

Central Nervous System Involvement in Non-Hodgkin's Lymphomas

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A. Introduction

In the past 10 years the involvement of the central nervous system (CNS) in non-Hodgkin's lymphomas (NHL) has become apparent as the results of systemic chemotherapy have improved and complete remissions (CR) have increased in both frequency and duration [3, 7]. However, most studies report on cases in which CNS lymphomas were identified through the recognition of neurological symptoms and cytological examination of cerebrospinal fluid (CSF). In some cases, there are only a few malignant lymphoma cells in the CSF of asymptomatic patients at diagnosis, and they are of uncertain clinical importance.

To date there is no biochemical marker whose presence or elevation above normal concentration correlates with the presence of malignant lymphoma. Therefore, in this study we present the results of pulse-cytometry analyses, measurements of vitamin B₁₂ level in CSF, and unsaturated vitamin B₁₂ binding capacity (UB₁₂BC) by CSF protein to assess their roles as indices of CNS involvement in NHL.

B. Material and Methods

Between 1981 and 1987 at the Institute of Hematology in Warsaw, 199 NHL patients were treated with combined polychemotherapy. In 13 cases CNS involvement was suspected on the basis of neu-

rological symptoms (Table 1). There were nine men and four women, aged between 19 and 59 years, in clinical stages III or IV.

In all of these patients and in another series of 17 cases with intermediate and high-grade NHL, the CSF was investigated as a routine procedure. Specimens were subjected to cytological examination after centrifugation with Cytospin 2-Shandon. Besides cytological examinations, DNA histograms (using PHYWE ICP 11 pulse-cytometer and computing according to the method described by Andreef [1], measurements of vitamin B₁₂ levels in CSF (CSF was concentrated on Minicon CS-15), and assessment of UB₁₂BC by CSF protein (using radioimmunological method described by Retief et al. [8]) were performed.

All patients with CNS involvement received methotrexate intrathecally (usually 15 mg every few days, for a minimum of six doses, or three beyond the first negative results on cytological examination), and in six cases of high-grade NHL additional cranial irradiation was performed.

C. Results

Malignant lymphoma cells were found in 21 specimens of CSF from 30 patients examined (including eight clinically asymptomatic cases). The histological classification of these patients is summarized in Table 2. The cytological changes of CSF in 21 cases were characterized by the presence of lymphoma cells which looked like lymphoblasts or parablasts and ranged in particular cases between

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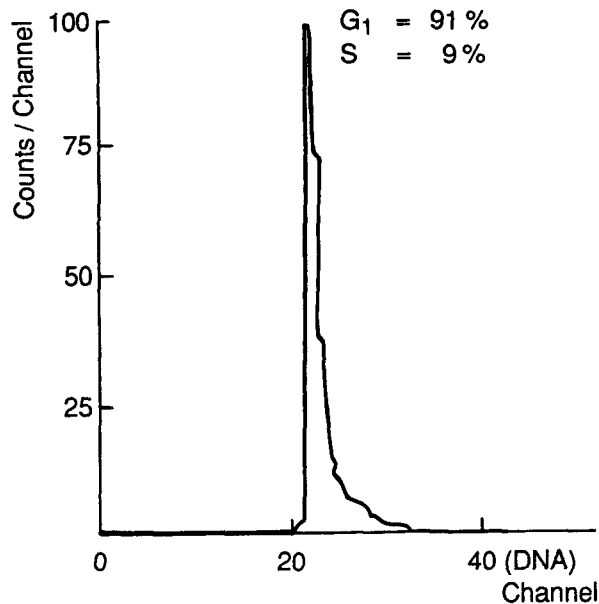


Fig. 1. DNA histogram of cerebrospinal fluid cells in patient F.M. without CNS involvement

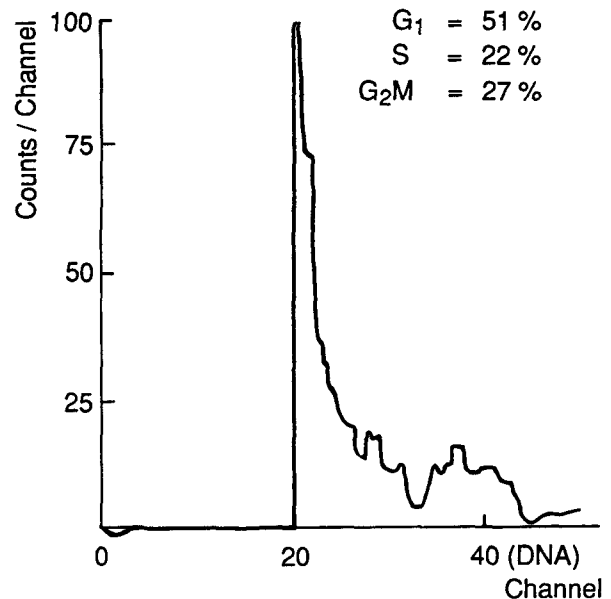


Fig. 2. DNA histogram of cerebrospinal fluid cells in patient S.R. with CNS involvement

Neurological symptoms	Number of patients
Headaches	5
Meningeal symptoms	2
Cranial nerve palsy	1
Peripheral nerve palsy	1
Polyneuropathy	7

Table 1. Neurological symptoms in 13 NHL patients with CNS involvement

Histological type of NHL (Kiel Classification)	Number of cases
1. High-grade lymphoblastic:	
– Burkitt type	1
– convoluted type	2
immunoblastic	3
2. Intermediate-grade centroblastic/centrocytic	5
3. Low-grade lymphoplasmacytoid	10
Total	21

Table 2. Histological classification of NHL patients with CNS involvement

6% and 93% of all presented in CSF cells.

In DNA histograms of patients without CNS involvement most cells were in the G_1 phase (Fig. 1). In DNA histograms of CSF in all the patients with

CNS involvement, including the eight asymptomatic cases, increased numbers of cells in the S and G_2M phases were found (Fig. 2). During the successful treatment the values decreased proportionally to the number of lymphoma cells

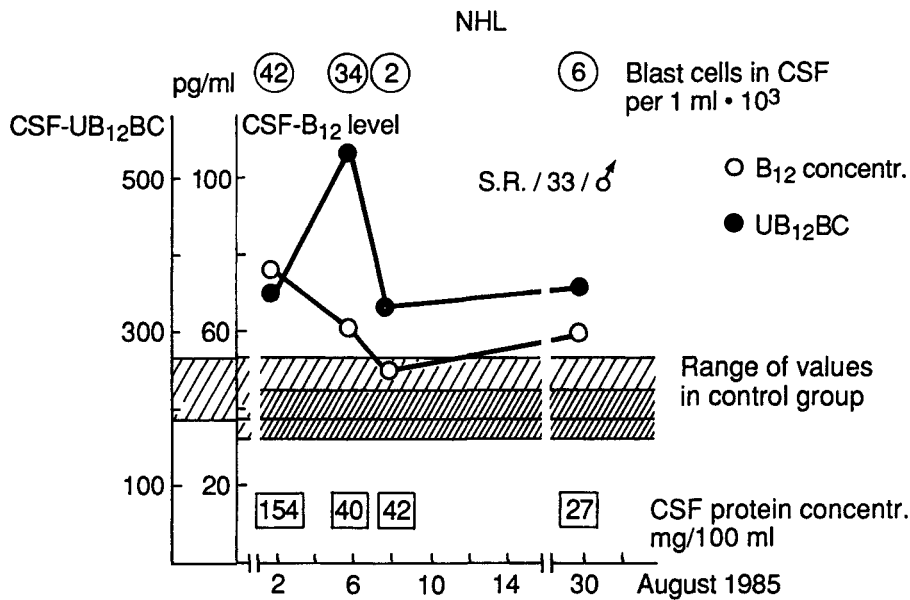


Fig. 3. The $UB_{12}BC$ by CSF proteins and CSF vitamin B_{12} level in NHL patient (S. R.) (the same case as in Fig. 2) during intrathecal treatment with Mtx and in relapse

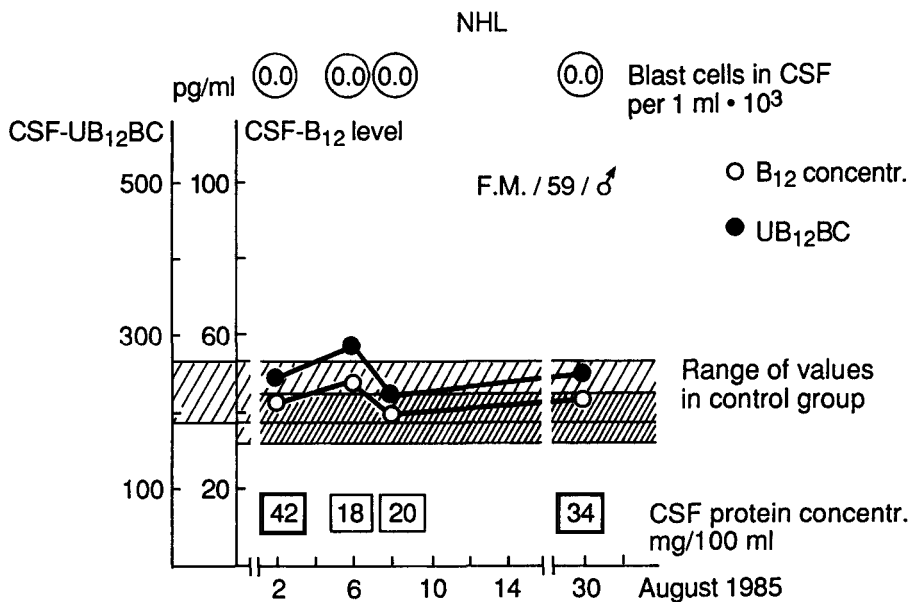


Fig. 4. The $UB_{12}BC$ by CSF proteins and CSF vitamin B_{12} level in NHL patient F. M. (see case in Fig. 1) (studies repeated four times during one month observation).

and increased again in relapse. The $UB_{12}BC$ by CSF protein and the vitamin B_{12} level in CSF were increased only in patients with CNS involvement (Fig. 3), including the eight clinically asymptomatic cases. Both became normal after successful treatment and increased again in relapse. In patients without CNS involvement the $UB_{12}BC$ and the vitamin B_{12} level remained normal (Fig. 4).

D. Conclusions

CNS involvement in NHL was found in 21 of our cases (10.5%). Of these cases,

eight were clinically asymptomatic. Cytophotometric analyses of DNA histograms and measurements of $UB_{12}BC$ and the vitamin B_{12} level proved the most accurate for confirmation of CNS involvement in clinically asymptomatic cases.

References

1. Andreef M (1980) Computer analysis of DNA histograms. University of Utrecht, p 36 (doctorate thesis)
2. Barligie B, Spitzer G, Hart JS, Johnson DA, Büchner T, Schumann J, Drewinko B

- (1976) DNA histogram analysis of human hemopoietic cells. *Blood* 48:245–258
3. Ersbol I, Schultz HB, Thomsen BLR, Keiding N, Nissen N (1985) Meningeal involvement in non-Hodgkin's lymphomas, incidence, risk factors and treatment. *Scand J Haematol* 36:487–497
 4. Glass JP, Melamed M, Chernik NL, Posner JB (1979) Malignant cells in cerebrospinal fluid (CSF). The meaning of a positive CSF cytology. *Neurology* 29:1369–1375
 5. Hansen M, Brynskov J, Christensen PA, Krinbel JJ, Gimsing P (1985) Cobalamin binding proteins (haptocornin and transcobalamin) in human cerebrospinal fluid. *Scand J Haematol* 34:209–212
 6. Konopka L, Pawelski S, Brodzki M, Wegier-Filipiuk B (1987) Cerebrospinal fluid vitamin B₁₂ concentration and its binding capacity in acute leukemias. Fourth international symposium on Therapy of Acute Leukemias, Rome, Feb 7–12 (program and abstr)
 7. Recht L, Straus DJ, Cirrincione C, Tzvi Thaler H, Posner JB (1987) Central nervous system metastases from non-Hodgkin's lymphoma: treatment and prophylaxis. *Am J Med* 84:425–435
 8. Retief FP, Gottlieb CW, Herbert V (1967) Delivery of Co⁵⁷B₁₂ to erythrocytes from alpha and beta globulin of normal B₁₂-deficient and chronic myeloid leukemia serum. *Blood* 29:837–851
 9. Swencz-Szczepanik K (1982) Examination of DNA content in leukemia cells of cerebrospinal fluid. Doctoral dissertation. Institute of Haematology, Warsaw