Archives of Emergency Medicine, 1987, 4, 155–161

Virus infection and knee injury

P. DRISCOLL, R. VENNER & G. B. CLEMENTS*

*Accident and Emergency Department, Western Infirmary, and *Institute of Virology, Glasgow, Scotland*

SUMMARY

Serological evidence of virus infection was sought in 31 consecutive patients presenting with knee swelling and compared with age/sex-matched controls. In a normal age/sex-matched control group, 42% of patients had evidence of recent or past infection with Coxsackie B virus, emphasising the care required in the evaluation of the significance of Coxsackie B neutralization titres in individual patients. Of 12 patients presenting with knee swelling and a history of a twisting injury, eight had serological evidence of recent or past infection with Coxsackie B virus, and one had evidence of a current adenovirus infection.

INTRODUCTION

Viruses may interact with the musculoskeletal system at a variety of levels: the joints, muscles or the nervous system. It is well established that some virus infections may result in an acute arthritis, for example, rubella, Chikungunya and hepatitis B. Arthritis has not been widely reported as an association with infection by other viruses. Recently, however, arthropathy has been reported in a proportion of parvovirus infections (Anderson *et al.* 1985). The clinical effects of acute infection by Coxsackie B virus as usually described, though wide ranging, do not include arthritis (Kibrick, 1974; Grist *et al.*, 1978). Coxsackie B together with some other viruses has been suggested as a cause of a 'post-viral fatigue syndrome' following infection in some patients.

This study was designed to determine if patients presenting to an accident and emergency department with a traumatic knee effusion had serological evidence of recent virus infection.

Correspondence: Mr P. Driscoll, Accident and Emergency Department, University College Hospital, London, England

METHODS

Design of the study

The study was originally initiated to investigate a possible link between viral infection and the spontaneous onset of a knee effusion. The trauma patients being included as controls. In each case, a careful history was taken based on a proforma to elucidate evidence of recent viral infection (for example, cough, aches and pains, and night sweats). Serum for viral titres was obtained from patients at their initial presentation and a convalescent sample 2 weeks later.

Virological investigations

Neutralizing antibodies to Coxsackie group B viruses type 1–5 were estimated by a micro-neutralization test (Bell & Grist, 1970). Coxsackie B IgM was measured by an ELISA (King *et al.*, 1983; McCartney *et al.*, 1986). The significance of elevated to Coxsackie B neutralization titres in the Glasgow area has recently been assessed O'Neill *et al.* (1983). A titre of $\geqslant 512$ had a 72% corellation with a clinical history suggesting 'recent' Coxsackie B infection. Titres of $\geqslant 256$ to Coxsackie B_2 and B_4, and $\geqslant 128$ to Coxsackie B_1, B_3 and B_5 are taken as evidence of previous infection.

Two age/sex-matched control groups were selected at random from the routine samples processed by the laboratory over the time the study was being carried out. One was a positive control composed of 'at risk of Coxsackie infection' samples where testing for Coxsackie B neutralizing antibody was indicated from the history, for example, chest pain, cardiac arrythmias or myalgia. The other was a negative control group where Coxsackie B tests were not indicated, for example, routine rubella screen.

Rubella IgM was estimated using an ELISA (Abbott) and rubella IgG by single radial haemolysis (SRH) (Northumbria Biologicals). A monospot was carried out and antibody to the following antigens was measured by routine complement fixation tests using Colindale reagents: psittacosis/LGV, mycoplasma pneumoniae, influenza A, influenza B, adénovirus, respiratory syncytical virus, herpes simplex, varicella zoster, cytomegalovirus, mumps and measles virus. Parvovirus IgM was tested for using a solid-phase IgM antibody capture radioimmunoassay (Cohen *et al.*, 1983).

RESULTS

Patients were divided into three groups on the basis of the history. No trauma was reported in eight patients (Group I), 11 had received a twisting injury to the knee (Group II) and the remaining 12 had received a direct blow (Group III).

Table 1 presents the serological results in the three groups. Unless otherwise stated, the injury had occurred during the previous 24 h. In the majority of cases, injury occurred while playing football.

In Group I (eight patients, four males and four females; average age, 27·6 years), one patient had detectable rubella IgM and a rising level of antibody to rubella as measured

Table 1 Significant serological results in patients presenting with knee effusion

Group	Patient number	History	Sex	Age	Serological results of significance
I	1		M	25	B3 256
No trauma	2		F	24	
	3	URTI Diarrhoea°	F	21	
	4		M	25	B1 128 B5 128
	5	URTI	F	24	
	6	URTI	M	25	Rubella SRH <4 to 11mm Rubella IgM + ve
	7	URTI	F	47	
	8		M	30	B3 256 B4 256
			Average 27·6		
II	9		M	30	B3 512
Twisting	10		F	19	B2 256
injury	11		M	26	
	12		M	26	B4 256
	13		M	21	B4 256
	14		M	16	B2 512
	15*		M	29	B4 256
	16	URTI Diarrhoea†	M	21	B2 256 B4 512
	17	URTI°	F	34	
	18	Recurrent injury	M	65	B3 128 CMV 256
	19	URTI Injury 2 weeks before	M	26	
	20	Direct blow 6 weeks before	F	32	adeno 128–256
			Average 28·7		
III	21		M	51	B4 512
Direct	22		M	22	B5 256
trauma	23		M	27	B2 512
	24	URTI† Injury 1 week before	M	45	
	25		M	26	B3 128
	26		F	42	
	27	Headaches	F	19	
	28		M	22	B1 128
	29		M	25	CMV 256
	30		F	18	
	31		M	29	B3 128
			Average 29·6		

URTI: upper respiratory tract infection.
° Right elbow also affected 2 weeks prior to presentation.
*Other knee also painful at time of injury.
†Two weeks prior to presentation.

by the SRH test, evidence of recent infection with rubella. None of these patients had evidence of a recent Coxsackie B virus infection but three, all males, had evidence of past infection. Four patients had symptoms consistent with a recent virus infection but only in the patient with rubella was this accompanied by serological evidence of recent infection.

In Group II (12 patients, nine males and three females; average age, 28·7 years), five patients had serological evidence of a recent virus infection, three (all males) with Coxsackie B, one with cytomegalovirus and one with adenovirus. A further five patients had evidence of previous infection with Coxsackie B including one patient who, in addition, had evidence of cytomegalovirus infection. Only one of these seropositive patients had symptoms suggestive of a virus infection at presentation. Two more patients with a history of upper respiratory tract infection had negative serology.

In Group III (12 patients, nine males and three females; average age, 28·7 years), three patients had serological evidence of a recent virus infection, two with Coxsackie B and one with cytomegalovirus, and a further four had evidence of previous infection with Coxsackie B. Symptoms compatible with recent virus infection were present in two patients, both had negative serology.

In none of the paired samples was there a rise in titre to Coxsackie B virus neutralizing antibody, nor was a significantly elevated level of Coxsackie B IgM detected. In contrast, rising titres were seen in each of the patients with elevated titres of antibody to adenovirus and rubella virus. No patient in the study showed serological evidence of having had a recent parvovirus infection on the basis of tests for parvovirus specific IgM.

Taking the 31 knee swelling patients as a single group, five (16%) had evidence of recent infection and 12 (39%) had evidence of past infection with Coxsackie B 1–5. Results of Coxsackie B neutralization tests on the two control groups, a normal group and an 'at-risk group' are presented in Table 2. The difference in the number of patients with negative serology in the two control groups is significant at the 5% level by the X^2 test. Taking all 31 patients in the knee swelling group together, the pattern of Coxsackie B titres is not significantly different from the two control groups. However, patients with a history of a twisting injury (Group II) show a distribution of Coxsackie B titres almost identical with the 'at risk of Coxsackie' control group, eight (67%) having evidence of a previous Coxsackie B infection. Two of the four patients in this group

Table 2 Number of patients with serological evidence of previous infection by Coxsackie B

Titre	Number of patients	Seronegative°	(%)	Seropositive+	(%)
All knee swelling groups	31	14	(45)	17	(55)
Groups I and III	19	10	(53)	9	(47)
Group II	12	4	(33)	8	(67)
'At risk of Coxsackie infection' controls	31	10	(32)	21	(68)
Normal controls	31	18	(58)	13	(42)

° Coxsackie B_2 and B_4 at <128; Cocksackie B_1, B_3 and B_5 at $\leqslant 64$.

\+ Cocksackie B_1, B_3 and B_5 at >128; Coxsackie B_2 and B_4 at $\geqslant 256$.

(seronegative for Coxsackie B) gave a history of recent upper respiratory tract infection and a third had elevated titres to adenovirus. The remainder of the knee swelling patients (Groups I and III) have an incidence of Coxsackie B infection very similar to the normal control group.

DISCUSSION

Patients who presented to an accident and emergency department with knee effusion were studied, nine (29%) had serological evidence of a recent virus infection, five presented with Coxsackie B, one with rubella, one with adenovirus and two with cytomegalovirus. The elevated titres to cytomegalovirus may result from either primary infection or reactivation of latent virus. A further 12 patients (39%) had serological evidence of past infection with Coxsackie B virus. The association of rubella infection with arthropathy is well-documented. The significance of the adenovirus and cytomegalovorus infections is difficult to assess in this relatively small group.

The significance of the elevated neutralizing titres to Coxsackie B virus must be evaluated carefully. Incidentally raised Coxsackie B titres of $\geqslant 512$ were found in 4% of a control group of individuals from the same geographical area in 1980–1981 (O'Neill *et al.*, 1983). In 1984, 87 healthy adults in the West of Scotland were tested for neutralizing antibody to Coxsackie B virus, and 5% had titres of $\geqslant 512$ and 12% of $\geqslant 256$ (McCartney *et al.*, 1986). The normal control group in the current study had a greater proportion with a significantly elevated level of Coxsackie B neutralizing antibody 10% $\geqslant 512$ and a further 32% with evidence of past infection. However, it should be noted that the average age of patients was 28·7 years and the incidence of Coxsackie B virus infections is higher in young people. It is well known that this background level of activity may vary with season and from year to year, and it also depends on the age distribution of the group.

Arthropathy is a feature of Coxsackie B virus infection not previously emphasized. There are three previous reports of an association between Coxsackie B virus infection and joint disease: Rahal *et al.* (1976), Hurst *et al.* (1983) and Luckt *et al.* (1984). All 12 patients in these series were admitted to hospital and suffered from a polyarthritis, usually as part of a more generalized disease process. A rising antibody titre to Coxsackie B virus, indicative of an acute infection, was seen in each of these cases, though in only $\frac{8}{12}$ was a titre of $\geqslant 256$ found. It is not possible to make detailed comparisons of absolute levels of Coxsackie B neutralizing antibody in samples tested independently in different laboratories. In this series, the mode of presentation was quite different, all patients had static neutralizing antibody titres to Coxsackie B and were managed as outpatients. With one exception, in whom both knees were affected, all were suffering from a monoarticular arthritis. These features suggest initial infection had occurred some time prior to presentation, a conclusion supported by the absence of symptoms of recent infection in most cases. Coxsackie B myocarditis also presents some time after acute infection, and is characterized by static neutralizing antibody titres and failure to isolate virus from the patient (O'Neill *et al.*, 1983; Grist & Bell, 1974). It is well established that Coxsackie B neutralizing antibodies may remain elevated for

several years following infection, and it may be that infection was either subclinical or too far in the past to figure in the history. Infection with enteroviruses other than Coxsackie B may produce an anamnestic response and lead to elevated levels of neutralizing antibody to Coxsackie B. Indeed, the authors would predict that other viruses in addition to Coxsackie B might be found associated with arthropathy if appropriate serological investigations could be carried out. Nine patients in the knee swelling group of this study had symptoms consistent with a recent virus infection but only two had significant serological findings. It is unclear at present what factors determine the pattern of response of an individual to Coxsackie B virus infection. Both viral and host genetic factors may be involved. Individual strains of Coxsackie B virus differ in their tissue tropisms in mice and individual mouse strains differ in their response to infection (Gamble, 1984).

The pathogenesis of the arthropathy may be due to a direct effect of virus on the joint either as a result of replication within the tissues or the deposition of immune complexes. The timing might favour the latter possibility in this series of cases but would not explain it being monoarticular. Alternatively, the pathogenesis may be indirect. Virus infection may render individuals more liable to be injured by reduction in joint proprioception, muscular coordination or power, or by diminution of general awareness and speed of reaction, or due to the production of knee effusions and pain with relatively less trauma than usual. Since the initial description of epidemic myalgia (Sylvest, 1934), skeletal muscle has been known to be a target for Coxsackie B virus infections in addition to the myocardium.

Recent work (Behan *et al.*, 1985; Jamal & Hansen, 1985; Arnold *et al.*, 1984) provides direct evidence for there being muscle weakness on exercise in some patients. Muscle weakness could clearly play an important role in knee injury during exercise like playing football by destabilizing the joint under stress. In this study, the majority of knee effusions in Groups II and III followed injury at football.

Virus infection may play a role in contributing to injury by yet another route: by affecting concentration and performance. Direct study of experimentally induced minor illness (colds and influenza) on the efficiency of human performance has been conducted (Smith *et al.*, 1987). Influenza impaired the ability to detect and respond quickly to stimuli at irregular intervals while colds impaired hand-eye coordination. A decrease in the sporting performance of four athletes with viral illness was recently reported (Roberts, 1985). In two of these cases, the athletes had elevated titres of Coxsackie B neutralizing antibody (one B_2 512, the other B_3 256).

In conclusion, patients presenting with knee joint arthropathy and a history of twisting injury have an increased probability of having evidence of previous virus infection. The authors postulate that investigation of patients presenting with injury to other joints stressed during sport could show a similar picture. A high proportion (42%) of the normal control group (average age 28·7 years) have evidence of recent or past infection with Coxsackie B virus emphasizing the care that is necessary in the interpretation of Coxsackie B neutralization results on individual patients. It remains to be seen whether particular individuals are especially susceptible to injury following virus infection. A prospective study is underway to correlate athlete's performance with serological evidence of recent infection.

ACKNOWLEDGEMENTS

We thank Mr G. Robinson, Miss J. Cameron, Miss I Coote and Miss B. O'Donnell for expert technical assistance, and Dr M. Anderson for performing the assays for parvovirus IgM. We also thank Dr E. J. Bell for carrying out the Coxsackie B IgM assays and for constructive comments.

REFERENCES

Anderson M. J., Kidd I. M. & Morgan-Capner P. (1985) Human parvovirus and rubella-like illness. *Lancet* **ii**, 663.

Arnold D. L., Bore P. J., Radda, G. K., Styles P. & Taylor D. J. (1984) Excessive intracellular acidosis of skeletal muscle on exercise in a patient with a postviral exhaustion/fatigue syndrome. *Lancet* **i**, 1367–9.

Behan P. O., Behan W. M. H. & Bell E. J. (1985) The post viral fatigue syndrome—an analysis of the findings in 50 cases. *Journal of Infection* **10**, 211–22.

Bell E. J. & Grist N. R. (1970) Further studies of enterovirus infections in cardiac disease and pleurodynia. *Scandinavian Journal of Infectious Diseases* **2**, 1–6.

Cohen B. J., Mortimer P. P. & Pereira M. S. (1983) Diagnostic assays with monoclonal antibodies for the human serum parvovirus-like virus (SPLV). *Journal of Hygiene* (Cambridge) **92**, 113–30.

Gamble D. R. (1984) Enteroviruses: polio: ECHO-, and Coxsackie viruses. In *Topley and Wilson's Principles of Bacteriology, Virology and Immunology*, Vol. 4, Brown F. & Wilson G. (eds), pp. 394–419. Baltimore, Williams & Wilkins.

Grist N. R., Bell E. J. & Assaad F. (1978) Enteroviruses in human diseases. *Progress in Medical Virology* **24**, 114–42.

Grist N. R. & Bell E. J. (1974) A 6-year study of Coxsackie B virus infection in heart disease. *Journal of Hygiene* (Cambridge) **73**, 165–72.

Hurst N. P., Martynoga A. G., Nuki G., Sewell J. R., Mitchell A. & Hugues G. R. V. (1983) Coxsackie B infection and arthritis. *British Medical Journal* **286**, 605.

Jamal G. A. & Hansen S. (1983) Electrophysiological studies in the post-viral fatigue syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* **48**, 691–4.

Kibrick S. (1974) Current status of Coxsackie and echovirus in human disease. *Progress in Medical Virology* **6**, 27–70.

King M. L., Bindwell D., Shaikh A., Voler A. & Banatvala J. E. (1983) Coxsackie B virus-specific IgM response in children with insulin-dependent (juvenile onset: Type 1) diabetis Mellitus. *Lancet* **i**, 1397–9.

Luckt F., Alexandre C., Fayard C., Gaudin O. G. & Mathevet N. (1984) Arthrites associees à des infections à virus Coxsackie B. *Revue du Rhumatisme et des Maladies Osteoarticulaires* **51**, 153–5.

McCartney R. A., Banatvala J. E. & Bell E. J. (1986) Routine use of u-antibody-capture ELISA for the serological diagnosis of Coxsackie B. virus infections. *Journal of Medical Virology* **19**, 205–12.

O'Neill D., McArthur J. D., Kennedy J. A. & Clements G. B. (1983) Coxsackie B. virus infection in coronary care unit patients. *Journal of Clinical Pathology* **36**, 658–61.

Rahal J. J., Millian S. J. & Noriega E. R. (1976) Coxsackie virus and adenovirus infection: association with acute febrile and juvenile rheumatoid arthritis. *Journal of the American Medical Association* **235**, 2496–501.

Roberts J. A. (1983) Loss of form in young athletes due to viral infection. *British Medical Journal* **290**, 357–8.

Smith A. P., Tyrrell D. A. J., Cogle K. & Williams J. S. (1987) Selective effects of minor illnesses on human performance. *British Journal of Psychiatry*, in press.

Sylvest E. (1934) Epidemic myalgia. In *Bornholm Disease*. Copenhagen, Levin and Muksgaard.