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Epidemics of haemorrhagic cystitis due to influenza A virus

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Summary

The present communication describes studies on thirty-three patients with haemorrhagic cystitis. The current epidemic variant of influenza type A virus, A/Tehran/5/75 (H_3N_2) [antigenically similar to A/Port Chalmers/1/73 (H_3N_2)], was recovered from the throats of eighteen and the urine of three patients. HI antibody rises to A/Tehran/5/75 virus were detected in over 50% of the cystitis patients tested.

Introduction

The role of viruses in diseases of the urinary tract and kidneys has been confirmed by many workers (Jensen, 1967; Koszinowski and Volkman, 1974; Burch and Sun, 1968) and it is now apparent that adenoviruses type 11 and 21 can cause haemorrhagic cystitis (Chiba *et al.*, 1974; Numazaki *et al.*, 1973; Mufson and Belshe, 1976). Reports on influenza as an aetiological factor in nephritis have been the matter of much speculation over the past several decades. Thomson and Macauley (1920) reported several cases of nephritis due to influenza some 50 years ago, and Alexander (1965) and Truc, Scillico and Marchal (1951) reported that influenza virus can indeed cause renal pathology.

Viraemia of influenza has been demonstrated on occasions both in man (Khakpour, Saidi and Naficy, 1969; Naficy, 1963; Stanley and Jackson, 1966) and animals (Hamre, Appel and Berlin, 1969) and influenza virus antigen has also been demonstrated in the kidneys (Ishida, Morizuka and Hinuma, 1964).

Because of the rarity of urinary tract involvement in influenza and in spite of some bulk of evidence in the literature, less attention has been paid to the fact that urinary involvement exists in some patients affected with influenza.

In recent epidemics of influenza in Tehran, Iran, many cases of haemorrhagic cystitis were reported and influenza virus was isolated from the urine and throat in some cases, meanwhile the antibody to influenza was raised concomitantly, as measured at the time, and after 6–8 weeks from the onset of the disease.

Materials and methods

Patient population

During an epidemic of influenza which lasted from February to April 1975 in Tehran, many affected individuals were reported with signs and symptoms of haemorrhagic cystitis: fever, general malaise, dysuria, increased frequency of urination and haematuria. The symptoms occurred with no immediate cause, haematuria was macroscopic and lasted for 3–5 days and then subsided immediately leaving no symptoms, and all patients recovered spontaneously.

The number of patients involved in the study was thirty-three of which twenty-seven were female and six were male, ranging in age from 14 to 39 years.

Specimens

Serum samples, throat wash and urine were obtained from all subjects on the first or second day of the onset of cystitis. The second serum samples were taken 6–8 weeks later. All sera were stored at −20°C, before using for serological tests. Throat wash and urine were either inoculated within a few hours of collection or stored at −70°C before inoculation.

Viral isolation

Each throat and urine specimen was inoculated in a volume of 0·2 ml into the amniotic cavity of 10-day-old embryonated eggs and amniotic fluids were harvested after 40 hr incubation at 35°C and overnight at 41°C. All amniotic fluids were tested for haemagglutination (HA) activity. HA-positive fluids were inoculated again but allantoically and HA-negative fluids were passaged once more amniotically. In the second passage, all HA-negative fluids were accounted as virus-free or negative and discarded.

Serological tests

Haemagglutination inhibition (HI) test was carried out according to the standard technique using one of the new isolated influenza viruses designated as A/Tehran/5/75.

Diagnostic cystoscopy was suggested to all affected individuals and seven of the thirty-three patients

TABLE 1. Results of HI antibody determination and urinalysis in patients with positive viral isolation

Patients			Viral isolation		Antibody titre*		Urinalysis		
No.	Sex	Age (years)	Throat	Urine	Acute	Convalescent	Culture	Red blood cells	Protein
1	F	19	+	—	≤1 : 20	1 : 640	0	Many	Trace
2	F	21	+	—	1 : 40	1 : 80	0	Many	—
3	F	20	+	+	1 : 40	1 : 1280	0	Many	—
4	F	32	+	—	≤1 : 20	1 : 80	*Escherichia coli* < 5000	20–30	—
5	M	27	+	—	1 : 640	1 : 640	0	Many	+1
6	F	18	+	—	1 : 80	1 : 160	0	Many	—
7	F	16	+	+	1 : 40	1 : 2560	0	15–25	—
8	M	31	+	—	1 : 160	1 : 320	0	Many	—
9	M	34	+	—	1 : 80	1 : 1280	*Staphylococcus* < 8500†	Many	—
10	F	22	+	—	≤1 : 20	1 : 40	0	Many	Trace
11	F	21	+	—	1 : 80	1 : 2560	0	Many	—
12	F	25	+	—	≤1 : 20	1 : 40	0	50–60	—
13	F	25	+	—	1 : 40	1 : 160	0	Many	—
14	F	24	+	—	≤1 : 20	1 : 640	0	Many	—
15	F	20	+	—	1 : 80	1 : 1280	0	Many	—
16	M	29	+	—	≤1 : 20	1 : 1280	0	Many	—
17	F	27	+	—	1 : 80	1 : 160	0	Many	—
18	F	29	+	+	≤1 : 20	1 : 640	0	Many	—

* HI antibody titre to A/Tehran/5/75 virus; † *Staphylococcus* coagulase positive.

TABLE 2. Results of HI antibody determination and urinalysis in patients with negative viral isolation

Patients			Antibody titre*		Urinalysis		
No.	Sex	Age (years)	Acute	Convalescent	Culture	Red blood cell	Protein
1	F	17	≤1 : 20	1 : 80	0	Many	—
2	F	19	≤1 : 20	1 : 1280	0	Many	—
3	F	24	1 : 160	1 : 80	0	Many	—
4	F	21	1 : 40	1 : 2560	*Escherichia coli* < 900	Many	—
5	M	20	1 : 160	1 : 320	0	Many	Trace
6	M	26	≤1 : 20	1 : 160	0	Many	—
7	F	28	1 : 640	1 : 640	0	Many	—
8	F	27	1 : 20	1 : 40	0	Many	—
9	F	35	1 : 1280	1 : 640	0	Many	—
10	F	39	1 : 40	1 : 160	0	20–40	—
11	F	23	1 : 80	1 : 640	0	Many	—
12	F	34	≤1 : 20	1 : 80	0	Many	—
13	F	30	≤1 : 20	1 : 40	*E. coli* < 7300	Many	Trace
14	F	21	1 : 40	1 : 320	0	Many	—
15	F	14	≤1 : 20	1 : 640	0	Many	—

* HI antibody titre to A/Tehran/5/75 virus.

accepted the procedure. On cystoscopy, the bladder was uniformly congested and haemorrhagic. No ulcer, polyp or other pathology was found. Intravenous pyelography (IVP) was performed in all and reported normal. Urine cultures for bacteriological studies remained negative during the course of the disease, except in four cases (Tables 1 and 2).

Results

Influenza virus was recovered from eighteen throat wash and three urine samples. Antigenic characteristics of new isolated virus from throat specimens was found to be influenza type A and closely related to the A/Port Chalmers/1/73. This antigenic characteristic was confirmed by WHO, World Influenza Centre, London.

HI antibody determination in paired sera revealed a great rise of antibody titre in most of the patients.

Tables 1 and 2 summarize these results from patients with positive and negative viral isolation.

Discussion

With the advent of laboratory procedures, it is now possible to recover viruses from the urine in certain diseases in which viraemia is present (Jensen, 1967; Zakstel'skaya, 1953; Smith and Aqino, 1971). Affection of the kidneys and urinary tract in viral diseases is also thought to result from the shedding

of viruses from kidney cells involved in generalized infection. In many instances, viruria will remain harmless and not significant clinically, but in some instances, in certain virurias, this can cause symptoms related to the affected parts of the urinary tract (Smith and Aqino, 1971). Haemorrhagic cystitis due to adenovirus II is a well established entity and viruria has been documented in such instances (Chiba *et al.*, 1974; Myking and Schreiner, 1974).

Recovery of influenza virus from patients' blood was reported only by a few workers (Khakpour *et al.*, 1969; Naficy, 1963; Stanley and Jackson, 1966) and in spite of the fact that renal pathology due to influenza has been reported on several occasions (Thomson and Macauley, 1920; Alexander, 1965; Truc *et al.*, 1951; Myking and Schreiner, 1974; Wilson and Smith, 1972), only in rare instances was virus isolated from the urine of affected individuals (Zakstel'skaya, 1953). The authors recovered influenza virus in the urine of three of thirty-three cases reported to their medical clinic with signs and symptoms of haemorrhagic cystitis. The cystitis lasted 2–5 days with manifestations of dysuria, frequency in micturition and haematuria. The correlation of increased antibody titre from the first day of the illness and 6–8 weeks later was carefully documented in most of the cases and increased titre was noted in these individuals, confirming the fact that although influenza virus could not be recovered in the urine of some patients, haemorrhagic cystitis was directly related to influenza infection as a part of its systemic and urinary tract involvement.

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