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Urinary excretion of *N*-acetyl- β -D-glucosaminidase in children

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SUMMARY The normal range for the urinary *N*-acetyl- β -D-glucosaminidase/creatinine ratio was determined in 82 children. The range was found to vary with age, and the distribution was found to be logarithmic. This test should help to detect renal tubular disease in children; it gave abnormal results in some of these children.

Recently there have been many reports on the value of urinary *N*-acetyl- β -D-glucosaminidase (NAG) for the detection of renal tubular disease in adults.¹⁻² There has been one report on its use in children.³ I report a normal range in childhood, and give the results in a few children who may have renal tubular disease.

Methods and subjects

Urine was obtained from children by midstream collection after informed consent had been obtained from at least one of their parents. The normal range was determined from children of friends, and from siblings of patients. In no case was there a history or family history that suggested renal disease. Urine was collected also from several children with a variety of diseases, and generally more than one urine sample was obtained from each. NAG was assayed fluorimetrically and the enzyme activity was divided by the creatinine concentration to take into account

varying rates of urine flow.² Creatinine was measured using a Technicon autoanalyser. One NAG unit equals 1 nmol of 4-methylumbelliferone released per hour at 37°C per μ mol creatinine. (One unit is equal to 11.3 nmol of 4-methylumbelliferone released per hour at 37°C per mg of creatinine). Since there is no sex difference in the excretion of NAG in adults,² the results from both sexes were combined.

Results

The normal excretion of NAG was determined in 82 children and was found to vary with age (Fig. 1). The distribution of excretion of the enzyme was found to be logarithmic (Fig. 2) and $\log_{10}$ values were used to calculate the normal range. For this purpose, three arbitrarily chosen age groups (12-59, 60-119, and 120-200 months) were selected to determine the mean and standard deviation. However, the other age groupings result in mean plus 2 standard deviation values which would fall very close to a line joining the three mean plus 2 standard deviation values shown.

Six children who required reimplantation of ureters because of severe reflux and recurrent infections despite prophylaxis all had normal NAG excretion levels before surgery. None was known to have intrarenal reflux although 2 had at least one kidney smaller than normal. A 1-year-old child with urethral valves and severe reflux had NAG excretion

Fig. 1 Urinary *N*-acetyl- β -D-glucosaminidase creatinine ratios in normal children. The logarithmic mean, and logarithmic mean ± 2 standard deviations are shown for each age range.

One NAG unit = 1 nmol/h per μmol creatinine which is equivalent to nmol/h per mg creatinine when multiplied by 11.3.

Fig. 2 Distribution of NAG by age in normal children. Because of the variation with age, it is necessary to examine the distribution over limited age ranges.

of 24 and 71 (normal range up to 21) units. One child with bilateral ureteroceles and hydronephrosis had normal levels.

One 12-year-old boy with corticosteroid-sensitive, presumed minimal change, nephrotic syndrome had NAG excretion of 11-30 (normal range up to 10) units during relapse. A 5-year-old girl with Schönlein-Henoch purpura had NAG levels of 4-16 (normal range up to 17) units, which increased to 9-25 units when proteinuria appeared. Two children with well-controlled galactosaemia and average IQs had normal NAG excretion. Two children with juvenile rheumatoid had increased excretion: the 10-year-old boy, 20 and 34 (normal range up to 12) units, was taking salicylates and the 8-year-old girl, 14 to 31 (normal range up to 13.5) units, was taking indomethacin and prednisone.

Discussion

The finding that NAG excretion is logarithmically distributed in normal children had not been reported. It is logarithmically distributed in neonates,⁷ and examination of data for normal adults² and children³ suggests that their data were not normally distributed because the mean minus 2 standard deviations value was less than zero on at least one occasion. This was no surprise as many biological variables are logarithmically distributed. The upper limit of the normal range given here is therefore higher than had been reported,³ and it varies more with age. High rates of urine flow (urinary creatinine less than 1 mmol/l; 8.84 g/l) may result in artificially high NAG levels.⁴ None of the normal children had a urinary creatinine <1 mmol/l. The effect of low rates of flow is unknown but it is thought to be less important (personal observation). No restriction on maximal urinary creatinine concentration was made.

It is disappointing that NAG appears to be of no value for detecting children in whom surgery is required to correct ureteric reflux, but the distal tubules and collecting ducts have the least NAG of all the tubular apparatus. This finding differs from that of a previous report,³ but that study might have been affected by an inaccurate normal range. Isoenzyme studies suggest that the children with glomerular disease probably had increased NAG excretion because of increased glomerular permeability,⁵ and not because of concurrent tubular damage.³ Galactosaemia, when poorly controlled, can cause tubular damage; increased NAG excretion may occur in poorly controlled children, but did not do so in the 2 well controlled children. The increased excretion in the children with juvenile rheumatoid is partly due to their drugs, but it may be due also to rheumatoid disease affecting the kidneys, since this

has been reported in adults.⁶ NAG should be as useful in children as it is in adults for the detection of renal tubular disease, provided an accurate normal range is used.

I record with regret the death of Miss Susan Tucker whose research did much to advance this subject, and thank Professor Scopes, Dr McSwiney, and Mr A Thompson for assistance.

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Maternal homocystinuria: studies of an untreated mother and fetus

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SUMMARY A 20-year-old woman with untreated homocystinuria was examined when she was 18 weeks' pregnant. Amniocentesis was performed and raised levels of homocystine and methionine were present in the amniotic fluid. Assay of cystathionine synthetase activity in cultured amniotic fluid cells showed the carrier state for homocystinuria. An abortion was performed because of the possible adverse effects of continuing the pregnancy both for the mother and the fetus. No pathological abnormality was found in the aborted fetus. Further data are needed to assess the possible teratogenic effects of maternal homocystinuria and the adverse consequences of pregnancy in the affected mother.

Homocystinuria comprises a group of autosomal recessive disorders of sulphur amino-acid metabolism. The most common type is due to a deficiency

of cystathionine synthetase, a pyridoxal phosphate-dependent enzyme which catalyses the reaction of serine with homocysteine to form cystathionine. This enzyme defect results in raised blood and urine levels of homocystine, methionine, and other sulphur amino-acids, and a lack of brain cystathionine. The clinical consequences vary and can include mental retardation, epilepsy, ectopia lentis, osteoporosis, skeletal anomalies (such as arachnodactyly and dolichostenomelia), fatty changes in the liver, and thrombotic vascular disease affecting any vessel in either the arterial or venous circulation. In many patients with cystathionine synthetase deficiency, treatment with pyridoxine appears to reverse the biochemical abnormalities and may prevent the development of manifestations of the disorder.¹ An affected, pregnant woman who had stopped treatment provided a unique opportunity to evaluate the effects of maternal cystathionine synthetase deficiency on the developing fetus.