

Cognitive (IQ, Academic Achievement) and Non-Cognitive (Anxiety and Depression) Functioning in Children Treated with Cranial Irradiation for Acute Leukemia

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Objective. To study the cognitive and non cognitive functioning in acute lymphoblastic leukemia (ALL) in different stages in relation to therapy and possible effects of cranial irradiation

Method: The sample was comprised of 52 with ALL who were divided into three groups , the first one (25 children) received (intravenous) IV , (intrathecal) IT chemotherapy (standard risk) , the second group comprised of (26 children) received IV, IT , prophylactic cranial irradiation 24 GY , the third group consists of 11 ALL children with CNS relapse received IV , IT , curative craniospinal irradiation and a control group comparable with the sample group in age, sex, socio-economic standard (30 children). Information on neuropsychological performance was obtained in a standardized manner using WISC-R for IQ, (Children Anxiety scale) CAS for anxiety, (Children Depression inventory) CDI for depression , and semistructured clinical interview based on CD-10 (1992).

Results: Children with ALL who were treated with chemotherapy alone were significantly more impaired on estimated IQ than comparison group in vocabulary subtest of VIQs but there was a significant decrease in FSIQ , PIQs, its subtests , VIQs in children treated with prophylactic cranial irradiation relative to comparison group, also there was a significant decrease in FSIQ, PIQ its subtests, VIQ its subtests in children with CNS relapse as compared to control group. As regard non cognitive functioning, children with CNS relapse were found to have a significant increase in depression as compared to those without CNS relapse .

Conclusion : Cognitive sequelae in children with leukemia has its impact by disease itself , by chemotherapeutic agents , and to higher extent by cranial irradiation particularly with high dose when it is given at young age.

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INTRODUCTION

Acute leukemias account for approximately 30 percent of malignancies occurring in childhood (Duffy and Civin, 1993). It constitutes 58.5% of all malignancies attending the Haematology- On-

cology Unit, Children's Hospital, Ain Shams University. It forms 31.12 per 100.000 outpatient clientelles in the same hospital (Khalifa et al., 1988).

Mental status examination can most conveniently be divided into two components, the cognitive and the non cognitive (Silberfarb, 1983).

One of the most significant late effects of therapy appears to be the neuropsychological (NP) problems (Chesells, 1983) & (Garcia et al.1993) . The long term consequences associated with cancer treatment of central nervous sys-

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tem were recognized first in the 1970s. Since then, there have been many reports of the neuropsychological late effects associated with CNS prophylaxis used in the treatment of childhood ALL (Eiser and Lansdown, 1977), (Eiser 1978), (Goff et al. 1980), (Meadows et al. 1981), Moss et al. (1981), Copeland et al. (1985), Girtl et al. (1992). These late effects include global deficits, such as declines in intelligence quotient (IQ). (Moore et al. 1991) stated that children who receive CNS treatment before the age of 5 years appear to be the most profoundly affected. Of potentially greater significance, female sex was the pre-eminant risk factor for central nervous system toxicity resulting from treatment.

In order to outline the NP changes responsible for delayed neurotoxicity following cranial irradiation, several studies have identified white matter abnormalities on histological examination. Phillips et al. (1991) found that cerebral white matter glucose metabolism was reduced in long term survivors of ALL, also auditory evoked responses have found an abnormal latency of P3 wave which related to cognitive processing time correlates with NP sequelae (Heukrodt et al., 1988), damage to the basic material of cerebrovascular endothelial cells (Rottenberg et al., 1977), glial cells probably more vulnerable in young age (Cavenus, 1980), and anatomical changes (Johnson et al., 1990).

Only about 25 percent of all cancer patients irrespective of their status and diagnosis, experience significant emotional distress that is often depressive in content (Lesko and Holland, 1990a).

The aim of the present work is to study the cognitive and non cognitive functioning in acute leukemia in different stages in relation to therapy and possible effects of cranial irradiation

SUBJECTS AND METHODS

A cross-sectional study was done on fifty two children attending the Hematological/ Oncology Clinic, Children's Hospital, Ain Shams University, within the ten- months period (from March 1st to december 30 1994).

Thirty normal children comparable for age, sex, and socioeconomic status were included as control (group I)

Group II included 52 children with ALL, 32 were males and 20 were females, they were further subdivided into three groups according to risk factors and mode of therapy, Group IIa, Group IIb, Group IIc.

Full medical and psychiatric history, thorough clinical examination, plain chest X-ray, Hb level estimation, RBCs count, total leukocytic and platelet counts, bone marrow aspiration and biopsy, lumbar puncture, liver function tests, included serum glutamic pyruvic transaminase (SGPT) and serum glutamyl oxalacetic transferase (SGOT), kidney function tests included, serum urea, creatinine and uric acid.

All patients as well as controls were subjected to semi-structural clinical interview based on the ICD-10 diagnostic criteria (1992) blocks F80-F89 (Behavioral and emotional disorders) with onset usually occurring in childhood and adolescence and Blocks F30-45 (Mood, affective disorders). Also the children and their parents were interviewed to obtain a longitudinal view of the child's learning history. Wechsler Intelligence Scale for Children- Revised (WISC-R). Children Anxiety scale (CAS), this scale was designed by Abdel-Hamied and El Nail (1991), it is an arabic version derived from Children's Manifest Anxiety Scale (CMAS) by Candless, Castaneda and Palermo. Children de-

pression inventory, this scale was designed by Abdel el- Fattah (1988). it is an arabic version derived from Children's Manifest Depression Scale by Kovacs.

Student "t" test, chi- square and correlation coefficient ... "r" test, were used for statistical analysis.

RESULTS

The control group consisted of 30 normal children, their ages ranged between (6-16) years with mean value (10.1 ± 2.54), 14 were males while 16 were females, their weight ranged between (21-52) Kg with mean value (33.9 ± 9.6) while their height ranged between (111-156) cm with mean value (132.6 ± 12.19).

Group IIa consisted of 15 children with ALL (standard risk) received intravenous and intrathecal chemotherapy. Their ages ranged between (5 4/12-16 6/12) years with mean value (8.2 ± 2.69). 8 were males while 7 were females, their weight ranged between (18-50) kg with mean value (26.33 ± 8.39) while their height ranged between (106-158) cm with mean value (122.4 ± 14.5).

Group IIb consisted of 26 children with ALL (high risk) received intravenous, intrathecal chemotherapy and prophylactic cranial irradiation (24 GY), their ages ranged between (5 7/12-16) years with mean value (10.06 ± 3.59), 18 were males while 8 were females. Irradiation - examination interval ranged between one month to 14 10/12 years , 6 children treated with cranial irradiation below or at the age of 5years and 20 children after the age of 5 years, their weight ranged between (18-61) Kg with mean value (32.15 ± 12.25), while their height ranged between (133.26+17.38).

Group IIc consists of 11 children with ALL with CNS relapse received in-

travenous, intrathecal chemotherapy and curative craniospinal irradiation (30 GY to the cranium and 24 GY to the spinal cord). Their ages ranged between (6 7/12-16) years with mean value (11.12 ± 3.13), 6 were males while 5 were females , irradiation-examination interval ranged between 5 months to 9 7/12 years, 2 children treated with cranial irradiation below the age of 5 years and 9 children after the age of 5years, their weight ranged between (18-61) kg with mean value(32.15 ± 12.25) while their height ranged between (108-169) cm with mean value (133.26 ± 17.38).

There was no significant decrease in IQs of children with ALL who have been treated with chemotherapy alone including IT triple therapy (group IIa) as compared to control group except in vocabulary subtest of VIQs, $p < 0.05$, but there was a significant decrease in FSIQs ($p < 0.01$), PIQs ($p < 0.05$) and its subtests picture completion, block design, and digit symbol ($p < 0.01$) and VIQs ($p < 0.05$) particularly in arithmetic $p < 0.05$ and digit span ($p < 0.01$) subtests in children treated with prophylactic cranial irradiation (24 GY) as compared to control group. Also there was a significant decrease in FSIQs ($p < 0.01$), PIQs ($p < 0.01$), and its subtests, picture completion ($p < 0.05$), block design ($p < 0.05$) and digit symbol ($p < 0.05$) and arithmetic ($p < 0.05$) and digit span $p (0.01)$ subtests of VIQs in children with CNS relapse who have been treated with therapeutic craniospinal irradiation (group IIc) as compared to control group.

The children with CNS relapse (group IIc) had significant decrease ($p < 0.01$) specifically on block design ($p < 0.05$) and digit symbol subtests ($p < 0.01$) and only in digit span subtests ($p < 0.05$) belonging to VIQ compared to non irradiated children who have been

treated with chemotherapy alone (group IIa) .

As regard irradiation dose there was a significant decrease in digit symbol subtests of PIQs ($p < 0.05$) in patients with CNS relapse treated with high dose of radiotherapy (group IIc) than in children treated with prophylactic radiotherapy 24 GY (group IIb). Also there was a significant decrease in PIQs ($p < 0.01$) particularly in block design and digit symbol subtests ($p < 0.01$) and digit span subtests ($p < 0.01$) belonging to VIQs in children who have been treated with cranial irradiation, VIQs and its subtests, but this decrease was not statistically significant except in comprehension subtests ($p < 0.05$) of

VIQs in the group with CNS relapse treated with high dose of cranial irradiation (group IIc) .

The correlation of IQs with time strongly suggested that more decline in IQs including FSIQs, VIQs specifically arithmetic and similarities subtests in children treated with irradiation whether prophylactic or therapeutic is larger with time since the diagnosis and treated by cranial irradiation as follow: FIQs - 0.32* , VIQs -0.04* , PIQs -0.19, comprehension -0.26, arithmetic- 0.34*, similarities- 0.39* , vocabulary -0.11 , digit span- 0.06, block design-0.83, digit symbol -0.17 at correlation coefficient "r" test significant ± 0.32 .

Table 1
IQs of Children with ALL (Groups II a + IIb + IIc) as Compared to IQ of Control Group

Group		Full Scale IQ	Verbal IQ	Performance IQ	Comprehension	Arithmetic	Similarities	Vocabulary	Digit span	Picture completion	Block design	Digit symbol
ALL II a+b+c No = 52	X ($\pm$ S.D)	104.5* 14.9	109.15 15.2	99.07* 14.48	11.96 2.47	10.21* 3.22	12.46 3.42	11.23 3.69	8.21** 2.54	10.11** 2.64	9.35* 2.19	8.25* 3.6
Control No = 30	X ($\pm$ S.D)	111.66 12.7	114.7 15.07	106.1 10.44	12.46 2.5	11.8 3.62	13.03 3.07	12.2 3.6	9.6 2.2	11.9 3.17	10.2 2.17	9.8 2.4

*= $P < 0.05$; ** = < 0.01

Table 2
IQs of Children with ALL (Groups II) as Compared to IQ of Control (Group I)

Group		Full Scale IQ	Verbal IQ	Performance IQ	Comprehension	Arithmetic	Similarities	Vocabulary	Digit span	Picture completion	Block design	Digit symbol
ALL (IIa)	X	109.4	111.6	14.55	11.33	11.067	13.53	10.33*	9.4	10.86	10.53	10.33
No = 15	($\pm$ S.D)	14.62	14.87	97**	2.63	3.08	4.08	3.45	2.61	3.2	1.846	4.27
ALL = (IIb)	X	102.6**	107.4*	93.5**	12.07	10.07*	11.92	11.19	7.76**	10.07**	8.88**	8.23**
No = 26	($\pm$ S.D)	15.9	17.2	14.3	2.63	3.22	3.22	3.97	2.7	2.82	2.13	3.31
ALL (IIc)	X	102.1**	110	93.5	11.3	9.3*	13.2	12.7	7.6	9.9*	8.8*	6.6**
No = 10	($\pm$ S.D)	11.05	10.53	10.8	1.9	3.28	2.56	2.93	1.2	2.94	2.27	1.8
(1) No = 30	X	111.66	114.7	106	12.46	11.8	13.03	12.2	9.6	11.9	10.2	9.8
Control	($\pm$ S.D)	12.7	15.07	10.44	2.5	3.62	3.07	3.6	2.2	3.17	2.17	2.4

Note: = $p < 0.05$; ** = $p < 0.01$. The significance here inside table between each group and the control group

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Table 3
IQs and the Age of the Children with ALL (Group IIb+ Group IIc) at the Start of Radiotherapy

Group IIb + IIc N= 36		Full Scale IQ	Verbal Performance IQ	Comprehension IQ	Arithmetic	Similarities	Vocabulary	Digit span	Picture completion	Block design	Digit symbol
≤ 5 No = 8	X	89**	92.5**	87.12**	10*	8**	9.37**	8.37**	6.75	8.12**	7.62*
	(±S.D)	6.16	8.12	8.7	2.7	2.26	2.13	2.19	1.48	1.45	2.32
	Range	(80-97)	(80-101)	(77-101)	(5-13)	(5-12)	(6-12)	(5-8)	(6-10)	(5-12)	(5-12)
> 5 No = 28	X	106.32	112.2	98.57	12.39	10.39	13.1	12.53	8	10.57	9.12
	(±S.D)	14.18	14.8	13.65	2.14	3.33	2.84	3.62	2.53	2.94	2.02
	Range	(80-131)	(80-142)	(77-119)	(7-16)	(5-17)	(5-19)	(7-17)	(4-14)	(5-16)	(4-13)
	P	**<0.01	**<0.01	**<0.01	*<0.05	**<0.01	**<0.01	**<0.01	**<0.01	**<0.01	*<0.05

Children who received CNS treatment (IT chemotherapy & cranial irradiation) before the age of 5 years had a significant decrease in FSIQs, VIQs (p < 0.01) and there was a significant decrease in all subtests except digit span & digit symbol subtests as compared to children who received the same treatment after the age of 5 years , but these two subtests were significantly decreased in children treated with chemotherapy & radiotherapy as compared to children with chemotherapy alone regardless of age at beginning of cranial irradiation .

Table 4
School Failure in Children with ALL (Group IIa , IIc) and Control Group

The variable	+ ve School Failure	Normal Educational Skills	Total	P
	No	%	No	%
Group IIa	1	6.67	14	93.33
Group IIb	8	30.77	18	69.23
Group IIc	4	36.36	7	63.64
Total	13	25	39	75
Group I	2	6.7	28	93.3
				P < 0.05
				P < 0.05

There was a significant increase in school failure in children with ALL as compared to a control group , and a significant difference among the three groups of ALL , but the school failure is more in group IIc & to a lesser extent in group IIb as compared to group IIa ,

Table 5
School Failure IQs of Children with Leukemia

The variable		Full scale IQ	Verbal IQ	Nonverbal IQ
Positive School failure No= 13	X	93.2**	100.21**	87**
	(±S.D)	9.08	8.75	10.39
Normal educational skills No= 39	X	108.67	112.33	103.64
	SD	13.95	15.35	12.95
	P	**<0.01	**<0.01	**<0.01

Children with + ve school failure as compared to leukemia children with normal educational - skills there was a significant decrease in FSIQs, PIQs, VIQs in leukemia children.

Table 6
The Prevalence of Anxiety and Depression Symptoms Among
Children with ALL as Compared to Control Group

The variable	Anxiety positive		Depression positive		Total
	No	%	No	%	
group IIa	3	20	3	20	15
group IIb	5	19.2	5	19.2	26
group IIc	5	45.5	5	45.5	11
Toatal	13	25	13	25	52

There was no significant difference in anxiety symptoms among the three groups of children with ALL (group IIa, group IIb, group IIc), but there was a significant difference in depression symptoms among the three groups, these symptoms in more in group IIc with CNS relapse and to a lesser extent in group IIb, also there was a significant increase in depression symptoms in children with ALL group IIc vs group IIa, also between group IIc vs group IIb.

DISCUSSION

The main goal of this investigation was to examine, at various points during the treatment of children with ALL, the effects of intrathecal chemotherapy, cranial irradiation whether prophylaxis or therapeutic on cognitive and non cognitive functioning.

Cognitive functioning

In our study, the cognitive functioning in children who were treated with chemotherapy alone fell within the average range in all aspect except vocabulary, these results agree with the results of Moore et al. (1992) who found that the NP performance in ALL treated without cranial radiotherapy was normal, but many studies have shown that chemotherapy alone even moderate dose of IT administered methotrexate does not appear to have long term effects on higher cognitive functions in children with tumors outside the CNS, (Tramaroff et al. 1982), (Copeland et al. 1985), (Fletcher and Copeland, 1988), (Dowell et al. 1989) and (Copeland et al. 1990), but (Roland et al. 1992), as he examined the off therapy patients who had completed a 3 years course of chemotherapy were

more impaired in tasks of higher order cognitive functioning than were those children whose leukemia diagnoses had been 1 year earlier.

The dose of radiotherapy

However, intelligence scores of children treated with prophylactic or therapeutic cranial irradiation were lower than those treated with chemotherapy alone, the difference was greatest on tests of PIQs, were minimal on VIQs, retrospective studies demonstrated significantly lower mean FSIQs in irradiated patients (Moss et al. 1981), (Roland et al. 1984), (Schliper et al. 1989), (whereas Ivnik et al. 1981) and Whitt et al. (1984) failed to confirm this finding. Among prospective studies Meadow et al (1981), Mulhuren et al. (1991) showed a significant advantage in the non irradiated groups as regard NP function

Our results support a pattern of intellectual and visual-motor integration deficits and a short term memory impairment, this has been reported by Whitt et al. (1984), Kaufman (1975) who found that three subtests, arithmetic (concentration), digit span (short term memory), digit symbol or coding (visual motor)

functioning were the most frequently reported deficit in childhood survivors of ALL. Cartier et al. (1992) found that the most impaired items were digit span & digit symbol, Garcia et al. (1993) found that children irradiated for intracranial tumors experienced deterioration in visual attention and memory, the results of Cousens et al. (1991) indicated that the cognitive processes were affected by CNS prophylaxis for ALL like short term memory, speed of processing, visuo-motor coordination & sequencing ability. Berta et al. (1994) suggested that the primary intellectual capacity in those children was not fully utilized, the PIQs on the average higher than the VIQs.

Appleton et al. (1990) found that those children with ALL treated with combined cranial irradiation -24GY or 30 GY, IT Methotrexate and systemic chemotherapy, their performance was significantly impaired in NP tests designed to assess concentration & short term memory. It is now well documented that certain group of children with ALL are more liable to develop NP difficulties when was given higher doses of irradiation this was observed in a study by Mulhern et al. (1987) who examined the toxicity of CNS irradiation administered in excess of 24 GY due to CNS relapse, they found severe NP deficits among a majority of these children. Reitan (1974) reported that the performance scale items especially digit symbol, coding are specifically among relapsed children who have been exposed to the damaging effects of cranial radiotherapy. Christie et al. (1994) concluded that the neurological and NP morbidity is significantly increased by the cranial irradiation after the relapse of leukemia.

The gender

On studying the sex difference, there was no gender discrimination as regards

IQs except in comprehension subtests of VIQs in group with CNS relapse treated with high dose of cranial irradiation, Schliper et al. (1989) found that irradiated girls scored lower than boys in most measures including Wechsler FSIQs, PIQs. (Waber et al. 1990) believed that sex differences were indicative of a fundamental interaction between postnatal neural development and other biological processes. Several hypotheses may account for the sex difference, first: females may be more sensitive or responsive to one or more of the treatment agents (Niemeyer et al., 1985), second: the apparent link between physical growth & behavioural functions, both of which are most dramatically affected females treatment at young ages, implicates an endocrine-related mechanism, interference with the development of hypothalamic control mechanism may affect subsequent brain development (Gechwind and Gulaburda, 1985), third: the observed differences may be a function of sex-related differences in maturation (Hicks and D'Amato 1978), since females generally mature more rapidly than males, a hypothesis based on generalized rate of maturation would predict that young females would be most vulnerable to treatment toxicity (Taylor and Ousted, 1972).

Age at diagnosis and irradiation

Nearly always there have been found to be primary risk factors for NP sequelae in ALL patients (Eiser and Landsdown, 1977) among their childhood ALL survivors found NP sequelae only within those children diagnosed prior to the age of 5, this finding has been replicated many times (Kato et al. 1993), Kingma et al. 1993), the reason for this age specificity may be the extent of myelination occurring in the younger child, this determines subsequently the degree to which this process is disrupted by the

CNS therapy, older children who have a significant degree of myelination already completed have few if any neurologic or NP sequelae (Gamis and Nesbit, 1991), this effect was reported by Jannoun (1983) who found that with increasing age (0-3, 3-6, and greater than the age of 6) the risk of intellectual dysfunction diminished. This has been observed in CT scan abnormalities of the CNS in patients previously treated with cranial irradiation (Carli et al., 1985), but (Goldwein et al., 1993) found the risk age was younger than 7 years of age at diagnosis, (Said et al. 1989) stated that the severity of after effects was related to younger age at the time of CNS prophylaxis and to a higher dose of cranial irradiation, but not to the time since CNS prophylaxis.

Irradiation-examination interval

It can be suggested that the earliest changes in IQ secondary to irradiation occur in the performance tests while the longer the duration after irradiation has been given the more marked the changes in VIQs are detected, this agrees with (Gamis and Nesbit, 1991) who found that the cognitive deficits in the long term survivors (>3 years) of childhood ALL as compared to their classmates and siblings but (Moore et al., 1991) stated that the interval between treatment and the emergence of cognitive impairments may be longer after lower CRTX dose and deficits in non verbal areas such as visual-motor integration may appear first before the deficit in verbal areas.

Academic achievement

When assessing for long term neurotoxicity associated with CNS treatment involving CRTX and IT chemotherapy, it is important to ask about specific areas of child's performance in school and to consider the time interval between treatment & follow-up. Cognitive deficits typically do not become apparent until

after ALL therapy has been completed, therefore it is critical that parents understand the importance of long-term follow-up evaluation and of ongoing communication with the child's teachers, the latter may be unaware of the child's previous cancer or of the potential for learning deficits to develop over time as a result of treatment.

Academic achievement and NP function of childhood cancer survivors has been assessed in previous studies (Deasy- Spinetta and Spinetta, 1978), (Lansky et al., 1984), (Moehe and Berg 1985), and (Peckhan et al., 1988) who found that most children with leukemia treated with chemotherapy, radiotherapy demonstrated a pattern of learning strengths and weakness characteristics of the learning disabled.

Tasks requiring freedom from distractibility have been found to be particularly difficult for the child surviving ALL therapy (Goff et al., 1980), (Sawyer et al., 1989) stated that children treated for leukemia are still performing significantly worse at school than matched control group, but (Gregory et al., 1994) showed no differences between cases, siblings or control children in terms of learning disabilities. As a result of this current investigation, it was concluded that there are late effects of CNS radiation that have an impact on academic achievement throughout time. Some children in our study exhibit significant learning deficits requiring special education placements, other children exhibit only minimal learning difficulties. Also (Jain et al., 1993) supported our recommendation that those children need for modification of the schedule of CNS prophylaxis and a comprehensive psychometric evaluation at regular intervals is essential for long term rehabilitation.

Non cognitive function

Changes here can be quite subtle and can be a reflection of cognitive deficits as the patient realizes at same level that they are impaired (secondary to cognitive effects), or may be present without any defect in cognition (primary non cognitive effect). The oncology literature, psychiatric side-effects are often submerged into two category of CNS side effects or combined with behavioral disorders Peterson and (Popkin 1980), Silberfarb et al., (1980). Emotional aspects of the ALL patients such as anxiety, depression, fear, anger, other observable behaviours can be assessed Silberfarb and Gear (1982).

Bishery et al. (1977) found that ALL cases were commonly associated with psychiatric manifestations in 77% of cases in contradistinction to Hodgkin or controls. Fergusson (1981) found that approximately third of cancer cases were significantly depressed, but Wrona Polanska (1989) had shown that the highest level of anxiety leads to disintegrated self-concept, while repression technique of anxiety reduction lead to compensation self-concept, both play a role in adaptive process. Sheryl (1992) suggested that self-reported of a health status of the survivors more passive than their peers and they reported more worries surrounding cancer related illnesses. Lesko and Holland (1990b) showed anxiety in cancer setting can be acute (related to disease itself or treatments), chronic or consequences of disorders that antedate and are exacerbated by patient's leukemia. In current study children with ALL with CNS relapse were found to have a significant increase in depression as compared to those without CNS relapse. In our opinion regarding this issues that in any child, psychological development is influenced both by the child's own temperamental and physical

characteristics, and by environmental circumstances he encounters. Children were suffering from long-standing illness face difficulties in their lives, at home and at school, which healthy adaptive patterns may respond with behaviour leading to a new and different family adaptive equilibrium which has its repercussion on the child.

Conclusion

Cognitive and non cognitive sequels in children with leukemia has its impact by disease itself, by chemotherapeutic agents and to higher extent by cranial irradiation particularly with high dose when it is given at a young age.

Recommendation

The goal is to provide a complete therapeutic program that include both cure of the child's cancer & reattainment of their original quality of life. It is hoped that by reducing the dose of cranial irradiation in CNS preventive therapy or avoiding it, less intellectual impairment will be seen in the future.

Emotional changes of the patients need to be assessed regularly for further supportive psychotherapeutic or psychopharmacological treatment, because of high incidence of depression symptoms in leukemia children with CNS relapse, cases of depression must be investigated carefully and regularly for possibility of CNS involvement.

To detect NP disorders, IQ tests must be done before the starting of treatment and regularly every year - after finishing the treatment.

The ideal educational setting would provide learning aids to overcome the areas of deficit specific to each child.

REFERENCES

- Abd El - Fattah K. (1988) : Depression scale for children D. (CDI). Dar EL- Nahda. Egypt . Book shop. Cairo.
- Abd EL Hamied M. and El-Nial M. (1991): Differences between anxiety and depression in children with rheumatic heart disease and in normal children 4th. Egypt Conference for Egypt children .
- Appleton, R.E.; Farrell, K.; Zaid, J.; Rogers, P. (1990): Decline in head growth and cognitive impairment in survivors of acute lymphoblastic leukemia. *Arch Dis Child* 65 (5) 530-4.
- Berta, J.; Roman, K.; Ciril. K.; Gabruea, P.; Lorna.Z.; and Tozica, A. (1994): Late sequelae in children treated for brain tumors & leukemia *Acta- oncologica* vol 33 No 2 pp 159-64.
- Bishry, Z.; Kamel, M.; Abd El-Fatah, S.; Khalifa, A.S (1977): Psychiatric study of acute leukemia in children . The Gazette of the Egypt . Ped Ass . (25), 259-266.
- Carli, M.; Perilongo, G.; Laverda, A. M. Dri- go, P.; Casara, G. L.; Martin, G. (1985): Risk factors in long term sequelae of CNS prophylaxis in successfully treated children with acute lymphoblastic leukemia. *Med. Pediat. Oncol.* 13: 334-340.
- Cartier, L.; Araya, F.; Castillo, J. L.; Ruiz, F.; Gormaaz, A.; Tajima, K. (1992): Progressive spastic paraparesis associated with human T- cell leukemia virus type (HTLV-I). *Intern. Med.* 31 (11) : 1257-61.
- Caveness, W. F. (1980): Experimental observations : delayed necrosis in normal monkey brain . In Gilbert H A , Kagan A R, eds . Radiation damage to the nervous system .New York N Y Revan , press 1 : 58.
- Chessells, J. M. (1983): Childhood acute lymphoblastic leukemia . Recent advances in biology and therapy . *Blood* ; 53:369-378.
- Christia, D.; Leiper, A.; Chessells, J.; Vargha -Khadem, F.; Neville, B. G. R (1994): Neuropsychological and neurological outcome after relapse of lymphoblastic leukaemia . *Arch. Dis. Child* 70: 275-280
- Copeland, D. R.; Dowell, R. E.; Fletcher, J. M.; Pfefferbaum- Levine, B.; Jaffe, N.; Ried, H.; Maor, M (1985): Neuropsychological sequelae of childhood cancer in long term survivors . *Pediat.* 75: 745-53
- Copeland, D. R.; Moore, B. D.; Francis, D.; Dowell, R. E.; Fletcher, J. M (1990): Central and peripheral nervous system effects of cancer treatment on children. A longitudinal study *J. Clin. Exp. Neuropsych.* 12 : 77.
- Cousens, P.; Ungerer, J. A.; Grawford, J. A.; Stevens, M. M (1991): Cognitive effects of childhood leukemia therapy ; a case for four specific deficits . *J. Pediat. Psychol.* 16(4): 475-88.
- Deasy Spinetta, P. and Spinetta, J. (1978) : The child with cancer in school . *Am. J. Pediat.* *Hemat. Oncol.* 2: 89.
- Dowell, R. E.; Copeland, D. R.; Judd, B.W (1989): Neuropsychological effects of chemotherapeutic agents. *Dev. Neuropsychol.* 5: 17-24.
- Duffy, B.G. and Civin, C.I. (1993): Pediatric leukemias and lymphomas . In Current therapy in oncology. 527-537.
- Eiser, C. (1978): Intellectual abilities among survivors of childhood leukemia as a function of CNS irradiation . *Arch. Dis. Child* 58: 391-29.
- Eiser, C. and Lansdown, R. (1977): Retrospective study of intellectual development. *Arch. Dis. Child* 5: 391-95
- Fergusson, J. H. (1981): Cognitive late effects of treatment for acute lymphoblastic leukemia in childhood *Top. Clin. Nurs* 2 (4) 21-9.
- Fletcher, J. M. and Copeland, D.R. (1988): Neurobehavioural effects of central nervous system prophylactic treatment

- of cancer in child *J Clin Exp Neuropsychol.* **10**: 495-537.
- Gamis, A.S and Nesbit, M. E. (1991): Neuropsychological (cognitive) disabilities in long term survivors of childhood cancer. *Pediatrician* **10**: 11-19.
- Garcia-Perez, A.; NarbonGarcia,J.; Sierrasesumaga, L.; Aguire-Ventallo, M.; CalvManuel, F. (1993): Neuropsychological outcome of children after radiotherapy for intracranial tumours. *Dev. Med. Child - Neurol.* Feb. **35**(2):139-48.
- Geschwind, N.O and Galaburda, A. M. (1985): Cerebral lateralization:biological mechanisms, associations and pathology I :hypothesis and a program for research. *Archives of neurology* **42**: 428-459.
- Giralt, J.; Ortega, J. J.; Olive, T.; Verges, R.; Forio, I.; Salvador, L. (1992): Long term neuropsychological sequelae of childhood leukemia, comparison of two CNS prophylactic regimens *Int J Radiat. Oncol. Biol. Phys.* **24** (1) 49- 53.
- Goff, J. R.; Anderson, H. R.; Cooper, P. F. (1980): Distractability and memory deficits in long term survivors of acute lymphoblastic leukemia *J Dev. Behav. Pediatr.* **1**: 158-163.
- Goldwein, J. W.; Radcliffe, J.; Packer, R. J.; Sutton, L. N.; Lange, B.; Rorke, L. B.; D'Angio, G. J. (1993): Results of a pilot study of low-dose craniospinal radiation therapy plus chemotherapy for children younger than 5years with primitive neuroectodermal tumors. *Cancer*, **71** (8): 2647-52.
- Gregory, K.; Parker, L.;Craft, A. W. (1994): Returning to primary school after treatment for cancer *Pediat. Hematol. Oncol.* Jan. Feb. **11**(1) 105-9.
- Heukrodt ,C.; Powazek, M.; Brown, W. S.; Kennelly, D.; Imbus, C.; Robinson, H.; Schant, S. (1988): Electrophysiological signs of neurocognitive deficits in long term leukemia survivors. *J Pediat. Psychol.*, 223-236.
- Hicks, S. and Dlamto, C. (1978): Effects of ionizing radiation on developing brain and behaviour In Gottlieb G, Ed *Studies on the development of behaviour and the nervous system*, Vol. 4 New York Academic press pp. 36-72.
- International Classification of Disease (1992): ICD-10 Classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines WHO, Geneva.
- Ivnik, R. J.; Colligen, R. C.; Obetz, S. w. (1981): Neurosychological performance among children in remission from acute lymphoblastic leukemia. *Develop Behav. Pediat.* **2**: 29-34.
- Jain, Y.; Choudhry, V. P.; Aryal, S.; Mehta, M. (1993): Neuropsychological abnormalities following CNS prophylaxis in children with ALL. *Indian J Pediat.* Sept. Oct. **60** (5) 675-81.
- Jannoun, L. (1983): Are cognitive and educational development affected by age at which prophylactic therapy is given in acute lymphoblastic leukemia? *Arch. Dis. Child*, **58**: 953.
- Johonson, B. E.; Patrones, N.; Hayes, W. (1990): Neurologic, computed cranial tomographic and magnetic resonance imaging abnormalities in patients with small-cell lung cancer:Further follow-up of 6to 13 years survivors. *J Clin Oncol.* **8**: 48-56.
- Kato, M.; azuma, E.; Ido, M.; Ito, M.; Nii, R.; Higuchi, K.; Ihara, T.; Kamiya, H.; Sakurai, M. (1993): Ten years survey off the intellectual deficits in children with acute lymphoblastic leukemia receiving chemoimmunotherapy. *Med. Ped. Oncol.* **21**(6) 435-40.
- kaufman, A. S. (1975): Factors analysis of the WISC-R at 11 age levels between 6 1/2 and 16 1/2 years *J Consult Clin Psychol.* **43**: 135-47.
- Khalifa, A. S.; Mokhtar, G. M.; Gaballah, M. and El kasheer, I.(1988): Clinico-epidemiological study of acute lympho-

- blastic leukemia in Egypt . Egypt. Heatol. 13(3-6) 167-188.
- Kingma, A.; Mooyaart, E. L.; Kamps, W. A.; Nieuwnhuizen, P.; Wilmink, J. T. (1993): Magnetic resonance imaging of the brain and neuropsychological evaluation in children treated for acute lymphoblastic leukemia at a young age . *Amer J Pediat. Oncol.* 15(2): 231-8.
- Lansky, S. B.; Cirms, N. V.; Lansky, L. L. (1984): Central nervous system prophylaxis :Studies showing impairment in verbal skills and academic achievement . *Am. J. Pediat. Hematol. Oncol.* 6: 183-190.
- Lesko, L. M. and Holland, J. C. (1990a): Psychosocial complications of leukemia In :Henderson E S & Lister T A,(eds) . Leukemia , 5th edn 31 :pp 769-792 W B . Saunders Company . Philadelphia & London.
- Lesko, L. M. and Holland, J. C. (1990b): Psychosocial adjustment in young adult following curative treatment for acute leukemia :a preliminary report USA Medical Conferences / Second National Symposium . Educational Booklet (p 55, abst NoA -22), (Available from leukemia society of America , 733Third Avenue, New York N Y, 10017.
- Meadows, A. T.; Massari, D J, Fergusson , J.; Gordon, J.; Littman, P.; and Mass, K. (1981): Decline in IQ scores and cognitive dysfunction in children with acute lymphocytic leukemia treated with cranial irradiation . *Lancet.* II, 10: 15-1018.
- Moehle, K. A. and Berg, R. A. (1985): Academic achievement and intelligence test performance in children with cancer at diagnosis and one year late . *Dev. Behav. Pediat.* 6: 62-64.
- Moore, I. M.; Kramer, J. H.; Warea, W.; Halberg, F.; Albin. A. R. (1991): Cognitive function in children with leukemia . Effect of radiation dose and time since irradiation . *Cancer.* 68(9): 1913-7.
- Moore, B. D.; Copeland, D. R.; Ried, H.; Levy ,B. (1992): Neuropsychological basis of cognitive deficits in long term survivors of childhood cancer *Arch. Neurol.* 49: 809-817.
- Moss, H.; Nannes, E.; Poplack, D. (1981): The effects of prophylactic treatment of the CNS on the intellectual functioning of children with acute lymphoblastic leukemia *Am.. J. Med.* 71: 47-52.
- Mulhern, R. K.; Ochs, J.; Fairclough, D.; Wasserman, A. L.; Davis, K. S.; Williams, J. M. (1987): Intellectual and academic achievement status after CNS relapse : A retrospective analysis of 40 children treated from acute lymphoblastic leukemia . *J . Clin. Oncol.* 5: 933-940.
- Mulhern, R. K.; Fairclough, D.; Ochs, J. (1991): A prospective comparison of neuropsychological performance of children surviving leukemia who received 18-GY ., 24 GY , or nocranial irradiation *J . Clin . Oncol.* 9 (8): 1348-1356.
- Niemeyer, C. M.; Hitchcock-Bryan, S.; Sallan, S.E. (1985): Comparative analysis of treatment programs for childhood acute lymphoblastic leukemia . *seminars in oncology*, 12: 122-130.
- Pechhan, V. C.; Meadows, A. T.; Bartel, N.; Marrero, O. (1988): Educational late effects in long term survivors of childhood acute lymphoblastic leukemia . *Pediat.* (81) No 1 : 127-133.
- Petrson, L. G.; Popkin, M. K (1980): Neuropsychiatric effects of chemotherapeutic agents for cancer . *Psychosomatics* 21: 141-53.
- Phillips, P. C.; Moeller J. R.; Sidtis, j. J. (1991): Abnormal cerebral glucose metabolism in long term survivors of childhood acute lymphoblastic leukemia . *Ann Neurol.* 29: 263-271.
- Ritan, R. M. (1974): Methodological problems in clinical neuropsychology. *Clinical neuropsychology : current status and ap-*

- plications PP. (19-46). By R M Reitan and L A Davison Winston, Washington, D. C.
- Roland, T. B.; Aqvi, M. S.; Roy, P.; Richard, G.; Red, S. S.; and Abdel Ragab (1992): Chemotherapy for ALL, cognitive and academic sequelae. *J of Pediat.* December, **121**: 855-9.
- Rottenberg, D. A.; Chernike, n. L.; Deck, M. D. F.; Ellis, F.; Ponsler, J. B. (1977): Cerebral necrosis following radiotherapy of extracranial neoplasms. *Ann. Neurol.* **1**: 339-357.
- Rowland, J.; Gildewell, O.; Silbley, R. (1984): Effects of different forms of CNS prophylaxis on neuropsychologic function in childhood leukemia. *J. Clin. Oncol.* **2**: 1327-1335.
- Said, J. A.; Stevens, P.; Waters, B. G.; Cousens, P. (1989): Neuropsychological sequelae of CNS prophylaxis in survivors of childhood ALL. *J. Const-Clin -Psychol.* April, **57** (2): 251-6.
- Sawyer, M. G.; Toogood, I.; Reice, M.; Haskell, C.; Bashurst, P. (1989): School performance and psychological adjustment of children treated for leukemia. A long term follow up. *Amer. J. Pediat. Hematol. Oncol.* Summer, **11**(2): 146-52.
- Schliper, A. F.; Esseltine, D. W.; Tarshis, M. A.; (1989): Cognitive function in long term survivors of childhood acute lymphoblastic leukemia. *Pediat. Hematol. Oncol.* **6**: 1-9.
- Sheryl, L. L. (1993): Views of childhood cancer survivors. *Cancer supplement.* May 15, Vol 71 No **10**: 3354-72.
- Silberfarb, P. M. (1983): Chemotherapy and cognitive defects in cancer patients. *Ann. Rev. Med.* **34**: 35-46.
- Silberfarb, P. M. and Greere, S. (1982): Psychological concomitants of cancer. *Clinical aspects. Amer. J. Psychother.* in press.
- Silberfarb, P. M.; Philibert, D.; Levine, P. M. (1980): Psychological aspects of neoplastic disease II Affective and cognitive effects of chemotherapy in cancer patients. *Amer. J. Psychiat.* **137**: 597-39.
- Tameroff, M., m.; Miller, D. R.; Murphy, M. L. (1982): Immediate and long term post-therapy neuropsychological performance in children with acute lymphoblastic leukemia. *J. Pediat.* **101**: 524-529.
- Taylor, D. C. and Ounsted, C. (1972): The nature of gender differences explored through onogenetic analysis of sex ratios in disease. In Ounsted C Taylor D (eds) *Genderdifferennces : Their ontology and significance* Edinburgh : Churchill Livingstone. PP. 215-240.
- Waber, D. P.; Urion, D. K.; Trabell, N. J.; Niemeyer, C.; Gelber, R.; and Sallan, S. E. (1990): Late effects of central nervous system treatment of acute lymphoblastic leukemia in childhood are sex dependent. *Develop. Medicine Neurology* **32**: 238-248.
- Whitt, J. K.; Wells, R. J.; Laurie, M. M. (1984): Cranial radiation in childhood acute lymphoblastic leukemia Neuropsychological sequelae. *Am. J. Dis. Child* **138**: 730-736.
- Wrona-Polenska, H. (1989): Methods of defense against anxiety and self concept of patients with leukemia. *Pol. Tyg. Lek* **44** (20): 446-8.

Le fonctionnement cognitif et Non cognitif chez les enfants souffrant de leucaemie et traité avec de l'irradiation

Cette étude a comme bute d'examiner le fonctionnement cognitif et non-Cognitif à different stages du leucaemie et les effets possibles du traitementet.

L'échantillon est pris sur 52 enfants, divisés en 3 groupes:

groupe (1): les enfants reçus chemotherapic

group (2): les enfants reçus chemotherapic + prophylactique irradiation craniale 24 Gy.

groupe (3): les enfants reçus craniospinal irradiation curative (les enfants avec relapse au systeme Nervaux - cranial)

Ses trois groupes sont compares avec des groupes des enfants contrôlé, ayant même age, sexe, (Niveau économiques social) et les echelles utilisés sont WISC-R pour examiner QI, CAS pour examiner l'anxiété, CDI pour examiner la depression et un entretien clinique semi-structuré basé-çelon ICD-10 les resultats de cette étude confirme qu'il ya une relation entre les changement au fonction cognitive Non cognitive avec la maladie elle même, les agents chemotherpautiqués et specialement l'irradiation craniale 9au grande proportion).