Autoantibodies to Tamm-Horsfall protein in detection of vesicoureteric reflux and kidney scarring

A. FASTH, L. Å. HANSON, AND A. W. ASSCHER

From the Department of Immunology, Institute of Medical Microbiology, University of Goteborg, Sweden, and KRUF Institute of Renal Disease, Welsh National School of Medicine, Cardiff

SUMMARY Measurement of IgG antibodies to Tamm-Horsfall protein (ATHA) in 92 bacteriuric schoolgirls aged 5-12 did not show a significant rise compared with the titres found in the sera of 24 healthy controls. ATHA titres showed no correlation with the presence of vesicoureteric reflux or kidney scarring and it is concluded that measurement of serum ATHA is of no value as a screening procedure for the detection of vesicoureteric reflux.

There is close correlation between the presence of vesicoureteric (VU) reflux and kidney scarring both in girls with symptomatic infections (Smellie and Normand, 1968) and in those in whom infection is detected during mass screening of apparently healthy schoolgirls (Kunin *et al.*, 1964; McLachlan *et al.*, 1975; Newcastle Asymptomatic Bacteriuria Research Group, 1975). Smellie and Normand showed that persistent symptomatic infections lead to failure of kidney growth and kidney scarring in those children in whom infection and severe degrees of VU reflux coexist. In piglets (Hodson *et al.*, 1975), rats (Morgan *et al.*, 1976), and in children below the age of 4 (Rolleston *et al.*, 1974) severe degrees of VU reflux which are associated with intrarenal reflux may lead to kidney scarring even in the absence of infection. It has therefore been argued (Bailey, 1973; Asscher, 1975) that to prevent the kidney scarring which is associated with urinary tract infection in childhood, it may be more important to screen for VU reflux than for bacteriuria. If this were the case, there is an urgent need for a noninvasive method of detecting VU reflux in apparently healthy children. In piglets with obstructive uropathy and VU reflux, Hodson *et al.* (1975) found high levels of anti-Tamm-Horsfall antibody (ATHA) and suggested that estimation of serum ATHA might be valuable as a screening method for VU reflux. We report a study of the value of serum ATHA determination in the detection of VU reflux and kidney scarring.

Subjects and methods

Ninety-two schoolgirls aged 5-12 with asymptomatic bacteriuria detected during a screening programme in Cardiff (Asscher *et al.*, 1973) participated in the study. All had been examined radiologically (McLachlan *et al.*, 1975) both by excretion urography and micturating cystography, and urinary tract infection due to *E. coli* in all cases had been confirmed by culture of the catheter specimen of urine obtained at the time the micturating cystograms were performed. Serum samples obtained at this time had been stored at -20°C except during a 12-hour power cut and during the 3-hour period of transport to Sweden. None of the children had received treatment for the infection before the sera were obtained. As controls we used sera from 24 healthy girls aged 2-10 in whom there was no history of urinary tract infection and in whom urine culture had been sterile. ATHA titres were measured by the enzyme linked immunoabsorbent assay as described by Hanson *et al.* (1976).

Results (Fig.)

The mean ($\pm$ SD) of the IgG ATHA titres expressed as a percentage of the reference serum in all 92 bacteriuric schoolgirls was 29% (± 17.7) as compared with 26% (± 10.4) in the 24 nonbacteriuric controls. This difference was not significant ($0.4 > P > 0.3$). The mean ($\pm$ SD) of the IgG ATHA titres in the 19 bacteriuric girls with scarred kidneys (columns 2 and 3) was 28% (± 21.3),

Received 14 November 1976

Fig. IgG Anti-Tamm-Horsfall Antibody (ATHA) titres in 92 schoolgirls aged 5-12 with asymptomatic bacteriuria. The data are arranged according to the radiological findings and the shaded area refers to the mean ATHA titre ± 1 SD found in the sera of 24 healthy girls aged 2-10. Note: The term scar refers to cortical scars juxtaposed to dilated calyces. Grades of vesicoureteric reflux were defined as follows: grade 1 = contrast medium refluxes into ureter but fails to reach kidney; grade 2 = contrast medium reaches kidney; grade 3 = contrast medium reaches kidney and calyces are distended.

and that of the 55 bacteriuric girls with normal x-rays (column 1) was 29% (± 16); the difference between these means was not significant ($0.9 > P > 0.8$). The mean IgG ATHA titre in the 32 bacteriuric girls with VU reflux (columns 3 and 4) was 26% (± 18.3). This did not differ significantly from that in the 55 bacteriuric girls with normal x-rays ($0.7 > P > 0.6$), nor from that found in the 24 healthy nonbacteriuric controls ($0.9 > P > 0.8$). Moreover, as shown in the Fig. (columns 5-7) no correlation existed between the severity of VU reflux and the IgG ATHA titres; the means being 34.5% (± 23.7) for grade 1 reflux, 20.6% (± 10.4) for grade 2, and 21.6% (± 14.2) for grade 3. IgM and IgA ATHA titres were not significantly different between the controls and the bacteriuric subjects either.

Discussion

Whereas a raised ATHA titre of the IgG class has been shown to occur with symptomatic renal parenchymal infection due to *E. coli* (Hanson *et al.*,

1976), our study failed to show a relationship between raised IgG ATHA titres and the presence of kidney scar and/or VU reflux. Nor did the IgM or IgA titres show any such relationship. To explain these negative findings it is necessary to consider why ATHA titres rise in symptomatic kidney infection. Hodson *et al.* (1975) postulated that tubular damage associated with infection or even VU reflux on its own leads to release of Tamm-Horsfall protein into the circulation and subsequent antibody production. If this is so it is surprising that no correlation between kidney scarring and VU reflux on the one hand and ATHA titres on the other has been found. Much evidence (Glynn *et al.*, 1971; Hanson, 1973; Roberts *et al.*, 1975; Svanborg Edén *et al.*, 1976) supports the view that the bacteria responsible for asymptomatic infections differ antigenically from those which produce clinical infection. An alternative explanation for the rise of serum ATHA in symptomatic kidney infections may therefore be that strains of *E. coli* responsible for symptomatic kidney infection share common antigens with Tamm-Horsfall protein. Strains which produce lower tract or symptomless infections might

not possess such crossed antigenicity and would not, therefore, produce a rise of ATHA titre.

Whatever the explanation for our negative results, it is clear that estimation of ATHA titres is of no value in screening for VU reflux. A suitable test is therefore still urgently needed.

References

- Asscher, A. W. (1975). Urinary tract infection: value of early diagnosis. *Kidney International*, **7**, 63-67.
- Asscher, A. W., McLachlan, M. S. F., Jones, R. V., Meller, S., Sussman, M., Harrison, S., Johnston, H. H., Sleight, G., and Fletcher, E. W. (1973). Screening for asymptomatic urinary tract infection in schoolgirls. *Lancet*, **2**, 1-4.
- Bailey, R. R. (1973). The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis-reflux nephropathy. *Clinical Nephrology*, **1**, 132-141.
- Glynn, A. A., Brumfitt, W., and Howard, C. J. (1971). K-antigens of *Escherichia coli* and renal involvement in urinary tract infection. *Lancet*, **1**, 514-516.
- Hanson, L. Å. (1973). Host-parasite relationships in urinary tract infections. *Journal of Infectious Diseases*, **127**, 726-730.
- Hanson, L. Å., Fasth, A., and Jodal, U. (1976). Auto-antibodies to Tamm-Horsfall protein, a tool for diagnosing the level of urinary-tract infection. *Lancet*, **1**, 226-228.
- Hodson, J., Maling, T. M. J., McManamon, P. J., and Lewis, M. G. (1975). Reflux nephropathy. *Kidney International*, **8**, Suppl. 4.
- Kunin, C. M., Deutscher, R., and Paquin, A. (1974). Urinary tract infection in schoolchildren: an epidemiological, clinical and laboratory study. *Medicine*, **43**, 91-130.
- McLachlan, M. S. F., Meller, S., Jones, E. R. V., Asscher, A. W., Fletcher, E. W. L., Mayon-White, R. T., Ledingham, J. G. G., Smith, J. C., and Johnston, H. H. (1975). The urinary tract in schoolgirls with covert bacteriuria. *Archives of Disease in Childhood*, **50**, 253-258.
- Morgan, M., Asscher, A. W., and Moffat, D. B. (1976). The role of vesico-ureteric (V-U) reflux in the pathogenesis of kidney scars in the rat. *Nephron*, **17**, 8-19.
- Newcastle Asymptomatic Bacteriuria Research Group (1975). Asymptomatic bacteriuria in schoolchildren in Newcastle upon Tyne. *Archives of Disease in Childhood*, **50**, 90-102.
- Roberts, A. P., Linton, J. D., Waterman, A. M., Gower, P. E., and Koutsaimanis, K. G. (1975). Urinary and faecal *Escherichia coli* o-serotypes in symptomatic urinary tract infection and asymptomatic bacteriuria. *Journal of Medical Microbiology*, **8**, 311-318.
- Rolleston, G. L., Maling, T. M. J., and Hodson, C. J. (1974). Intrarenal reflux and the scarred kidney. *Archives of Disease in Childhood*, **49**, 531-539.
- Smellie, J. M., and Normand, I. C. S. (1968). Experience of follow-up of children with urinary tract infection. *Urinary Tract Infection*, p. 123. Ed. by F. W. O'Grady and W. Brumfitt. Oxford University Press, London.
- Svanborg Edén, C., Hanson, L. Å., Jodal, U., Lindberg, U., and Sohl Akerlund, A. S. (1976). Variable adherence to normal human urinary-tract epithelial cells of *Escherichia coli* strains associated with various forms of urinary-tract infection. *Lancet*, **2**, 490-492.

Correspondence to Prof. A. W. Asscher, KRUF Institute of Renal Disease, Royal Infirmary, Cardiff CF2 1SZ.