Serological findings

	IgM antibody	IgG antibody	HPV-B19 DNA
8 July Serum	+	+	+
CSF	ND	ND	+
13 July Serum	+	+	+
CSF	ND	ND	-

ND=not done.

HPV-B19 DNA was also positive in serum and cerebrospinal fluid. However, in the cerebrospinal fluid HPV-B19 DNA was positive on 8 July but became negative on 13 July (see figure).

Discussion

In 1983, HPV-B19 was identified as the cause of erythema infectiosum by Anderson *et al.*¹ Therefore various pathological manifestations have been reported to be caused by HPV-B19. Dijkmans *et al* detected HPV-B19 DNA in the synovial fluid of a 33 year old woman with arthritis.³ Saint-Martin *et al* reported a 1 year old boy with myocarditis caused by HPV-B19.⁴ They found HPV-B19 structural proteins in the patient's myocardial tissue. In addition, aplastic crisis is a well known complication of HPV-B19 infection.

Central nervous system involvement, as in encephalitis and aseptic meningitis, is a rare complication of HPV-B19 infection, and there have been only a few reports of central nervous

system involvement associated with erythema infectiosum. Three case reports of encephalitis and one report of meningitis were found in a review of the recent literature.^{5,6} None of them, however, demonstrated direct evidence of central nervous system involvement by HPV-B19. The detection of HPV-B19 DNA in the cerebrospinal fluid of our patient by the PCR suggests that central nervous system invasion by the virus had occurred. To the best of our knowledge, this is the first report of the detection of HPV-B19 DNA in cerebrospinal fluid of a patient with a serologically probed HPV-B19 meningitis. The prognosis of aseptic meningitis due to HPV-B19 appears to be good, judging from our experience and a previous case report.

The widespread use of the PCR should help to determine the spectrum of HPV-B19 infection. Similar cases to ours will probably be detected and as yet unknown clinical manifestations may also be found.

- 1 Anderson MJ, Jones SE, Fisher-Hoch SP, *et al.* Human parvovirus, the cause of erythema infectiosum (fifth disease)? *Lancet* 1983; i: 1378.
- 2 Sevall JS. Detection of parvovirus B19 by dot-blot and polymerase chain reaction. *Mol Cell Probes* 1990; 4: 237-46.
- 3 Dijkmans BAC, van Elsacker-Niele AMW, Salismans MMM, van Albada-Kuipers GA, de Vries E, Weiland HT. Human parvovirus B19 DNA in synovial fluid. *Arthritis Rheum* 1988; 31: 279-81.
- 4 Saint-Martin J, Choulot JJ, Bonnaud E, Morinet F. Myocarditis caused by parvovirus. *J Pediatr* 1990; 116: 1007.
- 5 Balfour HH Jr, Schiff GM, Bloom JE. Encephalitis associated with erythema infectiosum. *J Pediatr* 1970; 77: 133-6.
- 6 Tsuji A, Uchida N, Asamura S, Matsunaga Y, Yamazaki S. Aseptic meningitis with erythema infectiosum. *Eur J Pediatr* 1990; 149: 449-50.

Serum interleukin-1 α and soluble interleukin-2 receptor concentrations in cystic fibrosis

P Greally, M J Hussain, D Vergani, J F Price

Abstract

Interleukin (IL)-1 and IL-2 may participate in the systemic inflammatory response and hypergammaglobulinaemia observed in patients with cystic fibrosis. Thirty seven patients with cystic fibrosis were compared with 25 normal controls. High IgG and IgM concentrations were associated with more severe pulmonary disease. IL-1 α and soluble IL-2 receptor concentrations were higher in the cystic fibrosis group than in the controls and also correlated with concentrations of IgG and IgM. These results suggest that these cytokines may contribute to enhanced immunoglobulin synthesis and silent inflammatory activity in clinically stable patients with cystic fibrosis.

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with cystic fibrosis despite the presence of intact local immune defences. Continuous bacterial exposure leads to the systemic spread of these vigorous, yet ineffective, local responses. This process may result in hypergammaglobulinaemia, which often correlates with the progression of pulmonary disease.¹ The vigorous inflammatory response, in which granulocytes predominate, may produce immunologically mediated pulmonary injury.²

Interleukin (IL)-1 and IL-2 are cytokines derived respectively from mononuclear phagocytes and T lymphocytes. They may participate in the initial immune responses to infectious stimuli and immunoglobulin production. Soluble IL-2 receptor (sIL-2R) is released after activation of mononuclear cells by IL-2 and is one indicator of T cell activation.³ We investigated whether these cytokines were participating in the heightened systemic inflammatory response in cystic fibrosis and whether there was

King's College Hospital,
London, Departments of
Child Health and
Thoracic Medicine
P Greally
J F Price

Department of
Immunology
M J Hussain
D Vergani

Correspondence to:
Dr Peter Greally, Cystic
Fibrosis Center, Division of
Pulmonology, Children's
Hospital of Pittsburgh, 3705
Fifth Avenue at De Soto
Street, Pittsburgh, PA 15213-
2583, USA.

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Bacterial adherence occurs in the lung of those

Table 1 Details of age, IL-1 α , and sIL-2R concentrations in patients with cystic fibrosis and controls

	Cystic fibrosis (n=37)	Controls (n=25)	p Value*
Mean (range) age in years	10.5 (5–19)	9.5 (4–16)	NS
Mean (95% CI) IL-1 α in pg/ml	471 (278 to 663)	254 (171 to 337)	<0.05
Mean (95% CI) sIL-2R in U/ml	416 (336 to 496)	280 (200 to 359)	<0.02

*Unpaired Student's *t* test.
CI=confidence interval.

Table 2 Comparison between group I (those with chronic infection) and group II (those with sterile cultures)

	Group I (n=20)	Group II (n=17)	p Value
Mean age in years	12.8	8.3	<0.001
Mean (SD) % predicted FEV ₁	51 (19)	84 (19)	<0.0001
Mean (SD) % predicted FVC	67 (16)	87 (20)	<0.001
Mean (SD) immunoglobulins in g/l			
IgG	19 (8)	11 (3)	<0.001
IgM	1.3 (0.6)	0.9 (0.4)	<0.05
IgA	3.3 (2.2)	1.6 (0.8)	<0.01
Geometric mean (95% CI) IgE in U/l	56 (21–158)	17 (7–43)	NS
Mean (95% CI) IL-1 α in pg/ml	555 (299–810)	361 (120–678)	NS
Mean (95% CI) sIL-2R in U/ml	362 (254–470)	431 (313–549)	NS

CI=confidence interval.

a relationship between them and both immunoglobulin concentration and the severity of airflow obstruction.

Patients and methods

Thirty seven clinically stable patients with cystic fibrosis were studied. Sputum or cough swabs were sent for routine bacteriology and forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured by spirometry. Blood samples were taken and analysed for concentrations of IgG, IgM, IgA, and IgE. Immune reactive levels of IL-1 α and sIL-2R were assayed using a modified two site enzyme linked immunosorbent assay (ELISA) as previously described.³ Blood was taken from 25 normal children who acted as controls. Data from the cystic fibrosis and control groups were compared using unpaired Student's *t* tests; correlation coefficients were calculated between variables and their significance was determined by linear regression analysis.

Results

Seventeen of the children with cystic fibrosis had sterile sputum cultures, two repeatedly grew *Staphylococcus aureus*, one grew both *S aureus* and *Pseudomonas aeruginosa*, and 17 were colonised with *P aeruginosa*. FEV₁ and FVC (mean (SD)% predicted) in the cystic fibrosis group was 65 (24)% and 76 (21)% respectively. Patients and controls were well matched with respect to age, however, the cystic fibrosis group exhibited significantly higher IL-1 α and sIL-2R immunoreactivity (table 1).

Table 3 Correlation coefficients (*r*) between cytokine concentrations, lung function values, and IgG and IgM concentrations

	IgG (g/l)	IgM (g/l)
IL-1 α (pg/ml)	0.18	0.35**
sIL-2R (U/ml)	0.33*	0.36**
FEV ₁ (% predicted)	-0.66***	-0.40**
FVC (% predicted)	-0.62***	-0.38**

*p<0.05, **p<0.05, ***p<0.001.

We subdivided the cystic fibrosis group into those who had chronic bacterial colonisation (group I, n=20) and those who had repeatedly sterile cultures (group II, n=17). Group I were older, had poorer lung function, and higher immunoglobulin concentrations than group II. Yet there was no significant difference in their cytokine concentrations (table 2).

IgG and IgM concentrations correlated with the severity of airflow obstruction. There was also a weak, but significant, correlation between cytokine concentrations and IgG and IgM (table 3). IL-1 α correlated with sIL-2R in the entire study group ($r=0.4$, $p<0.001$, $n=62$).

Discussion

Serum from patients with cystic fibrosis exhibits significantly greater IL-1 α and sIL-2R immunoreactivity than controls; these results suggest that there is immunostimulation in patients both with and without chronic infection. IL-1 is a chemoattractant for granulocytes and induces their degranulation. It is therefore a likely participant in the inflammatory response observed in the cystic fibrosis lung. IL-1 also upregulates IL-2 receptor expression on mononuclear cells and stimulates their release of IL-2 *in vitro*²; the positive correlation between the two suggests the existence of cytokine networking *in vivo*.

IL-1 is secreted in response to a number of stimuli including lipopolysaccharide, immune complexes, and the C5a component of complement. Our data may reflect either a primary response to infectious agents or a secondary response to immunological stimuli. Increased sIL-2R immunoreactivity was observed in children with sterile sputum, good pulmonary function, and normal immunoglobulin concentrations, findings which are consistent with those of Dagli *et al.*⁴ Data from both studies suggest that excessive immunostimulation may originate as a defence against infection. We postulate that it evolves into harmful inflammatory activity that ultimately leads to lung destruction.

The association between cytokine and IgG and IgM concentrations suggest that they may contribute to immunoglobulin synthesis *in vivo*. No relationship existed between them and serum IgA, which is mainly concerned with mucosal defence, or IgE, whose synthesis is thought to be regulated predominantly by IL-4. Significant correlations existed between IgG and IgM concentrations and the severity of pulmonary disease. It is tempting to assign a causal relationship between them. Yet hypergammaglobulinaemia may simply reflect the bacterial content of the cystic fibrosis lung. However, there are mechanisms by which hypergammaglobulinaemia can produce pulmonary injury: immune complex activation of complement and the excess generation of harmful complement degradation products. Indirect support for this hypothesis is also derived from a study where the beneficial effects of prednisolone on pulmonary function were accompanied by a significant fall in immunoglobulin concentration.⁵

Exoproteases derived from *P aeruginosa* not only cleave IL-2 and its soluble receptor *in vitro* but can also antagonise IL-1 and IL-2 activity.⁶

In addition, elastases derived from granulocytes are implicated in the proteolytic destruction of the cystic fibrosis lung and may degrade IL-1. Cytokines and their receptors may be exposed to these enzymes as cells circulate through the lung and this may explain the lack of correlation between cytokine immunoreactivity and chronic infection.

At present, the addition of anti-inflammatory drugs to treatment protocols may represent the best hope for maintaining lungs in good condition until treatments, which correct the basic defect, become available for subjects with cystic fibrosis. Therefore, further studies addressing the clinical effects of cytokine suppression are necessary in order to define further the nature of these responses.

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- 1 Wheeler WB, Williams M, Matthews WJ, Colten HR. Progression of cystic fibrosis lung disease as a function of serum immunoglobulin G levels: a 5 year longitudinal study. *J Pediatr* 1984; **104**: 695-9.
- 2 Male D, Champion B, Cooke A. *Cytokines. Advanced immunology*. 2nd Ed. London, New York: Gower Medical Publishing, 1991: 11.3-11.5.
- 3 Roubin LA, Kurman C, Fritz ME, *et al*. Soluble interleukin-2 receptors are released from activated human lymphoid cells in vitro. *J Immunol* 1985; **135**: 3172-7.
- 4 Dagli E, Warner JA, Besley CR, Warner JO. Raised serum soluble interleukin-2 receptor concentrations in cystic fibrosis patients with and without evidence of lung disease. *Arch Dis Child* 1992; **67**: 479-81.
- 5 Auerbach HS, Williams M, Kirkpatrick JA, Cotten HR. Alternate day prednisolone reduces the morbidity and improves pulmonary function in cystic fibrosis. *Lancet* 1985; **ii**: 686-8.
- 6 Kharazmi A. Interactions of *Pseudomonas aeruginosa* with the cells of the immune system. *Antibiot Chemother* 1989; **42**: 42-9.