PAPERS AND ORIGINALS

Factors in Pathogenesis of Central-nervous-system Leukaemia

R. J. WEST, J. GRAHAM-POLE, R. M. HARDISTY, M. C. PIKE

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Summary

Eighty-three (50%) of 165 children with acute lymphoblastic or acute stem-cell leukaemia presenting during 1958-70 developed leukaemia of the central nervous system (C.N.S.). The rate of incidence of this complication is fairly constant throughout the first two-and-a-half years of the disease, but falls thereafter. The incidence of C.N.S. leukaemia is inversely correlated with the platelet count at the time of initial diagnosis of leukaemia, and directly correlated with the total leucocyte count and the presence of lymph-node enlargement. The major effect of initial leucocyte count is on the time of onset of clinical symptoms. It is suggested that leukaemic cells usually enter the C.N.S. from the blood as a result of intracranial petechial haemorrhage occurring around the time of initial diagnosis of leukaemia, and that the time for subsequent development of symptoms of C.N.S. disease is largely determined by the number and replication rate of leukaemic cells which gain access to the C.N.S. at that time. The increasing frequency of diagnosis of C.N.S. leukaemia in recent years is not wholly explained by increasing survival, and may in part be related to changes in the pattern of antileukaemic therapy.

Prophylaxis for C.N.S. leukaemia should be instituted as early as practicable after diagnosis; the identification of a high-risk group may permit this to be done selectively.

Introduction

In recent years central nervous system (C.N.S.) complications of acute leukaemia in childhood have been diagnosed with increasing frequency, and this has generally been attributed to the longer survival achieved with modern therapy (Steffy, 1962; Hardisty and Norman, 1967; Evans, Gilbert, and Zandstra, 1970). It is seen more frequently in lymphoblastic leukaemia, but with more prolonged survival it is occurring increasingly commonly in other cytological types.

The C.N.S. does not contain lymphoid tissue, and C.N.S. invasion by leukaemic blast cells is presumed to occur from the blood. The blood-brain barrier then protects these cells from the action of drugs given systemically, allowing them to proliferate even when there is continuing haematological remission. It has also been postulated that these leukaemic cells in the C.N.S. may then serve as a reservoir from which the bone marrow may be "reseeded," with consequent haematological relapse (Johnson, 1964; George *et al.*, 1968; Evans *et al.*, 1970).

Treatment of C.N.S. leukaemia currently consists in either intrathecal chemotherapy or craniospinal irradiation or both. These provide temporary relief but are usually followed by relapse of C.N.S. disease. Prophylactic regimens are under trial in a number of centres in an attempt to prevent or delay the onset of C.N.S. complications (Melhorn *et al.*, 1970; Aur *et al.*, 1971; Medical Research Council, 1971). We have examined the relation between systemic and C.N.S. leukaemia in order to establish which patients are most at risk of this complication so that the place of prophylactic treatment might be more clearly defined.

Patients and Methods

The records were examined of all 198 patients diagnosed as suffering from acute lymphoblastic or acute stem-cell leukaemia seen at the Hospital for Sick Children between August 1958 and October 1970. Eight of these children were excluded from further analysis because relevant records were incomplete, nine because they failed to achieve initial remission, and 16 because haematological relapse or C.N.S. disease had occurred before their referral to the hospital. (The last-mentioned exclusions

Department of Haematology, Hospital for Sick Children, Great Ormond Street, London W.C.1

R. J. WEST, M.R.C.P., D.C.H. Research Fellow
J. GRAHAM-POLE, M.R.C.P., D.C.H., Research Fellow
R. M. HARDISTY, M.D., F.R.C.P., Professor

D.H.S.S. Cancer Epidemiology and Clinical Trials Unit, Oxford University, Oxford

M. C. PIKE, PH.D. Director

were necessary to permit unbiased statistical analysis of the data.) Of the remaining 165 children (83% of the original total) 83 developed C.N.S. leukaemia. Twenty-nine of these C.N.S. leukaemia patients were the subject of a previous report (Hardisty and Norman, 1967).

The evidence for C.N.S. leukaemia was the occurrence of accepted clinical features associated with the presence of leukaemic cells in the cerebrospinal fluid. The date of diagnosis was taken as that of the diagnostic lumbar puncture.

The data were analysed statistically by life-table methods (Mantel, 1966; Peto and Peto, 1972). To avoid bias patients were included in the analysis only from the date of arrival at the hospital and not from the date of diagnosis. Patients dying without developing C.N.S. symptoms were regarded simply as not being seen after the date of death. That is, a patient dying 300 days, say, after initial diagnosis without having developed C.N.S. disease is dealt with exactly as if he had not died but had simply not been followed up after that time.

Results

Eighty-three (50%) of the 165 patients included in the survey developed C.N.S. leukaemia. Once C.N.S. involvement had occurred it tended to be recurrent, the 83 patients having a total of 194 episodes (mean 2.3, range 1-11 episodes per patient). The estimated proportion of patients with C.N.S. disease in relation to time from diagnosis of leukaemia is shown in Fig. 1. The life-table analysis estimates that in the absence of "non-C.N.S." mortality three-quarters of the patients would have developed C.N.S. disease by two-and-a-half years, after which the incidence rate of this complication falls.

FIG. 1—Incidence of C.N.S. leukaemia in whole group of 165 patients with acute lymphoblastic leukaemia. The proportion of patients surviving without having developed C.N.S. disease is shown; each point represents the time at which an individual patient developed C.N.S. disease or died without having done so.

In Table I are shown the numbers of patients in various subgroups defined by factors present at the initial diagnosis of leukaemia, together with the observed and expected numbers developing C.N.S. leukaemia. The number of C.N.S. relapses that would be expected in that subgroup is shown, after allowing for their durations of exposure to risk, if the prognosis regarding C.N.S. leukaemia was the same for each subgroup.

Neither age nor sex appears to influence the development of C.N.S. leukaemia, and these two factors are not considered further. The rate of C.N.S. involvement was lower for patients diagnosed in each of the years 1958-65 than in each of the years 1966-70, even after allowance had been made for the increased survival during the latter period (Table II). Allowance for this secular difference was made in all calculations on the influence of other factors on the incidence of C.N.S. disease.

TABLE I—Analysis of Possible Prognostic Factors in Development of C.N.S. Disease in Acute Lymphoblastic Leukaemia

Factor	No. in Group	No. with C.N.S. Relapse	Expected No. with C.N.S. Relapse	No./Expected No. with C.N.S. Relapse	χ^2 (D.F.)	P
Sex:						
Female	76	39	39.66	0.98	0.02 (1)	0.89
Male	89	44	43.34	1.02		
Age (years):						
0-	75	42	35.12	1.20	2.50 (2)	0.29
4-	55	24	29.21	0.82		
7+	35	17	18.67	0.91		
Liver enlargement:						
Yes	116	60	53.58	1.12	2.25 (1)	0.13
No	49	23	29.42	0.78		
Spleen enlargement:						
Yes	123	69	59.22	1.17	5.69 (1)	0.02
No	42	14	23.78	0.59		
Node enlargement:						
Yes	109	63	48.15	1.31	11.71 (1)	<0.001
No	56	20	34.85	0.57		
Organ enlargement:						
All	77	45	34.08	1.32	11.05 (3)	0.01
2	46	23	20.68	1.11		
1	25	11	17.34	0.63		
None	17	4	10.90	0.37		
Leucocytes/mm ³ :						
0-	48	23	30.02	0.77	7.47 (2)	0.02
5,001-	30	15	19.91	0.75		
10,001+	87	45	33.07	1.36		
Platelets/mm ³ :						
0-	22	16	10.66	1.50	9.45 (3)	0.02
10,001-	60	36	28.82	1.25		
50,001-	36	14	18.98	0.74		
100,000+	36	12	19.54	0.61		
Not recorded ..	11	5				

In all calculations adjustment has been made for calendar year of diagnosis.

TABLE II—Effect of Calendar Year of Diagnosis on Development of C.N.S. Disease in Acute Lymphoblastic Leukaemia

Calendar Year	No. in Group	No. with C.N.S. Relapse	Expected No. with C.N.S. Relapse	No./Expected No. with C.N.S. Relapse	χ^2 (D.F.)	P
1958-65	78	30	40.55	0.74	5.47 (1)	0.02
1966-70	87	53	42.45	1.25		

PLATELET COUNT

The lower the initial platelet count the greater the incidence of C.N.S. disease (Table I). The slopes of the survival curves plotted in Fig. 2 show the rate of development of C.N.S. leukaemia in patients with presenting platelet counts of 50,000/mm³ or below and in those with higher counts. The much increased rate in the "low" platelet group persisted into the third year from initial diagnosis; beyond that time the number of surviving patients without C.N.S. disease in the low group was very small. The rate of occurrence of C.N.S. leukaemia in the "high" platelet group slowed noticeably towards the end of the second year.

FIG. 2—Incidence of C.N.S. leukaemia in patients with initial platelet counts up to 50,000/mm³ and over 50,000/mm³.

TABLE III—Analysis of Effect of Splenic and Liver Enlargement on C.N.S. Relapse Rate in Acute Lymphoblastic Leukaemia

Organ Enlarged	No. in Group	No. with C.N.S. Relapse	Expected No. with C.N.S. Relapse	No./Expected No. with C.N.S. Relapse	χ^2_1	P	After Adjustment for Enlargement of Nodes			
							Expected No. with C.N.S. Relapse	No./Expected No. with C.N.S. Relapse	χ^2_1	P
Spleen:										
Yes	123	69	59.22	1.17	5.69	0.02	{ 63.94 19.06 }	{ 1.08 0.73 }	1.93	0.16
No	42	14	23.78	0.59						
Liver:										
Yes	116	60	53.58	1.12	2.25	0.13	{ 58.02 24.98 }	{ 1.03 0.92 }	0.24	0.63
No	49	23	29.42	0.78						

In all calculations adjustment has been made for calendar year of first treatment.

LEUCOCYTE COUNT

The initial total leucocyte count was positively associated with the incidence of neurological involvement (Table I); a similar correlation was observed with the initial blood blast-cell count. The rate of development of C.N.S. disease in the subgroups of patients whose initial leucocyte counts were above and below 10,000/mm³ are shown in Fig. 3. Initially the rate was greater in those with high counts at presentation, but from about 40 weeks after diagnosis the rate of occurrence of new cases was approximately equal (shown by the survival curves becoming parallel).

FIG. 3—Incidence of C.N.S. leukaemia in patients with initial total leucocyte counts of up to 10,000/mm³ and over 10,000/mm³

ORGAN ENLARGEMENT

The development of C.N.S. disease was more frequent in patients with enlargement of liver, spleen, or lymph nodes at diagnosis (Table I). The effect of lymph node enlargement on incidence was greater than the effect of either liver or spleen, and was only slightly less than the effect of enlargement of all three organs. This effect persisted at least into the third year from diagnosis (Fig. 4).

INTERACTIONS BETWEEN FACTORS

Associations have been shown between various presenting features in patients with acute lymphoblastic leukaemia (Hardisty and Till, 1968). Thus there is a correlation between high blast count (or total leucocyte count) in the peripheral blood, thrombocytopenia, and organ enlargement; similarly, a low leucocyte count and a high platelet count are often associated with an absence of clinical enlargement of liver, spleen, and lymph nodes. We therefore examined our data for the effect of interactions between these factors.

FIG. 4—Incidence of C.N.S. leukaemia in patients with or without lymph node enlargement at time of initial diagnosis.

It is shown in Table III that after allowance has been made for the prognostic association with C.N.S. disease of lymph node enlargement there is no further significant association with enlargement of liver and spleen. In all further analysis of results we have, therefore, ignored these last two factors. The individual associations with incidence of C.N.S. involvement of each of the three remaining factors—platelets, total leucocyte count, and lymph-node enlargement—could not be explained in terms of the effect of the other two.

The group of patients diagnosed in the years 1958-65 had less thrombocytopenia at presentation than those diagnosed in 1966-70, but lymph-node enlargement was more common in the earlier group. When allowance is made for these and for the total leucocyte count the difference between the two time periods remains.

Discussion

It is presumed that blast cells enter the C.N.S. from the blood and intracranial petechial haemorrhages would provide a possible mechanism. Such haemorrhages are most likely to occur in thrombocytopenic patients, and the finding of a rising incidence of C.N.S. disease with increasing degrees of thrombocytopenia at initial diagnosis supports this concept. We have observed xanthochromic cerebrospinal fluid in thrombocytopenic leukaemic children in whom lumbar punctures have been done at the time of presentation, confirming that subclinical subarachnoid leakage of blood can occur at a time when blast cells are present in the peripheral blood.

In our patients haematological relapses are usually diagnosed early, so that the platelet counts seldom fall on these occasions to the low levels seen at presentation (except terminally). If initiation of C.N.S. disease is related to thrombocytopenia it will therefore most commonly occur around the time of initial presentation. When all patients in whom blast cells have gained

access to the C.N.S. at this time have developed overt C.N.S. disease the rate of onset of this complication will fall. For the present series such a fall occurred during the third year (Fig. 1), a finding also noted by others (Hagbabin and Zuelzer, 1965; Evans *et al.*, 1970).

A correlation between high total leucocyte count at presentation and increased incidence of C.N.S. complications has been reported (Melhorn *et al.*, 1970). A high leucocyte count is likely to be associated not only with the access of a relatively large number of cells to the C.N.S. at the time of seeding but also with a higher rate of replication of the cells within the C.N.S. For both these reasons the higher the leucocyte count the earlier symptoms of C.N.S. disease might be expected. Our findings bear out this expectation in that they show (Fig. 3) that the difference in incidence rate between patients with leucocyte counts above and below 10,000/mm³ is confined to the first 10 months, after which the rate of onset of C.N.S. disease is independent of initial leucocyte count. The leucocyte count thus appears to affect chiefly the time of onset of C.N.S. disease. The association of lymph-node enlargement with increased incidence cannot be explained by correlation with the leucocyte count; indeed, the association persists throughout the course of the disease (Fig. 4). We have no explanation for this effect.

The increasing frequency of C.N.S. leukaemia in recent years has usually been attributed to longer survival and increasing diagnostic awareness, but a possible contributory effect of newer drugs has also been suggested (Evans *et al.*, 1970). The method of analysis we have used on our data shows that the higher proportion of patients affected in 1966-70 cannot be completely explained in terms of increasing survival in more recent years. Diagnostic awareness of this complication may have increased over the years, but examination of available necropsy records suggests that undiagnosed C.N.S. disease was not more common in this hospital during the earlier period. It therefore seems unlikely that underdiagnosis explains the difference between the two periods. If the increase is at least partly real the possibility must be considered that recent more intensive systemic chemotherapy has played a contributory part, perhaps through immunosuppression.

The use of prophylactic regimens for C.N.S. leukaemia is increasing (Melhorn *et al.*, 1970; Aur *et al.*, 1971; Medical Research Council, 1971). We conclude from this study that prophylaxis stands a greater chance of success if used very soon after diagnosis, when leukaemic cells have already gained access to the C.N.S. but are still present there in relatively small numbers. Furthermore, in assessing the results of any prophylactic trial, allowance must be made for the effect of differences in initial leucocyte and platelet counts and in lymph-node enlargement between treatment groups. Finally, if prophylaxis is not to be used on all patients, the identification of a high-risk group with initial high blood leucocyte count, thrombocytopenia, and lymph-node enlargement will enable a useful selection to be made.

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References

- Aur, R. J. A., *et al.* (1971). *Blood*, 37, 272.
- Evans, A. E., Gilbert, E. S., and Zandstra, R. (1970). *Cancer*, 26, 404.
- George, P., *et al.* (1968). *Journal of Pediatrics*, 72, 399.
- Hardisty, R. M., and Norman, P. M. (1967). *Archives of Disease in Childhood*, 42, 441.
- Hardisty, R. M., and Till, M. M. (1968). *Archives of Disease in Childhood*, 43, 107.
- Hagbabin, M., and Zuelzer, W. W. (1965). *Journal of Pediatrics*, 67, 23.
- Johnson, R. E. (1964). *Journal of the National Cancer Institute*, 32, 1333.
- Mantel, N. (1966). *Cancer Chemotherapy Reports*, 50, 163.
- Medical Research Council (1971). *British Medical Journal*, 4, 189.
- Melhorn, D. K., Gross, S., Fisher, B. J., and Newman, A. J. (1970). *Blood*, 36, 55.
- Peto, R., and Peto, J. (1972). *Journal of the Royal Statistical Society. Series A*, 135, 185.
- Steffy, J. M. (1962). *Journal of Pediatrics*, 60, 183.

Comparison of Beclomethasone Dipropionate Aerosol and Prednisolone in Reversible Airways Obstruction

S. LAL, D. M. HARRIS, K. K. BHALLA, S. N. SINGHAL, A. G. BUTLER

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Summary

This paper describes a double-blind crossover trial of prednisolone and beclomethasone dipropionate aerosol in 38 steroid-dependent patients with reversible diffuse airways obstruction. Altogether there was no difference

in the patient's preference of the two treatment groups or in the number of times they used their bronchodilator aerosol, or in the forced expiratory volume in one second, vital capacity, or peak expiratory flow rate in the two treatment groups. The plasma cortisol levels when the patients were on the aerosol were much higher than when they were on prednisolone. The use of inhaled aerosol steroids seems to be preferable as it eliminates the usual complications of oral steroid therapy.

General Hospital, Bury, Lancs

S. LAL, M.B., F.R.C.P., Consultant Physician
K. K. BHALLA, M.D., M.R.C.P., Registrar
S. N. SINGHAL, M.B., M.R.C.P., Clinical Assistant

Research Division, Allen and Hanburys Limited, Ware, Herts

D. M. HARRIS, M.B., D.OBST.R.C.O.G., Head of Medical Services
A. G. BUTLER, B.Sc., Clinical Trials Officer, Medical Services

Introduction

Corticosteroids are an established treatment for asthma, and doses up to 7 mg of prednisolone may be sufficient to keep patients symptom-free. Even after prolonged use the risk of pituitary-adrenal axis suppression is minimal (Robinson *et al.*, 1962). When taken by mouth, however, they act systemically