinary protein:creatinine ratio in these children is usually less than 20 mg/mmol.

Transient proteinuria

Proteinuria is often found in association with fever and following exercise; although the mechanism is unclear, both appear to be benign phenomena.[3] Most instances of unexpected proteinuria will be due to transient proteinuria.

Exercise proteinuria usually occurs after a period of strenuous and exhausting exercise and disappears within 24 to 48 hours.

Febrile proteinuria disappears within seven to 10 days of resolution of the febrile illness.

The urinary protein:creatinine ratio in these children is usually less than 100 mg protein/mmol creatinine.

Postural proteinuria

This widely studied, apparently benign, phenomenon may persist for many years but is of uncertain cause.[4] The pattern of proteins suggests a nonglomerular origin, but the proteinuria is reversed by corticosteroids.

The level of proteinuria rarely exceeds 2 g over 24 hours or more than 100 mg protein/mmol creatinine.

An ambulant and a recumbent urine specimen are analysed to confirm this diagnosis:

- the recumbent urine will have less than 20 mg protein/mmol creatinine
- the ambulant urine will usually have more than 50 mg protein/mmol creatinine.

Follow up is not required.

Fixed proteinuria

Fixed (nonorthostatic) proteinuria of greater than 20 mg protein/mmol creatinine is associated with a high incidence of clinically significant renal disease, and detailed investigation and follow up are recommended.[5] This proteinuria may be tubular or glomerular in origin.

Tubular proteinuria

Tubular proteinuria is marked by the presence of a range of low molecular weight proteins, the most studied of which is β_2-microglobulin.

This form of proteinuria is seen in association with obstructive uropathies, 'reflux nephropathy', renal dysplasia and a variety of inherited disorders affecting the renal tubules, such as cystinosis.

The total urinary protein content is usually less than 100 mg protein/mmol creatinine.

Glomerular proteinuria

In nephrotic syndrome with minimal change, the proteinuria is usually highly selective (with albumin predominating); in most other forms of glomerulonephritis, the proteinuria is poorly selective and progression to renal failure occurs frequently.

Figure 1 (left). Seventeenth century test for proteinuria. Urine in the silver teaspoon was warmed over a candle to test for coagulation, indicating the presence of protein.

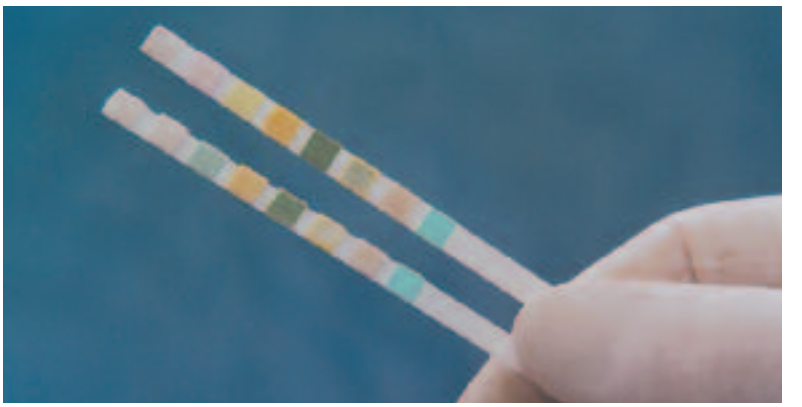

Figure 2 (above). Modern semiquantitative urinanalysis with dipsticks. The third square from the tip is testing for protein. The stick on the right is negative, and the one on the left is positive (3 g/L).

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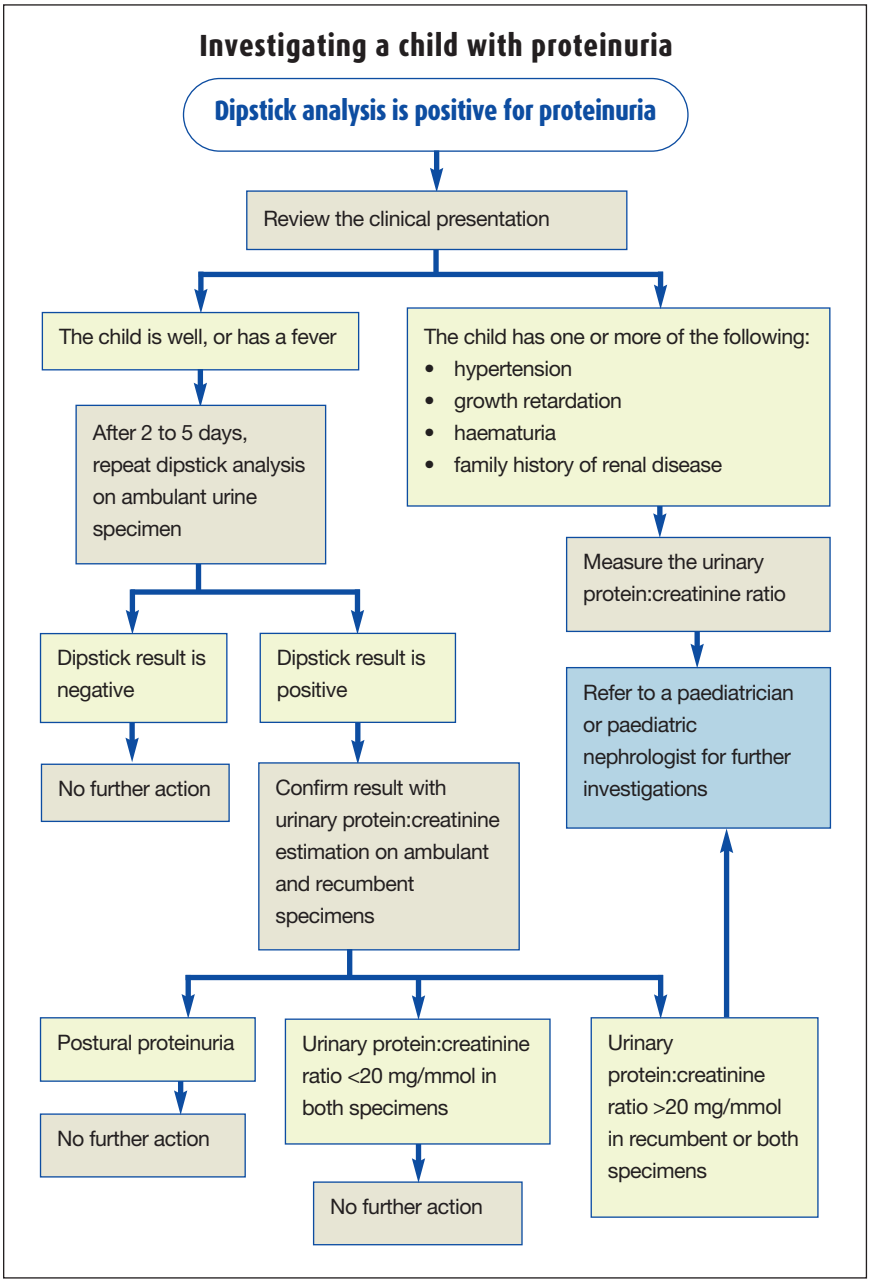

Recent studies suggest persistent proteinuria may produce secondary renal damage which may be ameliorated by angiotensin converting enzyme inhibitors.

From 1.5 to 3 g of protein may be excreted in 24 hours and the urinary protein to creatinine ratio is usually more than 100 mg protein/mmol creatinine; in nephrotic patients, the ratio is usually more than 350 mg protein/mmol creatinine.

Further investigation

Investigation begins with review of the current clinical presentation. The child's growth and development must be reviewed, and a full physical examination is performed to exclude oedema, hypertension and any physical anomalies. A full family history is taken to exclude inherited renal disease.

If there are no additional clinical abnormalities and transient proteinuria is probable, the dipstick urinalysis should be repeated two or three days after the fever has resolved – use an early morning specimen to avoid confusion with postural proteinuria. If that specimen is positive by dipstick, it should be submitted to the laboratory for estimation of the protein:creatinine ratio.

When transient and orthostatic proteinuria have been excluded, referral to a paediatrician or paediatric nephrologist would be appropriate. More detailed investigations are indicated to exclude structural abnormalities, defined forms of glomerulonephritis and evidence of pre-existing impaired renal function.

The flowchart on this page summarises the approach to investigation.

Conclusion

The urinary protein to creatinine ratio is the confirmatory investigation-of-choice in a child who is found to have unexpected proteinuria. MT

References

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