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Streptococcal pharyngitis in general practice. 2. A note on dual infection and transient urinary abnormalities

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SUMMARY

In an uncompleted study in 1965 microscopic haematuria in the second or third week after acute pharyngitis was found four times more often in patients with either microbiological or clinical evidence of dual infection with both group A streptococci and a virus than in patients with evidence only of infection with group A streptococci.

Prospective studies of the role of viruses in the aetiology of transient haematuria and of acute post streptococcal glomerulonephritis are feasible in general practice and would be most productive if concentrated in children 5–9 years of age.

INTRODUCTION

Why acute nephritis follows some infections with group A streptococci is not known. In 1965 when the study reported here was carried out, the theory was that only certain types of group A streptococci (then types 4, 12 and 49) were 'nephritogenic'. This theory still prevails [1] though the number of types thus described has increased over the years [2, 3]. The search for a specific nephritogenic constituent of the streptococcal cell continues [4]; others pursue familial susceptibility [5].

Studies in that practice in 1958 and 1959 suggested that either 'nephritogenicity', if it existed, was not a sufficient cause of nephritis [6, 7] or that only a very small proportion of patients yielding nephritogenic streptococci had streptococcal infection. In 1963 an unusual cluster of post streptococcal conditions occurred amongst my patients at a time when both streptococcal infections and infectious mononucleosis-like illnesses were prevalent [8] and at the end of that year a patient developed acute nephritis following a sore throat due to group A streptococci and a primary infection with herpes simplex virus [9]. In the following year a girl of 3 whose sister had clinical and urinary evidence of acute nephritis was found to be excreting protein and red cells. Nose and throat swabs yielded type 12 group A streptococci and adenovirus type 5.

The full picture of acute nephritis is not often encountered in general practice but urinary abnormalities without other signs of nephritis after acute streptococcal sore throat are relatively common [7, 10, 11]. Such abnormalities may be found in contacts of patients with acute nephritis [12–14]. The histological picture of acute nephritis may be demonstrated in patients with urinary abnormalities alone [15, 16]. It is reasonable to infer that proteinuria and haematuria after acute

pharyngitis may, at least in a proportion of cases, be due to subclinical acute glomerulonephritis. Elucidation of the circumstances in which such abnormalities occur might therefore give an indication of the actiology of acute post streptococcal glomerulonephritis.

In 1964 a study was planned to determine whether, in patients with serologically confirmed streptococcal infection of the throat, simultaneous infection with a virus was associated with a higher incidence of urinary abnormalities than was infection due to two common 'nephritogenic' types [12 and 4] or to other types alone. It was anticipated that it would take 3 or 4 years to collect sufficient cases but a year later I moved to another practice. By that time only a few cases of proven dual infection had been identified. Recent analysis however has revealed findings worth reporting as a stimulus to further work.

The method is described in detail in the previous paper [17].

RESULTS

Group A streptococci were isolated only from patients with pharyngitis (defined as an illness in which the patient complained of sore throat or exhibited exudate or marked redness of the throat).

Over the 12 months 113 episodes of acute pharyngitis were seen within 48 h of the onset of symptoms. Six episodes have been excluded. In three children satisfactory swabs could not be obtained. In three children swabs for virus culture could not be taken within 2 days of the onset of symptoms; in two bacterial culture yielded group A type 12 streptococci and in the third group A streptococci with the agglutination pattern 5/27/44. In all three children urines tested after the first week contained red cells.

The remaining 107 episodes occurred in 102 individuals. In 49 episodes group A streptococci were isolated alone. In four episodes both group A streptococci and a virus were isolated: echovirus type 7 plus type 12 streptococci in a girl of 18 months, herpes simplex virus (HSV) plus type 12 streptococci in her mother aged 28, coxsackie A9 virus plus type 11 streptococci in a girl 8 years old and in a man of 42 years HSV together with beta-haemolytic streptococci not of groups A, C or G on the first swab and group A streptococci on the second swab taken 72 h after the onset of sore throat. This man was not identified for follow-up as the streptococci isolated were not typed.

Swabs yielded type 12 streptococci alone in 10 episodes and type 4 alone in 3 episodes.

Twenty-five patients were identified for follow-up but six were not followed up for various reasons (too young to bleed, confusion over urine specimens, menstruation, left the area). Blood could not be obtained in two children during convalescence and in another the second specimen was contaminated.

Complement fixation tests were negative in all episodes.

Urinary abnormalities

All patients were asked at the first contact to submit urines on the ninth day after the onset of sore throat. In 40 episodes at least one specimen of urine was submitted for testing. Protein (more than at trace) was noted in 3 of the 19

Table 1. *Haematuria by result of throat culture: all episodes of pharnygitis*

		First week		After first week	
	No.	No. tested	Haematuria	No. tested	Haematuria
Virus alone	12	1	0	4	1
GpA alone	49	19	5	20	7
GpA + virus	4	3	0	3	2
Other*	42	4	0	11	0
Total	107	27	5	38	10

* Swab yielded beta-haemolytic streptococci not of groups A, C or G or did not yield a pathogen.

patients yielding group A streptococci and none of the 13 patients not yielding group A streptococci tested on the ninth day. After the ninth day protein was present in the urine of 2 of the 21 patients yielding group A streptococci who were tested and in 1 of the 5 not yielding group A streptococci: a girl 10 years old whose antistreptolysin (ASL) titre was 300 U/ml 31 days after the onset of sore throat.

Casts were found in only one patient (who also had proteinuria but not haematuria) a girl 11 years old, whose swab had yielded group A streptococci type 11.

Microscopic haematuria (not exceeding 20 rbc/cmm in any case) was found only in patients yielding group A streptococci with one exception: a child whose swab yielded coxsackie B virus alone (ASL titres 85 and < 50 U/ml) (Table 1).

In 10 patients followed up there was serological evidence of contemporaneous streptococcal infection. Microscopic haematuria was noted after the first week in 3 out of 5 patients yielding type 12 and the 1 patient with dual infection in this group; in none of the 4 patients yielding other types was microscopic haematuria found after the first week.

Dual infection

In four patients, as previously mentioned, there was microbiological evidence of dual infection. One, a child 11 months old, was not subjected to venepuncture or followed up; another, a man of 42 years, was not bled as the streptococci were not typed.

In six children the appearance of the throat at the first contact was recorded as unusual. In two tiny yellow ulcers and in four tiny or faint spots in the throat were recorded at the first contact suggesting herpangina rather than streptococcal pharyngitis. Two of the six children yielded coxsackie A viruses alone and one beta-haemolytic streptococci not of groups A, C or G alone. The other three children yielded group A streptococci alone but all were siblings of children who had sore throats at the same time and who yielded viruses (coxsackie A virus alone, coxsackie A virus plus type 12 streptococci, echovirus plus type 12 streptococci).

In another child, a boy 6 years old, whose swab yielded type 11 streptococci the throat at the first contact was normal but at follow-up on the third day after the onset of symptoms a few tiny spots were noted on the tonsils. In this case there was no known contact with a patient with a virus infection.

Table 2. *Patients with possible dual infection*

	Sex	Age (years)	Swabs: Gp A type	Swabs: Virus	ASL u/ml: Serum 1	ASL u/ml: Serum 2	Haematuria: First week	Haematuria: After first week	Comments
JN1†	F	1½	12	Echo 7	—	—	nil	—	Urine not collected after 7th day
JG	F	8	11	Cox A9	0	> 800	nil	+	
EN	F	28	12	HSV	320	310	nil	nil	Mother of JN 1 and 2
MB†	M	42	NT*	HSV	—	—	—	+	First swab yielded haemolytic streptococci not ACG; second swab GpA
AG	M	5	11	neg	0	0	+	+	Brother of JG
JN2	F	8	12	neg	165	315		+	Sister of JN1
ML	F	14	12	neg	320	350	+	+	Sister yielded coxsackie A4
GC†	F	5	3	neg	—	—	—	+	Infection mono-nucleosis type illness after scarlatina
TS	M	6	11	neg	240	0	nil	nil	No known contact with virus infection

* NT. = not typed.
† Not subjected to venepuncture.
0. failed to obtain blood.

Table 3. *Haematuria in patients yielding group A streptococci with and without evidence of virus infection*

Evidence of virus infection	No.	First week		After first week	
		No. tested	Haematuria	No. tested	Haematuria
Present	9	7	2	8	6
Absent	16	15	4	16	3
Total	25	22	6	24	9

Another child, a girl 5 years old (G.C.), who had not been identified for follow-up, developed enlargement of glands, liver and spleen a week after an acute sore throat (not treated with antibiotics), with scarlatinal rash, yielding type 3 streptococci. This infectious mononucleosis-like illness lasted 10 days. Such illnesses in children are usually due to infection with the Epstein–Barr virus or cytomegalovirus [18].

Thus in three children yielding only group A streptococci clinical and circumstantial evidence, and in two children yielding only group A streptococci clinical evidence, suggested concurrent virus infection.

There were therefore 9 patients (7 of them among the 19 systematically followed up) in whom microbiological or clinical evidence suggesting dual infection with both group A streptococci and a virus was found (Table 2). In two the ASL titres indicated contemporaneous streptococcal infection and in two streptococcal infection beginning before the illness for which they consulted. Type 12 streptococci were isolated in four of these cases and other types in four. Microscopic haematuria after the first week was found in 6 of the 8 tested (including all 3 patients yielding types other than 12 or 4) as compared with 3 of the 16 patients yielding group A streptococci alone in whom evidence suggesting virus infection was not found (Table 3). These proportions were compared using Fisher's exact test (two-sided); the proportion with haematuria after the seventh day was significantly greater in those with evidence of dual infection ($P < 0{\cdot}05$).

DISCUSSION

Proteinuria was infrequent and slight in the patients tested and was noted only in those yielding group A streptococci or with serological evidence of streptococcal infection (one patient).

With one exception, microscopic haematuria was found only in patients yielding group A streptococci either alone or with a virus. In the second or third week after pharyngitis over a third (9 out of 23) of all patients yielding group A streptococci were found to have microscopic haematuria.

Half of those with serological evidence of contemporaneous streptococcal infection had microscopic haematuria in the second or third week. Haematuria was noted in the one case of dual infection in this group. The numbers are too small to allow significant differences between type 12 and other types to emerge.

In a total of 9 patients there was microbiological or clinical evidence suggesting dual infection; in 6 of the 8 tested, microscopic haematuria was found as compared with 3 out of 16 with no evidence of dual infection. In the absence of proof of dual

infection in seven of these patients, the difference between the two groups, formally significant at 5%, can only be claimed to suggest that there may be a causal relationship between dual infection and microscopic haematuria after the first week following acute pharyngitis.

Coxsackie viruses were isolated from the siblings of two children with haematuria whose swabs yielded group A streptococci, from one child with haematuria whose swab also yielded type 11 streptococci and from one child with haematuria in whom streptococcal infection was not demonstrated.

Coxsackie viruses have been isolated from patients with acute nephritis [19, 20] and nephritis has been reported following echovirus infections [21] and other virus infections [22] but the role of viruses in the aetiology of glomerulonephritis is not clear [23]. Prospective studies are needed to establish their contribution, if any, to acute post streptococcal glomerulonephritis and transient urinary abnormalities. This report demonstrates that such studies are possible in general practice and with the techniques now available a higher yield of viruses may be achieved [24]. The yield of dual infections may be further increased if children between the ages of 5 and 9 are the subjects of study. In that age group the chances of dual infection are greater than in other age groups; isolations of group A streptococci are at their peak and isolations of viruses, though not as frequent as in those under 5, are still relatively common [17]. The incidence of acute post streptococcal glomerulonephritis peaks around the age of 6 [25, 26] – as, in the light of these findings, one would expect if dual infection is an important determinant of the condition.

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