Complement fixing antibody responses to virus infection in children with acute lymphoblastic leukaemia

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SUMMARY Thirty children with acute lymphoblastic leukaemia (ALL) were studied and had a virus isolated. Only 50% produced a significant rise in complement fixing (CF) antibody titre compared to 100% of normal children. The failure to produce antibodies was unpredictable. CF antibodies are not a reliable guide to virus infections in children with ALL.

Humoral immune responses are of major diagnostic importance in virus infections.¹ In children with leukaemia, virus infections are being increasingly recognised as a cause of illness and death.^{2,3} Several children with acute lymphoblastic leukaemia (ALL) in Newcastle upon Tyne did not develop the usual antibody rise in response to a virus infection.³ In order to clarify this problem we have surveyed a larger group of children with ALL from whom a virus was isolated and from whom paired sera were taken for antibody determination.

Patients and methods

From 1974 to 1978 children with ALL attending either of the two major hospitals in Newcastle upon Tyne were investigated virologically whenever a respiratory virus infection was suspected. A diagnosis of a virus infection was made either by the fluorescent antibody technique (FAT) or by culture.⁴ All of the viruses were identified by both the FAT and by culture except for adenovirus and cytomegalovirus, which were only cultured. Whenever possible, blood was taken at the start of the illness and during the convalescent period, and the titre of complement fixing antibody was determined by the method of Bradstreet and Taylor.⁵ Clinical details of the illness and the leucocyte count were also recorded.

CONTROLS

The control group consisted of 33 patients who had been admitted to the same hospitals with a suspected virus infection. Their ages ranged from 1 to 17 years

(mean 6.1, SD 5.3 years). A virus was identified from each child, either by FAT or by culture, and paired sera were taken during the acute and convalescent phases of the illness. None had leukaemia or was on immunosuppressive treatment.

Results

Paired sera were available for 30 virus isolations from children with ALL. There were 14 boys and 13 girls and their ages ranged from 2 to 13 years (mean 5.8, SD 3.1 years). Viruses were isolated from three girls on each of two separate occasions, and one child had an illness during which influenza A and respiratory syncytial virus were both isolated. From five other children another virus was isolated at the same time as that for which the antibody titres were measured (3 H-strain rhinoviruses, 1 echovirus type 3, and 1 herpesvirus hominis). The titres of antibody, in both acute and convalescent phases, to the viruses isolated are shown in the Figure. Comparison is made with the normal children, all of whom showed at least a fourfold antibody rise or had an initial antibody titre of at least 1/128. Fifteen of the children with ALL demonstrated a fourfold rise or more to the virus infection, and 15 did not respond. There was no difference in the sex ratio or in the age of those who responded compared to the non-responders. The severity of the clinical illness and the current state of the children are shown in the Table. There is no difference between the two groups. The mean total white cell count and lymphocyte count at the time of diagnosis of the infection was $3.9 (1.2) \times 10^9/l$ in the responding and $4.0 (1.3) \times 10^9/l$ in the non-responding groups. There was no

Present state and severity of illness in children with ALL, according to the presence or absence of CFT antibody response to a virus infection

	CFT rise	No CFT rise
Present state		
Alive and well	8	8
Relapse	—	1
Dead	6	4
Severity of illness		
Asymptomatic	1	3
Minor symptoms	6	6
Serious illness	4	3
Life threatening	3	2
Associated with death	1	1

difference in the mean length of time between diagnosis of the leukaemia and of the virus infection in the two groups, and there was no particular period of treatment during which they were unlikely to respond. Three of the children who had other viruses isolated simultaneously produced an antibody rise and three did not.

Discussion

It is a widely held belief that a rise in complement fixing antibody titre is a satisfactory method of diagnosing a virus infection when methods for either rapid virus diagnosis or viral culture are not readily available. The present data confirm our original impression that in children with ALL reliance on a rise in antibody titre will result in many virus infections being missed.

This failure to produce humoral antibodies may result in increased severity of illness in some children with leukaemia and may also account for the pro-

longed period for which viruses are sometimes excreted in this condition.³ The role of complement fixing antibodies in the host defence against virus infections is not clear. It may be that they do not play a major role and simply reflect the production of other, perhaps more important, local antibodies which can coat the virus and halt its replication.⁶ The reason why half of the children with ALL did not produce antibodies is not clear. It does not appear to be related to sex, time from diagnosis, a particular phase of chemotherapy, age, white count, or severity of illness and therefore appears to be entirely unpredictable.

Borella and Webster⁷ have reported some impairment of the immune response to virus infections in children with leukaemia. Attempts at immunisation with live virus vaccine in children with leukaemia have shown variable results. Bosu *et al.*⁸ demonstrated a uniform failure of IgM response to polio vaccine administration, which persisted for up to six months after the child had stopped immunosuppressive treatment. Gross *et al.*, using a haemagglutination inhibition (HAI) technique, found that 37% of children on immunosuppressive therapy for malignant disease responded to influenza vaccination compared to 92% who were not on treatment.⁹ They, too, found no correlation between the immune response and the peripheral white blood cell count. On the other hand, Izawa *et al.*¹⁰ and Ozaki *et al.*¹¹ have shown that live varicella vaccine usually produces a satisfactory CF and neutralising antibody rise in children with leukaemia, and Sumaya *et al.*¹² and Smithson *et al.*¹³ have reported no difference in satisfactory immunisation rates against influenza viruses in children with malignant disease and in

normals. The different conclusions reached in these various studies may result from the different techniques used to detect antibodies (HAI, CFT, neutralisation) and to the varied state of immunosuppression of the children, some being on and others off treatment.

Children with ALL are more susceptible to multiple virus infections occurring simultaneously than are normal children.¹⁴

The presence of two viruses might inhibit the CF response to one, as may occur when two live virus vaccines are given together,¹⁵ although, more recently, satisfactory immunisation rates have been reported with up to four vaccines given at the same time.¹⁶

It is possible that more sensitive tests for measuring antibody responses, such as immunofluorescence, ELISA, or radioimmunoassay, might detect a response in those children who do not produce a CFT rise. At present neutralisation tests and, where appropriate, the HAI are the best measures of the immune status of the patient to a particular virus infection. However, the role of cell-mediated immunity also needs to be considered.

We conclude that humoral complement fixing antibody responses are not a reliable guide to virus infections in children with ALL and that the more general acceptance of this will lead to a greater awareness of the importance of using culture and immunofluorescence techniques in addition to CF tests for the diagnosis of virus infections in children. It is only by the use of all the available diagnostic tools for the recognition of viruses and a thorough study of all the immune responses, employing the most advanced techniques, that the true significance of virus infections in the life and death of children with leukaemia will be understood.

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