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# Carcinoembryonic antigen, alphafetoprotein and alpha and beta subunits of human chorionic gonadotropin in plasma of children with acute leukaemia

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The plasma carcinoembryonic antigen, alpha-fetoprotein and the alpha and beta subunits of human chorionic gonadotropin levels were measured by radioimmunoassay in 44 children with acute leukaemia. These markers were determined repeatedly every 3 months at different stages of the disease (at onset, in complete remission, during bone marrow and extramedullary relapse). Elevated CEA levels were present in 64% of children at the onset of acute leukaemia and during bone marrow relapse. Elevated CEA levels decreased during induction treatment and they became normal with attainment of complete remission. In 7/12 patients who developed bone marrow relapse elevated CEA levels and in 4 of them raised levels appeared 3–4 months before there had been any other evidence of relapse. In 6/13 patients with extramedullary relapse, elevated CEA levels were found. AFP, alpha and beta hCG values in different stages of the disease were elevated sporadically; they did not reflect the activity of leukaemia.

Since the discovery of carcinoembryonic antigen by Gold and Freedman [10] there has been an intense interest in studies of tumour markers. Three of the best characterized tumour markers are carcinoembryonic antigen (CEA), alphafetoprotein (AFP) and human chorionic gonadotropin (hCG). Up to now, the majority of investigations were done in adults with solid tumour [1, 2, 4, 22, 8, 18, 19, 21, 22].

The purpose of the present paper was to evaluate the usefulness of serial determination of CEA, AFP, alpha and beta hCG in plasma of children with acute leukaemia (AL).

## Material and Methods

Forty four children aged from 2 to 14 years suffering from acute leukaemia were included in this study. There were 32 boys and 12 girls. Acute limphoblastic leukaemia (ALL) was diagnosed in 41, and acute myeloblastic leukaemia (AML) in 3 patients. Six of them died during induction treatment. CEA, AFP, alpha and beta hCG were determined repeatedly every 3 months at different stages of leukaemia (at onset, complete remission, bone marrow and extramedullary relapse) by double-anti-

body radioimmunoassay technique [6]. Statistical significance between means was tested using the "u"-test and Student's $t$ test at the significance level of $p = 0.05$.

## Results

The upper normal limits for plasma CEA, AFP, alpha and beta hCG in healthy children were established by us earlier [6]; they were less than 4.1 ng/ml for CEA, and less than 12.2 ng/ml of AFP, less than 1.0 ng/ml for alpha hCG, and less than 0.4 ng/ml for beta hCG.

Plasma concentrations of CEA and AFP in children with acute leukaemia are shown in Figs 1 and 2.

### *CEA in plasma*

Elevated plasma concentrations of CEA at the onset of AL and bone marrow relapse were found in 28/44 cases (63.6%). Slightly elevated concentrations in the range of 4.2–10.0 ng/ml were found in 18/44 patients, and in 10 other children CEA levels were high. The highest were 53.0 ng/ml and 65.0 ng/ml, tenfold higher than accepted as the upper limit of normal. The mean plasma CEA level at the onset of leukaemia was 8.43 $\pm$ 12.4 ng/ml, significantly higher than the mean level in healthy children (0.83 $\pm$ 1.60 ng/ml) and higher than the mean level in complete remission (2.75 $\pm$ 3.94 ng/ml), $p < 0.05$. Among children at the onset of AL the highest mean was 5.5 ng/ml. During remission it was 1.5 ng/ml, and in healthy children 0.0 ng/ml. Elevated CEA levels at the onset of AL decreased during induction treatment and they became normal with attainment of complete remission (Fig. 3). During complete remission, CEA levels were estimated repeatedly and the highest values were analysed. In 11/38 patients was the plasma CEA level elevated; the highest one was 21.5 ng/ml, 4 months before the child's death during bone marrow relapse.

### *AFP in plasma*

In 4/44 children elevated AFP levels were found at the onset of AL. The highest concentraton was 100.0 ng/ml. Repeated assays revealed that the AFP values of all of the positive patients returned to normal values of less than 12.2 ng/ml with the attainment of complete remission. Elevated plasma AFP levels in complete remission were observed in 4/38 children.

The mean AFP level in plasma at the onset of leukaemia was 5.81 $\pm$ $\pm$ 15.7 ng/ml, not significantly higher than the mean during complete remission (3.63 $\pm$ 7.9 ng/ml) and in healthy children. The mean AFP level was 1.4 ng/ml at the onset of AL, 1.0 ng/ml during complete remission, and 1.5 ng/ml in healthy children.

### *Alpha and beta hCG in plasma*

The alpha hCG levels in plasma at the onset of AL as well as during complete remission were lower than the upper limit of normal, 1.0 ng/ml. The mean alpha hCG level at the onset of AL was 0.07 $\pm$ 0.2 ng/ml and during remission 0.1 $\pm$ 0.2 ng/ml/$p >$ $> 0.05$). Elevated beta hCG levels at the onset of AL were found in 1/44

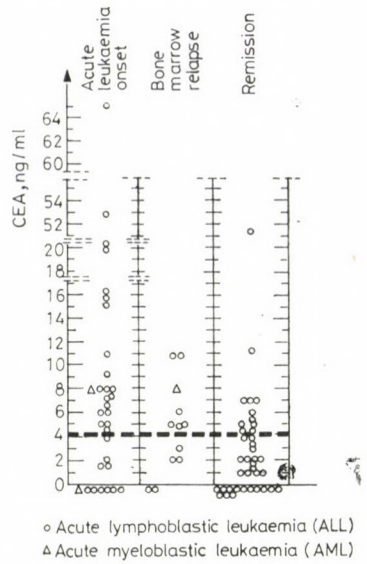


FIG. 1

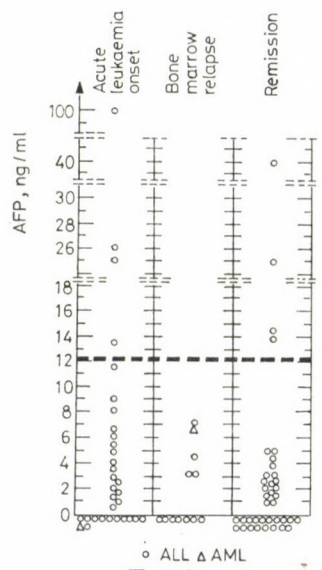


FIG. 2

and during remission in 1/38 cases. The augmented values dropped to normal in further observations. No statistical differences were found between the mean beta hCG level at the onset of ALL ($0.03 \pm 0.1$ ng/ml) and in complete remission ($0.03 \pm 0.2$ ng/ml).

*Serial plasma CEA, AFP, alpha and beta hCG determinations*

The plasma levels of tumour markers were determined repeatedly during the course of chemotherapy and after the cessation of treatment. In 12

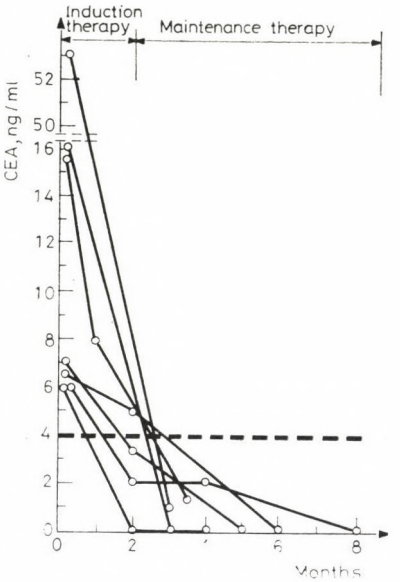


FIG. 3

children with AL, successive bone marrow relapses were observed. In 7/12 elevated CEA levels were found, and in 4 of them raised levels appeared 3–4 months before the bone marrow relapse. The plasma AFP, alpha and beta hCG levels in bone marrow relapses were normal and their behaviour during different stages of the disease did not reflect activity of leukaemia.

In 13 children an extramedullary relapse occurred during haematological remission: 12 times in the CNS and once in the testis. In 6/13 patients raised CEA levels were observed while AFP, alpha and beta hCG levels were below the upper limit of normal. The elevated CEA levels were found in 5 cases of CNS relapse (the highest concentration was 24.0 ng/ml), and in one boy with leukaemic infiltration in the testis (9.5 ng/ml). We did not observe the progression of CEA levels in successive determinations before a CNS relapse had appeared.

A representative patient in whom the CEA levels seemed to be well correlated with the activity of leukaemia (Fig. 4) was the boy with leukaemic infiltration in the testis. Eight months after the cessation of therapy the plasma CEA level was 4.0 ng/ml. Five months later this rose to 9.0 ng/ml but no symptoms of relapse could be found. After 5 further months the boy was admitted with leukaemic infiltrations in the testis without symptoms of bone marrow relapse, then the CEA level increased to 9.5 ng/ml. After orchiectomy, irradiation of the testis and chemotherapy the boy had a level of 8.5 ng/ml which then fell to

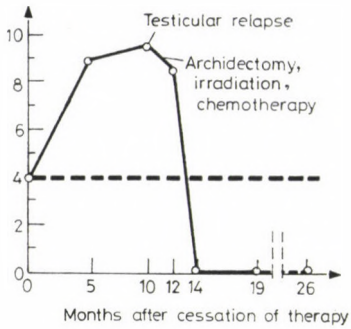


FIG. 4

0.0 ng/ml. During further 12 months the boy was still in complete remission and plasma CEA concentration was still undetectable.

## DISCUSSION

The usefulness of measuring CEA, AFP, alpha and beta hCG levels in paediatric malignancy has not been clarified although in children with active neuroblastoma and retinoblastoma raised levels were reported which fell to normal if treatment was successful [18, 7, 9, 11, 14, 20]. We have not found any report discussing the behaviour of CEA, AFP, alpha and beta hCG in haematological malignancies of children. On the other hand, elevated CEA levels in plasma were noted in adults suffering from leukaemia [3, 8, 18, 13]. Lamerz and Fatah-Moghadam [12] who summarized the data in this field reported that among 94 leukaemic patients CEA levels were elevated in 35%. In our study we have found raised CEA levels in 28/44 children (64%) with AL. Elevated CEA levels in children at the onset of AL returned to normal within 2–3 months after complete remission. In 4/12 patients a CEA level augmented to above the upper limit of normal preceded by 3–4 months the occurrence of a bone marrow relapse. A similar observation was that in a boy with extramedullary relapse in whom increased CEA levels preceded over five months the leukaemic infiltration in the testis. The question arises, what causes the high activity of plasma CEA in children with AL?

In the present study we could not decide whether leukaemic cells produced and released CEA. It cannot be excluded that leukaemic blasts produced and liberated CEA or that destruction of the intestinal mucosa rich in CEA due to its leukaemic infiltrations produced the high CEA activity in plasma. It should also be considered that anti-CEA antibodies used in our assay might crossreact with CEA-like glycoproteins such as nonspecific cross-reacting antigen (NCA). In this case, a high activity of plasma CEA might be caused by the liberation of NCA from leukaemic cells, or it may have

depended upon the destruction of tissues made rich in NCA by leukaemic infiltrations.

The high activity of CEA in plasma of leukaemic patients may also depend on the condition of the liver. This organ may be unable to metabolize normal amounts of CEA produced in the intestinal mucosa or cope with the increased CEA production during regenerative processes.

Thus, all the above mentioned possibilities or their combinations may produce elevated CEA levels in plasma. The answer to the question on what this depends requires further investigations of the nature and behaviour of CEA in children with leukaemia.

The plasma AFP level in children with AL was elevated in 9.1% of the cases. Evaluating the behaviour of AFP in different stages of the disease, we suggest that AFP did not reflect the activity of leukaemia. Similar views are shared by several authors [5, 15, 16, 17]. Also, the elevated beta hCG level had an incidental character, and the alpha hCG level did not reach the upper limit of normal, and this seems to exclude the use of determining hCG subunits as a marker of AL.

## References


1. Beaty J., Terz J. Value of carcinoembryonic antigen in clinical medicine. Progr Clin Cancer 8:9–29, 1982
2. Bell H: Alpha-fetoprotein and carcinoembryonic antigen in patients with primary liver carcinoma, metastatic liver disease and alcoholic liver disease. Scand J Gastroenterol 17:897–905, 1982
3. Booth S, King J, Leonard J, Dykes P: Serum carcinoembryonic antigen in clinical disorders. Gut 14:794–9, 1973
4. Bosl G, Geller N, Cirrincione C: Serum tumor markers in patients with metastatic germ cell tumors of testis, a 10-years experience. Am J Med 75:29–35, 1983
5. Chudwin D, Ruckinagel D, Scholnik A, Waldman T, McIntire K: Fetal hemoglobin and alpha-fetoprotein in various malignancies. Acta Haematol 58:288–93, 1977
6. Domaniewski J, Balcar-Boroń A, Wysocki M: Concentration of tumor markers (CEA, AFP, alpha and beta subunits of hCG) in cerebrospinal fluid in children with inflammatory diseases of the central nervous system. Acta Paediatr Hung 27(2): 115–121, 1986
7. Felberg N, Michelson J, Shields J: CEA family syndrome. Abnormal carcinoembryonic antigen levels in asymptomatic retinoblastoma family members. Cancer 37:1397–402, 1976
8. Freedman S: Carcinoembryonic antigen, current clinical applications. J Allergy Clin Immunol 50:348–57, 1972
9. Frens D, Bray P, Wu J, Lahey M: Carcinoembryonic antigen assay: Prognostic value in neural crest tumors. J Pediatr 88:591–94, 1976
10. Gold P, Freedman S: Demonstration of tumor specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med 121:439–62, 1965
11. Knöpfe G, Becker M, Rotthauwe H: Alpha-1-Fetoprotein. Physiologie, Pathologie und diagnostische Bedeutung mit besonderer Berücksichtigung des Kindesalters. Klin Paediatr 189:207–26, 1977
12. Lamerz R, Fateh-Moghadam A: Carcinofetale Antigene. II-Carcinoembryonales Antigen (CEA). Klin Wochenschr 53:193–203, 1975
13. Laurence D, Neville A: Fetal antigens and their role in the diagnosis and clinical management of human neoplasms Br J Cancer 26:335–55, 1972
14. Mann J, Lakin G, Leonard J: Clinical applications of serum carcinoembryonic antigen and alphafetoprotein levels in children with solid tumours. Arch Dis Child 53:366–75, 1978
15. Masopust J, Kithier K, Radi J, Kontecky J, Kotal L: Occurrence of alphafetoprotein in patients with neoplasms and non-neoplastic diseases. Int J Cancer 3:364–73, 1968
16. Masseyeff R, Cassuto J, Krebs B, Andoly P, Dujardin P: Alphafetoprotein

radioimmunoassay in blood diseases. N Engl J Med 291:532, 1974
17. Mihalev A, Tzingilev D, Sivakov L: Radioimmunoassay of alphafetoprotein in the serum of patients with leukemia and malignant melanoma. Neoplasma 23:103–7, 1976
18. Reynoso G, Chu M, Holyoke D: Carcinoembryonic antigen in patients with different cancers. JAMA 220:361–65, 1972
19. Rosen S, Weintraub B, Vaitukaitis J: Placental proteins and their subunits as tumor markers. Ann Intern Med 82: 71–83, 1975
20. Sugimoto T, Sawada T, Kusunoki T: Immunologic and biochemical studies on the carcinoembryonic antigen–like substance in human neuroblastoma. Pediatr Res 13:91–5, 1979
21. Szymendera J, Zborzil J, Sikorowa L, Lenko J, Kamińska J, Gadek A: Evaluation of five tumor markers (AFP, CEA, hPL and $SP_1$) in monitoring therapy and follow-up patients with testicular germ cell tumors. Oncology 40:1–10, 1983
22. Vaitukaitis J: Peptide hormones as tumor markers. Cancer 37:567–72, 1976
23. Wang J, Sinks L, Chu T: Carcinoembryonic antigen in patients with neuroblastoma. J Surg Oncol 6:211–17, 1974

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