Erythema infectiosum in a village primary school: clinical and virological studies

JAMES G. TUCKERMAN, MRCGP

THOMAS BROWN, MSc, PhD

BERNARD J. COHEN, PhD

SUMMARY. In a questionnaire response to an outbreak of erythema infectiosum in a village primary school, 55 (46%) of the 121 pupils reported an illness with rash. Three of the 12 members of staff also developed a rash. Onset in most affected children was indicated by the classical 'slapped cheek' appearance of erythema infectiosum with subsequent spread of the rash to the extremities. However, in 17 (35%) of 49 children who provided additional clinical data, the rash spread either in the reverse direction or not at all. Nineteen children (39%) reported recurrence of the rash.

Serological studies confirmed that human parvovirus was the cause of the outbreak. Forty-six (44%) of 104 children investigated had significant levels of virus-specific immunoglobulin (Ig)M and/or IgG antibodies consistent with recent infection. Most infections occurred in older children. Human parvovirus infection was also confirmed in five of the 12 adults. These studies revealed a substantial number of subclinical episodes — 14 (22%) of 64 subjects who remained well had serological evidence of recent infection with human parovovirus. Significantly, 43 individuals (37% of those investigated) remained seronegative despite frequent exposure to infection within the school. This finding, together with the observed temporary interruption of the outbreak which coincided with school holidays substantiates the view that human parvovirus has a relatively low infectivity and requires close person-to-person contact for its transmission.

Introduction

ERYTHEMA infectiosum (fifth disease or 'slapped-cheek' syndrome) is a benign, acute, exanthem of childhood. Since it was first recognized as a separate entity distinct from rubella by Escherich, numerous outbreaks of the disease have been reported from various parts of the world, notably the USA.[1-4]

Erythema infectiosum most commonly affects children of primary school age and outbreaks occur frequently in schools. Under these circumstances, the typical facial rash with its 'slapped-cheek' appearance facilitates clinical diagnosis. However, in isolated cases the disease can be mistaken for rubella or other erythemata.

Until recently, the cause of the disease was unknown but Anderson and colleagues[5] have reported retrospective serological studies of an outbreak of erythema infectiosum in a London primary school which have implicated human parvovirus as the likely aetiological agent. Similar findings have been made in Japan[6] and Canada.[7]

J.G. Tuckerman, General Practitioner, Buckie; T. Brown, Lecturer in Bacteriology, University of Aberdeen; and B.J. Cohen, Senior Microbiologist, Public Health Laboratory Service Virus Reference Laboratory, Colindale.

© *Journal of the Royal College of General Practitioners*, 1986, **36**, 267-270.

In December 1983 an outbreak of erythema infectiosum occurred in the primary school in Portknockie, a small coastal fishing village near the town of Buckie in the north-east of Scotland. This episode signalled the start of an extensive epidemic in Grampian Region which prompted a great deal of interest. The school outbreak presented an ideal opportunity to study the clinical features of erythema infectiosum and also to ascertain the aetiological role of human parvovirus.

Method

Clinical data

During the early stages of the outbreak a questionnaire was sent to the parents of each child attending the school. Each questionnaire was accompanied by a letter from the Headmaster containing details of the clinical features of fifth disease as described in a circular issued by the District Medical Officer. The parents were asked if they believed their children had had the illness and, if so, to provide the dates of onset as well as any personal observations with regard to symptoms.

A second questionnaire was sent to the parents of those children who were found either to be seropositive for human parvovirus infection or to have had definite recent history of a rash. In keeping with the prospective nature of the study, these forms were handed out during the middle and latter stages of the outbreak and so yielded more detailed information about the symptomatology of the disease.

Clinical data for the members of staff were obtained in consultations.

Serological investigations

Sera obtained initially from eight children revealed no evidence of recent rubella infection but provided the first indication that human parvovirus was the likely cause of the outbreak. For all subsequent studies, pin-prick samples of blood were taken from the thumb and collected on either squares of sterile blotting paper or standard Guthrie PKU test cards. Labelled samples were sent for testing to the Virus Reference Laboratory where blood-soaked areas were cut from the paper or test card samples and eluted into phosphate buffered saline (0.5 ml, pH 7.2). All specimens were tested for the presence of anti-human parvovirus immunoglobulin (Ig)M and IgG antibodies.[8] For both immunoglobulin classes, levels of 1.0 radioimmunoassay (RIA) units or more were considered positive. Anti-human parvovirus-negative specimens were subsequently tested for human parvovirus antigen by radioimmunoassay.[8]

Results

Clinical data

The first questionnaire was returned by 106 of the 121 pupils attending the school. The second questionnaire was returned by 65 children — six children with a history of a rash either did not receive or did not return the second questionnaire because they were absent from school.

The first case of erythema infectiosum was diagnosed clinically on 4 December 1983 and from that date to the end of March 1984 55 children (29 boys and 26 girls) were reported to have had an illness with rash consistent with the description of the disease issued to the parents. Figure 1 illustrates the progress

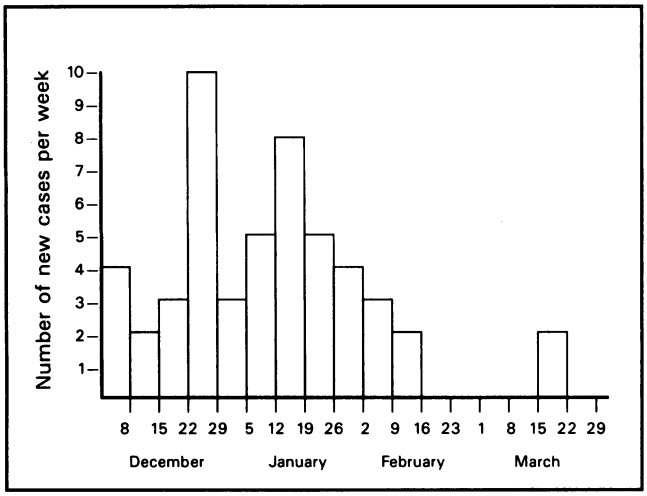

Figure 1. *Distribution of 51 cases of erythema infectiosum by week of onset (December 1983 – March 1984 inclusive).*

of the school outbreak by week of onset. The histogram excludes four cases for which the exact dates of onset were not known. Two peaks were observed, one in late December and the other in mid-January. The classes containing the youngest and oldest children showed the lowest clinical attack rates (22% and 20% respectively). The intermediate classes were affected equally with attack rates ranging from 44% to 53%. Three of the 12 members of staff developed a mild, exanthematous illness during the outbreak.

The first indication of the disease in most cases was a flushed, 'slapped-cheek' appearance (Table 1). The rash was reported to spread from the face to the extremities in 32 (65%) of the 49 affected children who returned the second questionnaire and in the reverse direction in seven children (14%). The rash apparently did not spread in 10 cases (20%). The rash usually disappeared after four or five days although it was said to have persisted for more than 10 days in nine children. Nineteen children experienced recurrences of the rash, notably after swimming (10 cases, 53%) or following exposure to heat (10, 53%), cold (5, 26%) or sunlight (4, 21%). Emotional stress was thought to be a factor in one child. Symptoms accompanying the rash with their frequency of occurrence are shown in Table 2. These were usually mild but pruritis was a disturbing feature for many children. Arthralgia was reported in three children, two of whom had no history of a rash.

The parents were asked if any other members of the family had been affected by the rash. Thirty-four (52%) of the 65 families answered in the affirmative and those affected were mainly children of pre-school age.

Serological investigations

Specimens for seroanalysis were obtained from 104 children and the 12 members of staff — 21 children and one adult submitted follow-up samples four to six weeks later. The 116 subjects were allocated to four groups according to arbitrarily chosen levels of anti-human parvovirus IgM and/or IgG antibodies expressed in RIA units.

Group 1. This comprised 45 children and four adults who had serological evidence of recent human parvovirus infection as indicated by the presence of virus-specific IgM antibody (> 1 RIA unit) or IgG antibody at high (> 100 RIA units) or significantly rising levels in paired specimens. In addition, this group included one child and one adult with evidence of probable recent infection (anti-human parvovirus IgM < 1 RIA unit, IgG > 80 RIA units or rising moderately in paired specimens).

Table 1. Characteristics of rash in 49 children with clinically diagnosed erythema infectiosum.[a]

Characteristic	Number (%) affected
Initial site of rash	
Face	37 (*75*)
Extremities	11 (*22*)
Trunk	1 (*2*)
Duration (days)	
1–5	23 (*47*)
6–10	16 (*33*)
> 10	9 (*18*)
Not known	1 (*2*)
Recurrence?	
Yes	19 (*39*)
No	27 (*55*)
Not known	3 (*6*)
No. of recurrences	
1	9 (*47*)
>1	9 (*47*)
Not known	1 (*5*)

[a]Data from the second questionnaire returned by 49 of 55 children with a rash.

Table 2. Frequency of associated symptoms in 49 children with clinically diagnosed erythema infectiosum.[a]

Symptoms	Number (%) affected
Itchy rash	31 (*63*)
Fever	19 (*39*)
Decreased appetite	17 (*35*)
Coryza	16 (*33*)
Headache	14 (*29*)
Pharyngitis	13 (*27*)
Sore eyes	9 (*18*)
Diarrhoea	8 (*16*)
Nausea or vomiting	5 (*10*)

[a] Data from the second questionnaire returned by 49 of 55 children with a rash.

Group 2. This comprised three children whose sera gave equivocal results (IgM < 1 RIA unit, IgG 50–79 RIA units).

Group 3. This included 13 children and six adults with low to moderate serum levels of anti-human parvovirus IgG antibody (1–49 RIA units) that could only be ascribed to past infection.

Group 4. This consisted of 42 children and one adult who were anti-human parvovirus negative.

Attack rates for children in Group 1 (Table 3) were highest in those aged between eight and 10 years. Of 104 pupils tested, a total of 46 (24 boys and 22 girls) had serological evidence of recent or probable recent infection, an overall attack rate of 44%. A similar proportion of members of staff appeared to have been infected during the outbreak (Table 3), although the number investigated was much smaller; four females and one male possessed anti-human parvovirus antibody. Table 3 also includes clinical attack rates — children aged between six and 10 years showed the highest rates of clinical infection.

Clinical data were available for all the subjects investigated serologically. Of the 51 individuals (48 children and three adults) who volunteered a history of recent illness including rash, 36 (71%) had serological evidence of recent infection with human

Table 3. Attack rates according to serological (group 1) and clinical findings by age.

Age (years)	Serological findings			Clinical findings		
	Number seropositive	Number tested	Percentage attack rate	Number of cases	Number exposed	Percentage attack rate
Children						
4	3	3	*100*	1	3	*33*
5	2	13	*15*	4	16	*25*
6	6	17	*34*	10	18	*56*
7	3	13	*23*	7	13	*54*
8	10	18	*56*	10	21	*48*
9	10	17	*59*	10	18	*55*
10	10	14	*71*	9	20	*45*
11	2	9	*22*	4	12	*33*
Total	46	104	*44*	55	121	*45*
Adults						
24–52	5	12	*42*	3	12	*25*

parvovirus, three yielded equivocal serological data, eight were considered to have had past infection and four were seronegative. Similarly, of the 64 subjects who had no clinical manifestations, 11 had anti-human parvovirus antibody levels consistent with past infection and 39 were seronegative, giving an overall correlation of 78% between clinical and laboratory findings. Interestingly, 12 children and two adults (22%) had serological evidence of recent infection although they apparently remained well. The clinical assessment of one seropositive child was frustrated by conflicting answers on the two questionnaires.

None of the seronegative specimens was found to contain human parvovirus antigen.

Discussion

The clinical features of erythema infectiosum observed during this outbreak generally conformed to previous descriptions.[1-4] In most affected children the rash began as a malar flush, then spread as a maculopapular eruption to the extremities and finally faded to a characteristic lacy or reticular appearance. However, the rash was first noted on the extremities in 22% of affected children, and thereafter spread to the face in 12%. While the data obtained by questionnaire may not be entirely reliable, inaccurate reporting is unlikely to account for such a high proportion of children with atypical erythema. Indeed, others have reported the first appearance of the rash at sites other than the face, notably the arms and trunk.[4,7]

Transient recrudescences of the rash of erythema infectiosum may occur over a period of several weeks following the initial eruption, especially after bathing, exercise, excitement or exposure to sunlight.[3,4] Recrudescence occurred in 67% of affected children during an outbreak in a London primary school in March 1983[5] but in this study only 19 of 49 children (38%) were said to have experienced recurrence of the rash and in approximately half of these the rash reappeared only once. Given the location of Portknockie and the time of year when the outbreak occurred, it is possible that the children were exposed less frequently to whatever external or environmental factors trigger recrudescence.

Symptoms accompanying the rash largely matched those described in previous reports.[2-7] Pruritis was particularly frequent and fever, anorexia and headache were common. Upper respiratory tract symptoms were also prominent. The shape of the epidemic curve is notable in showing two peaks whereas previous accounts have generally indicated one.[2-5] It is likely that this distribution was due to a temporary interruption of the outbreak by the school holiday over the Christmas and New Year period. This feature is consistent with person-to-person transmission of infection, possibly by the respiratory route.[7,9]

Three children suffered arthralgia with pain and stiffness, but no swelling of affected joints. Two of these children had no rash. None of the five infected adults experienced joint pain or swelling although arthralgia is known to be associated with erythema infectiosum in older patients.[4,10-12]

This is the first outbreak of erythema infectiosum to be investigated prospectively by both clinical and virological observations. It has the merit that serological tests were carried out on almost all members of the school population regardless of clinical history.

The choice of a finger-prick sampling method using filter papers or cards was dictated by the large number of subjects involved and by the acceptability of the procedure. However, this may have reduced the effectiveness of serological assays as pretest dilutions could not be made as accurately as from venous blood specimens and it is possible that alternative sampling procedures would have revealed definite evidence of recent infection in some subjects allocated to Groups 2 and 3. Nevertheless, clinical and laboratory findings correlated well in that 71% of subjects who had a rash also had firm serological evidence of recent infection with human parvovirus. Conversely, there was no evidence of recent infection in 78% of those who remained well.

This study also revealed a substantial number of subclinical infections, a finding that is perhaps not surprising in the light of the inapparent infections known to be caused by other viruses such as rubella.[13] Plummer and colleagues have reported similar observations.[8] The implications of such inapparent infections are unknown. It is likely that they are of little significance in the young unless there is a risk of infection, for example, in children with hereditary disorders of the blood.[14] However, infection without a rash in adults may pose problems. Arthritis is often the sole manifestation of parvovirus infection, particularly in women, and it may be difficult to suggest a cause in the absence of serological investigations.[12] Severe, intrauterine infection of the fetus following asymptomatic or atypical infection of the mother during pregnancy has also been reported.[15,16]

Clinical attack rates in the Portknockie children peaked over a wider age range than those calculated on the basis of serological findings. Factors contributing to this discrepancy may have been the failure to detect significant virus-specific IgM anti-

body levels in some finger-prick samples and the occurrence of asymptomatic infections, particularly in older children. However, the observations largely agree with previous reports of peak infection rates in children aged approximately six to 10 years, with a bias towards older children within this group.[2,3,5] The tendency for erythema infectiosum to occur in older children suggests that it is less infectious than other childhood diseases such as measles and chickenpox.[17] Other features of the present outbreak support this view, such as the observed temporary decline in the number of cases over the holiday period. Moreover, 42 children and one adult (37% of the total number investigated) appeared to have escaped infection and were seronegative, despite continual exposure within the confines of the school.

These data provide further strong evidence that the human parvovirus is the causative agent of erythema infectiosum and extend the list of disease manifestations. The classical features of 'slapped-cheek' syndrome may not always be present and a significant number of infections are asymptomatic. The application of specific virological procedures to the study of future episodes may well reveal other consequences of human parvovirus infection.

References

1. Shaw HLK. Erythema infectiosum. *Am J Med Sci* 1905; **129:** 16-22.
2. Greenwald P, Bashe JW Jr. An epidemic of erythema infectiosum. *Am J Dis Child* 1964; **107:** 30-34.
3. Ager EA, Chin TDY, Poland JD. Epidemic erythema infectiosum. *N Engl J Med* 1966; **275:** 1326-1331.
4. Lauer BA, MacCormack JN, Wilfert C. Erythema infectiosum. An elementary school outbreak. *Am J Dis Child* 1976; **130:** 252-254.
5. Anderson MJ, Lewis E, Kidd IM, *et al.* An outbreak of erythema infectiosum associated with human parvovirus infection. *J Hyg Camb* 1984; **93:** 85-93.
6. Okabe N, Koboyashi S, Tatsuzawa O, Mortimer PP. Detection of antibodies to human parvovirus in erythema infectiosum (fifth disease). *Arch Dis Child* 1984; **59:** 1016-1019.
7. Plummer FA, Hammond GW, Forward K, *et al.* An erythema infectiosum-like illness caused by human parvovirus infection. *N Engl J Med* 1985; **313:** 74-79.
8. Cohen BJ, Mortimer PP, Pereira MS. Diagnostic assays with monoclonal antibodies for the human serum parvovirus-like virus (SPLV). *J Hyg Camb* 1983; **91:** 113-130.
9. Anderson MJ, Pattison JR. The human parvovirus: brief review. *Arch Virol* 1984; **82:** 137-148.
10. Wadlington WB, Riley HD. Arthritis and hemolytic anemia following erythema infectiosum. *JAMA* 1968; **203:** 473-475.
11. White DG, Woolf AD, Mortimer PP, *et al.* Human parvovirus arthropathy. *Lancet* 1985; **1:** 419-421.
12. Reid DM, Reid TMS, Brown T, *et al.* Human parvovirus-associated arthritis: a clinical and laboratory description. *Lancet* 1985; **1:** 422-425.
13. Horstmann M. Rubella. In: Evans AS (ed). *Viral infections of humans: epidemiology and control.* 2nd edition. New York: Plenum, 1982: 519-539.
14. Davidson RJ, Brown T, Wiseman D. Human parvovirus infection and aplastic crisis in hereditary spherocytosis. *J Infect* 1984; **9:** 298-300.
15. Brown T, Anand A, Ritchie LD, *et al.* Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet* 1984; **2:** 1033-1034.
16. Knott PD, Welply GAC, Anderson MJ. Serologically proved intrauterine infection with parvovirus. *Br Med J* 1984; **289:** 1660.
17. Mortimer PP. The 80th year of fifth disease. *Br Med J* 1984; **289:** 338-339.

Acknowledgements

We thank Dr D.J.C. Cameron, Mrs Theresa Campbell, Mrs Janet Murray and Miss Marie Buckley. We greatly appreciated the cheerful and enthusiastic cooperation of Mr Frank Reynolds, Headmaster of Portknockie Primary School, and the school staff, pupils and their parents, without whom the investigation would not have been possible.

Address for correspondence

Dr J.G. Tuckerman, The Health Centre, Benreay, Seaview Place, Buckie, Banffshire AB5 1JT.