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Late effects of therapy in children previously treated for leukaemia or malignant tumour

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The late sequelae of leukaemia and tumour therapy are discussed. The most important and/or the most frequent are neuro-psychologic disturbances, deformities of the bones, the decreased reproduction capacity and the second tumours. Because of the rapidly growing number of cured patients a better knowledge of the occurrence, aetiology, prophylaxis and rehabilitation of these changes is needed.

The improving survival rate of children with malignant disease, especially ALL, non-Hodgkin lymphoma and Wilms tumour resulted in a gradual increase in the number of cured patients. Hence the recognition of late effects of irradiation and chemotherapy, their reduction and the rehabilitation of these patients is now of great importance. This is also shown by the data of the American Late Effect Study Group presented in 1979: of 290 patients 166 (57%) had late effects and 106 (64%) of the 166 patients had clinically significant symptoms [14].

In the present paper the late sequelae of leukaemia therapy will be discussed not taking into consideration the permanent changes due to the serious infections of children suffering from malignant disease. The late side effects of the therapy of malignant solid tumours in children will be mentioned only briefly.

Materials and Methods

STH and TSH determination was performed after the i.v. administration of TRH and the infusion of l-arginine. The TSH-level was determined by the Byk–Mallinckordt kit, while STH by radioimmunoassay. The metopiron test was used for examination of the hypophyseal-adrenal function [21].

The psychological tests used in the evaluation were the Wechsler Intelligence Scale for Children modified for Hungarian standards and the "World Test", where the children could choose objects from 250 pieces to construct their world [22].

Cytogenetic examinations were made in short time cultures of the peripheral blood evaluated by conventional Giemsa staining, further Giemsa-trypsin banding and Hoechst–Giemsa staining after BrdU incorporation [23].

Abbreviations: ALL = Acute lymphoblastic leukaemia; STH = Somatotropic hormone; TSH = Thyroid stimulating hormone; TRH = Thyreotropine releasing hormone; CT = Computerized tomography; IQ = Intelligence quotient; MTX = Methotrexate; ACTH = Adrenocorticotropic hormone; LH = Luteinizing hormone; FSH = Follicle stimulating hormone; GH = Growth hormone

TABLE I

Age at onset of disease years	No.	Verbal		IQ performance		Full scale	
		m	SD	m	SD	m	SD
1–14	24	111.88	10.52	106.33	10.89	110.25	11.26
>6	9	110.89	12.72	115.0	14.07	114.33	13.37
<6	15	112.47	9.45	101.13	10.66	107.89	8.29
CNS							
2400 R	15	113.53	7.97	107.4	13.17	111.86	9.15
>2400 R	9	109.11	14.08	104.56	14.84	107.56	14.38

RESULTS AND DISCUSSION

There is considerable controversy on the neurologic sequelae of leukaemia. Some authors [28, 31] reported no alterations, others found after several years of methotrexate therapy and prophylactic cranial irradiation cerebral necrosis and gliosis, which caused encephalopathy and mental deficiency [12]. Peylan-Ramu et al [18] found by CT in 25–30% of the cases periventricular dilatation, cortical atrophy and white matter changes, which was confirmed by Clausen and Pedersen [4] in a prospective study. The clinical symptoms found by German authors [8, 32] were a good cognitive function, but a decreased speed test and concentration ability, especially in mathematics. The distress of neuromotor function: coordination, postural reactions by closed eyes, were more expressed in children treated before 6 years of age. We found a normal IQ in long surviving leukaemic patients and a slightly decreased performance in those whose disease began before 6 years of age (Table I). The prospective study of the IQ scores and cognitive functions made by Meadows et al [15] in ALL children treated with cranial irradiation is different from our observations. They found a reduction in overall IQ score, learning capacity and academic performance. This was more expressed in younger children and in those, whose original IQ was higher than in the others (Table II). The full manifestation of these alterations was at 3 or more years after the irradiation. Meadows and Evans [12] suppose that irradiation enhances the intracerebral absorption of methotrexate. The discrepancy between the results of different investigators could be explained by several factors. *(i)* Therapy was

TABLE II

Changes in IQ by initial IQ [15]

IQ range	No. of children	Test 3-test 1 (Average change)
110–132	6	−23.5
86–109	12	−8

not the same. In some protocols the total quantity of methotrexate administered intrathecally during the treatment was quite high, while we gave all in all 5 doses and of these only 2 after irradiation. This means a total dose of 60 mg/m² MTX while e.g. 132 mg is recommended for standard risk children and 252 mg for high risk cases in the latest Memphis Protocol. It is, however, known that the higher cumulative dose of methotrexate and its administration after irradiation of the brain increases the likelihood of neurotoxicity [11]. *(ii)* The fractionation of irradiation, further the age dependent thickness and density of the cranial bones are also different. *(iii)* The tests used for the examination of these children were also different in the studies.

The psychological study of children 3.5 or more years after the irradiation [22] revealed severe emotional problems: decreased interest in the environment, anxiety, disturbed self image, isolation, and decreased motivation (Table III). Many psychological problems were found in the families of these patients; inconsequent education, problems in marital connections, psychological disturbances in the sibs and isolation of the family (Table IV). All these problems were markedly reduced by psychologic care of the patients and their families (psychotherapy, creative activity, music therapy, education, social care).

TABLE III

Effect of psychological care in per cent of total number of patients

Patient groups	No. of cases	Anxiety	Disturbed self-image	Slowing of movements	Fear of death	Isolation
Leukaemia						
No psychological care	25	100	92	60	64	62
Psychological care	34	38	42	20	15	23
Control	24	21	2	8	4	21

TABLE IV

Psychologic problems in the families of long surviving leukaemic children (per cent)

Group	No. of families	Inconsequent education	Disturbed matrimonial connections	Psychological problems of siblings	Narrowing of motivation	Isolation of family
No psychological care	25	92	79	73	49	60
Psychological care	34	64	24	21	12	19
Controls	20	37	25	18	19	24

There are controversies also concerning the endocrinological effect of leukaemia and tumour therapy. After irradiation for tumours of the central nervous system excluding those of the adenohypophysis, the eye and middle ear and including in the field of radiotherapy the hypothalamo-pituitary region, isolated growth hormone deficiency, short stature, in some cases deficiency of TSH, ACTH and gonadotropins, even panhypopituitarism could be observed with a delayed onset [17, 19]. The dose of irradiation in acute leukaemia of children is substantially less than that for solid tumours. Most authors observed, however, a progressive fall of growth hormone response with increasing time after the prophylactic irradiation [20, 25], while other authors [7, 21, 30] found normal growth and normal STH, TSH, ACTH, LH and FSH levels. Normal height and a normal reaction to arginine provocation of GH secretion was observed by Dickinson et al [6], too. The peaks of growth hormone after arginine infusion were, however, somewhat lower in our study than in the controls in spite of the normal growth of children (Figs 1, 2).

The gonadal functions as well as the health of the offsprings seem to be normal after leukaemia therapy. Shalet et al [26], however, found the mean tubular fertility index = percentage of seminiferous tubules containing spermatogonia to be 51%. In contrast, these figures after combination chemotherapy for Hodgkin's disease are disastrous [27, 33].

Males usually have a normal progression of pubertal development, however, the FSH values were higher and all were azoospermic after an interval of 2.4 to 8 years after completion of treatment. Thus it seems that tubular cells are more sensitive to MOPP or MVPP therapy than the Leydig cells. Females may have amenorrhoea [3], but about 40%

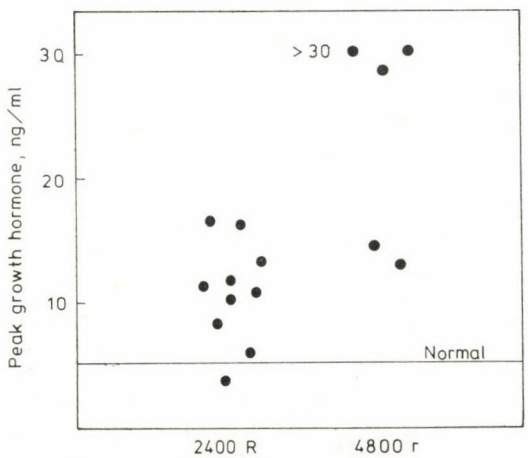

FIG. 1. Growth hormone levels after prophylactic irradiation of the head

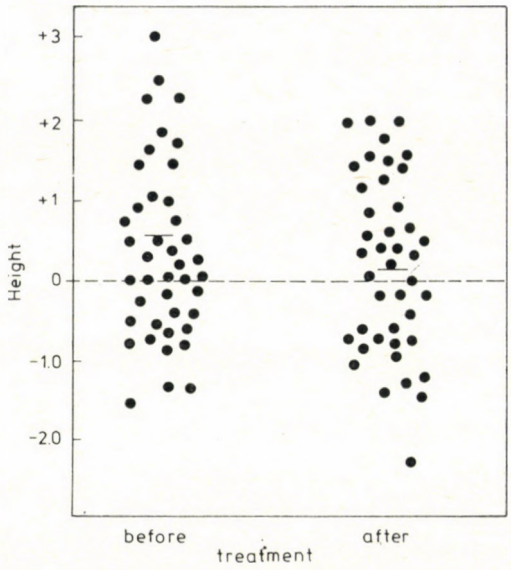

FIG. 2. Height of children before and after treatment of leukaemia

have regular menstrual cycles with evidence of ovulation in some of them. In lymphoma with irradiation of the abdomen the later sterility could be prevented by previous oophoropexis in 75% of the patients [5].

The chromosome aberrations observable several years after leukaemia therapy were studied by some authors in order to determine the long term effects on the chromosomes of such a treatment by mutagenic cytotoxic drugs. Miller et al. [16] found aberrations in four of seven children with ALL, three deletions, one balanced translocation and one inversion. In our own study four aberrations were found in the 12 examined patients [23]. The difference between our patients and the controls was not significant. In the post-treatment group of patients with Wilms tumour an almost two-fold occurrence of stable aberrations was found by Miller et al [16], which underlines the role of radiotherapy in the aetiology of these rearrangements. The frequency of sister chromatid exchange is also normal according to our examinations [23] but the number of 2nd cycle cells was always lower in the treated children, than in the controls. Hence we suppose that the mean cell cycle time of the posttreatment patients is different from the controls. This may be due to a change in lymphocyte subclass distribution or selection of cells with a different cell cycle time or purely a bias due to individual variations. Further studies are needed to prove this supposition and to evaluate its significance.

The frequency of second tumours is increased after complex therapy of the primary tumour [2, 29, 13]. According to several authors, beyond

ten years from diagnosis the most important causes of morbidity and mortality are second primary neoplasms [10, 13, 24]. The occurrence of a second malignancy in Hodgkin's disease was 270 in a follow up study of 1553 patients [1], while in a previous publication only 100 was calculated [5]. Whether an increased susceptibility or a somatic mutation induced by the complex therapy was responsible for the phenomenon is an open question. According to the preliminary results of our studies an increased number of chromosome mutations could be induced in vitro by a chemical mutagen in leukaemic patients being in full remission.

As far as solid tumours are concerned there are still other late effects, which are only listed here. These are,

1) local bone growth impairment and scoliosis after bone (i.e. spinal) irradiation especially in children under 6 years of age;

2) local lesions after irradiation of the brain, spinal cord and peripheral nerves;

3) pulmonary fibrosis;

4) renal damage and hypertension [9];

5) chronic cystitis and contracted bladder;

6) damage of the gastrointestinal tract, liver and pancreas.

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