SHORT REPORT

Adenovirus associated haematuria

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Adenovirus is a common respiratory virus in children and is known to cause acute haemorrhagic cystitis, particularly in the immunosuppressed. In immunocompetent children with adenoviral infection the incidence of haematuria was 18.6%, with 2.4% of these children having macroscopic haematuria and upper tract involvement.

Adenovirus causes 5–8% of respiratory disease in infants and has many other clinical manifestations.¹ It has been reported in immunocompetent children² and is well described in the immunosuppressed. Acute haemorrhagic cystitis is commonly caused by adenoviral serotypes 11 and 21.³ IgA nephropathy, a common cause of haematuria, has been associated with adenovirus. A case of adenovirus and herpes simplex virus has been described in which granular depositions of adeno and herpes simplex viral antigens were detected in the glomerular mesangium.⁴ The association with haematuria has also been seen in reports of positive adenovirus immunofluorescence on throat swabs in patients with glomerulonephritis.⁵ However, in one previous study of emergency presentations of adenovirus, haematuria was described as a rare clinical finding.⁶

This study was designed to investigate the incidence of haematuria in adenoviral infections in the immunocompetent population, and to assess associated clinical features predisposing to haematuria.

METHODS

We performed a retrospective cohort study on all immunocompetent children with adenovirus isolated from culture or immunofluorescence over a 15 month period. The children were reviewed in the emergency department of a tertiary paediatric institution that annually reviews 45 000 patients. Diagnosis of adenovirus was made by culture with cyanomalous monkey kidney cells as the primary cell line and human embryonic fibroblasts. Positive cytopathic cultures were confirmed by direct immunofluorescence. Cultures were

held for three weeks before being declared negative. Nasopharyngeal aspirates were tested using direct immunofluorescence with an adenovirus specific monoclonal antibody (Dako Imogen, USA). Microscopic haematuria was defined as $10\text{--}100 \times 10^6/\text{l}$ and macroscopic haematuria as $>100 \times 10^6/\text{l}$ red blood cells per high power field. Epi Info version 6 was used to calculate proportions and exact binomial confidence intervals. SPSS v10 was used for the Mann-Whitney U test to determine any difference in ages, and StatXact 4.0.1 to perform a Fisher's exact test to compare presentations in children with or without haematuria.

RESULTS

Eighty two children were identified from 150 positive results, after duplications and immunosuppressed children were excluded. Of the 43 children with urine samples documented, eight children were identified with haematuria (18.6%). A sensitivity analysis was performed because no urine samples were collected in 39 children. Adjusting for children without urine specimens as though they were negative leaves a total of eight children out of 82 who had haematuria in the sample group. Therefore, there was at least a 9.8% incidence of haematuria in this population (95% CI 4.3 to 18.3) (see fig 1). The children were predominantly infants; however the incidence of haematuria was greater in older children ($p = 0.037$). The median age of children with urinalysis was 16 months and without was 13 months.

The majority of children presenting with adenovirus had primarily respiratory symptoms with fever and systemic symptoms. There was no association with the clinical presentation and the presence of haematuria ($p = 0.698$). In all groups there was a male predominance (table 1).

Of the six children with microscopic haematuria, none had casts on microscopy and all urine cultures were sterile. Their clinical presentations were variable and all except one were admitted to hospital.

The first child with macroscopic haematuria and proteinuria was a 9 year old girl who presented with fever, rash, coryza, conjunctivitis, and dark urine. Urine microscopy showed $>100 \times 10^6/\text{l}$ red blood cells per high power field with

Table 1 Clinical characteristics of patients with adenoviral infection

	Macro haematuria	Micro haematuria	No haematuria	No urine sample
Number	2	6	35	39
Sex	2F	2F:4M	14F:21M	16F:23M
Median age	N/A	60 months	16 months	13 months
Temperature $>38^\circ\text{C}$	2	6	29	N/A
Temperature $<38^\circ\text{C}$	0	0	6	N/A
Transfer	0	1	4	N/A
Admitted	2	5	32	N/A
Presentations				
Upper/lower RTI	0	3	18	N/A
Gastrointestinal	0	1	7	N/A
Rash	0	1	3	N/A
Mixed	1	0	6	N/A
Other	1	1	1	N/A

RTI, respiratory tract infection.

Figure 1 Flow diagram of urine results.

moderate amounts of granular and occasional cellular casts. This resolved on follow up examination. The second was a 19 month old girl who presented with abdominal pain, fever, and vomiting. She was diagnosed with intussusception. Adenovirus was isolated from a stool culture taken at the time of the acute illness. Her urine microscopy showed $>100 \times 10^6/l$ red blood cells per high power field, with dysmorphic red blood cells, occasional cellular casts, and moderate numbers of hyaline casts.

DISCUSSION

This study shows that haematuria is commonly associated with adenovirus in an immunocompetent paediatric population. Occasionally it can cause macroscopic haematuria requiring follow up. There have been reports of haematuria associated with adenovirus, especially immunosuppressed children or those with acute haemorrhagic cystitis; however, this is the first retrospective cohort study investigating the incidence of haematuria in an immunocompetent population with acute adenoviral infection.

In contrast to the clinical presentation of acute haemorrhagic cystitis, our patients with haematuria were systemically unwell with high fevers, with the majority requiring hospital admission. The haematuria in all but one case was incidental and not part of the presenting symptoms. No child had urinary symptoms. The presenting symptoms were varied in all of the groups studied and no particular presenting factor predicted the risk of associated haematuria.

Haematuria is a frequent presentation requiring nephrological follow up. In this group a surprising number had microscopic haematuria. In only the two patients with macroscopic haematuria were there urinary signs of

inflammation with associated proteinuria and casts suggesting upper tract involvement. This suggests that adenoviral associated microscopic haematuria, while common, is relatively benign, but when macroscopic haematuria or associated proteinuria are present it may have caused or unmasked an underlying glomerulonephritis.

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