ORIGINAL RESEARCH

GROWTH AND PUBERTY AFTER TREATMENT FOR ACUTE LYMPHOBLASTIC LEUKEMIA

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Over the last 20 years, after combining treatment of chemotherapy and radiotherapy, there has been an improvement in the survival rate of acute lymphoblastic leukemia patients, with a current cure rate of around 70%. Children with the disease have been enrolled into international treatment protocols designed to improve survival and minimize the serious irreversible late effects. Our oncology unit uses the international protocol: GBTLI LLA-85 and 90, with the drugs methotrexate, cytosine, arabinoside, dexamethasone, and radiotherapy. However, these treatments can cause gonadal damage and growth impairment**.**

PATIENTS AND METHOD: The authors analyzed 20 children off therapy in order to determine the role of the various doses of radiotherapy regarding endocrinological alterations. They were divided into 3 groups according to central nervous system prophylaxis: Group A underwent chemotherapy, group B underwent chemotherapy plus radiotherapy (18 Gy), and group C underwent chemotherapy plus radiotherapy (24 Gy). Serum concentrations of LH, FSH, GH, and testosterone were determined. Imaging studies included bone age, pelvic ultrasound and scrotum, and skull magnetic resonance imaging.

RESULTS: Nine of the patients who received radiotherapy had decreased pituitary volume. There was a significant difference in the response to GH and loss of predicted final stature (Bayley-Pinneau) between the 2 irradiated groups and the group that was not irradiated, but there was no difference regarding the radiation doses used (18 or 24 Gy). The final predicted height (Bayley-Pinneau) was significantly less (P = 0.0071) in both groups treated with radiotherapy. Two girls had precocious puberty, and 1 boy with delayed puberty presented calcification of the epididymis.

CONCLUSION: Radiotherapy was been responsible for late side effects, especially related to growth and puberty.

KEY WORDS: **Endocrine dysfunction in lymphoblastic leukemia. Growth and acute leukemia. Puberty in lymphoblastic leukemia.**

Advances in oncologic therapy have increased the survival rates of childhood acute lymphoblastic leukemia (ALL), but the aggressive nature of chemotherapy (ChT) and radiotherapy (RT) can damage normal tissues and hence affect the endocrine glands, leading to hormonal dysfunctions. Among other effects, the iatrogenic effects of treatment may affect growth and puberty. In treatment for ALL, different protocols have been designed to improve survival and minimize late effects. It seems as though the younger the patient, the greater the potential for late effects of treatment[1,2].

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The objective of this paper is to relate the influence of the basic disease, the age of child, as well as the treatment (ChT and or RT) on growth and puberty according to the different protocols used in our unit.

PATIENTS AND METHOD

Twenty patients (12 boys, 8 girls)

were sequentially studied, all treated for ALL, being in remission at least for 2 years. Their ages ranged from 8 to 17 years at the endocrinological evaluation (Table 1). None of them had initial central nervous system involvement. Nine of them were older than 12 years. The patients were enrolled into an international protocol (GBTLI LLA-85 and 90) for 2.5 years. They were divided into 3 groups according to CNS prophylaxis: A) 5 patients underwent ChT (intrathecal methotrexate, cytosine, arabinoside, and dexamethasone); B) 6 patients underwent ChT plus RT with 18 Gy; and C) 9 patients underwent ChT plus RT with 24 Gy.

Serum concentrations of LH, FSH, GH, and testosterone were determined by immunofluorometric assay (IFMA) using commercially available kits (Delphia-Pharmacia Diagnostic) after stimulation with GnRH, glucagon/insulin, and hCG, respectively. The cut-off limits of GnRH-stimulated LH to distinguish prepubertal and pubertal subjects were 9.6 IU/L in boys and 6.9 IU/L in girls[3]. Normal response for testosterone was considered to be >160 ng/dL or >150 ng/dL above basal levels. Seventeen patients underwent 2 tests for GH, and the remaining 3 underwent only 1 test. A normal response for GH after stimulation was considered to be ³10 ng/dL[4]. Imaging studies included bone age (Greulich-Pyle), pelvic ultrasound, and scrotum and skull magnetic resonance imaging (MRI). We determined the pubertal stage using the Tanner criteria, and we defined growth deficiency as height below the 3rd percentile or –2.0 SD (NCHS).

RESULTS

In 9 of the patients who received RT, mainly in group C (24 Gy) the pituitary volume as determined by MRI was decreased. In 13 out of 15 patients from groups B and C, and 1 from group A, stimulation tests revealed a low GH response: peak <5.7 ng/mL. Both groups B and C had low height after RT regardless the dose used (18 or 24 Gy). Groups B and C had low GH response to glucagon, which was significantly different when compared to group A (P = 0.0087). No difference was observed between groups B and C. The final predicted height (Bayley-Pinneau) was significantly less (P = 0.0071) in both groups treated with RT, compared to group A. Groups B (60%) and C (83%) had a lower growth ve-

Table 1 - Anthropometric growth and pubertal data of the children.

														LHRH Test		HCG Test	Estradiol	Progester	US
	Name	Sex	O. T.	CA	BA	Weight	Height	Pubertal Stage	GV	Target Height	GH Stimulation Test	IGF-1	MRI	LH (UI/L)	FSH (UI/L	Testost. (ng/dL)	(pg/mL)	(nmol/L)	Abdomen
			(years)	(years)	(years)	(percentile)			cm/year	(percentile)	Peak GH (ng/mL)	(ng/dL)	(Brain)	Peak	Peak	Peak			Pelvis
Group A	L.S.F	F	6.5	12.6	12.0	25-50	50-75	B3 P4	8.0	25-50	14.0	582	normal	43	9.1	...	54	0.2	Normal
	L.M.F	F	2.0	8.0	11.0	50	75	B3 P2	5.0	25-50	7.7	184	Stalk deviation	5.0	9.4	...	6.8	0.3	Normal
	V.N.S.	M	6.5	12.4	12.0	25-50	50	P2 G3	7.0	10-25	12	338	normal	22.0	2.4	1160	...	...	Normal
	T. S.	F	5.5	10.6	13	> 97.5	> 97.5	B2 P4	4.0	75	27	449	Bulging Pituitary	35.0	9.5	...	76.6	0.4	Normal
	F.A.S	M	3.5	10.6	8.5	90	3-10	P1 G1	3.5	3-10	14	530	Normal	4.8	2.4	400	...	...	...
Group B	J.A.R.L.	M	4.0	8.5	6.0	10	3	P1 G1	3.5	75	4.3	...	Normal	2.5	9.1	326	...	...	Normal
	F.R.V.	M	2.5	15.75	14.5	10-25	10-25	P5 G5	8.5	25-50	7.0	133	↓Pituit	12	9.4	1440	...	...	Normal
	A.G.S.	M	4.0	9.0	10.0	3-10	< 3	P1 G1	4.0	...	7.7	57	↓Pituit	2.6	2.4	114	...	...	Normal
	D.B.S.	M	5.5	10.0	9.5	10-25	3-10	P1 G1	7.0	25	9.7	150	↓Pituit	7.9	9.5	413	...	...	Normal
	A.M.	M	12	17.0	14.0	25-50	10	P3 G2	2.5	10-25	1.0	...	Normal	...	...	46	...	...	Calcif. Epipidymus
	E.V.N.	M	9.0	13.25	11.5	25-50	< 3	P2 G2	...	50-75	5.8	...	Normal	17.9	3.7	802	...	...	Normal
Group C	W.B.B.	M	5.5	12.75	11.5	10-25	3	P1 G3	8.5	25	1.9	141	↓Pituit	23	6.6	934	...	...	Normal
	J.E.L.	M	4.5	11.75	11.5	50	10	P2 G2	1.0	50-75	2.8	155	↓Pituit	8.7	1.8	573	...	...	Normal
	R.S.S	M	5.5	13.25	11.0	3-10	< 3	P1 G2	...	25 - 50	2.8	...	↓Pituit	17	3.7	943	...	...	Normal
	R.K.	M	8.5	14.7	14.0	10-25	< 3	P3 G3	1.5	10	7.2	208	Pineal Cyst	49	5.3	1350	...	...	Normal
	F.C.	F	6.5	15.4	15.0	25	3-10	B5 P4	...	50-75	6.8	430	Normal	19	6.7	...	34	0.5	Normal
	E.M.	F	6.5	11.25	11.0	25-50	3-10	B3 P2	3.5	10 - 25	4.3	407	↓Pituit	49	14	...	46	0.6	Enlarged Uterus
	C.L.	F	8.5	12.4	13.0	90-97.5	< 3	B4 P2	4.5	10 - 25	5.5	189	↓Pituit	26	4.4	...	173	2.5	Normal
	T.C.G.	F	5.0	12.5	9.5	3	< 3	B1 P1	...	10 - 25	9.6	210	Calcific. Basal Nucleus	...	...	...	...	0.5	Normal
	T.N.	F	3.0	12.9	15.0	10-25	< 3	B4 P4	2.0	10 - 25	5.3	166	↓Pituit	22	12.2	...	...	...	Enlarged Spleen

Group A - True Basic Risk - no RT; Group B - Basic Risk - 18 Gy RT; Group C - High Risk - 24 Gy RT; OT: out of therapy; CA: chronological age; BA: bone age; GV: growth velocity; TH: target height; US: ultrasound; MRI: magnetic resonance image; GH: stimulation test; glucagon and/or clonidine test; N: normal; Calcif E: calcification of the epididymis

locity compared to group A (20%).

On the other hand, concerning the impact of cytotoxic agents on gonadal function and pubertal development in this study, 2 girls had precocious puberty (groups A and C) and one 17-yr-old boy with epididymis calcification had delayed puberty (stimulated testosterone was 46 ng/dL). All of the 15 pubertal patients showed normal basal and peak LH and FSH levels after the GnRH test.

DISCUSSION

The aggressive nature of ALL therapy is responsible for neoplastic cell eradication, but the iatrogenic effects can affect the child's growth and normal endocrine functions, leading to pituitary and gonadal deficiencies[4-8]. The consequences are especially severe in children, since developing tissue is highly susceptible to damage. The drugs can cause precocious toxic effects, but the late effects are mainly due to RT[9-11] .

Children who were very young at the time of irradiation tend to develop sequelae such as growth impairment and early puberty[12,13]. Only one 3-year-old girl among the 5 patients of the group A showed low levels of GH and a reduction in predicted final height. The GH stimulation test revealed significantly different levels of the hormone between irradiated and non-irradiated groups (P = 0.0087), although no difference was found regarding the dose of radiation. We observed a reduction in predicted final height (Bayley-Pinneau) of the ChT plus RT-treated as compared to the ChT-treated groups (P = 0.0071), but we found no difference with regard to the dose of radiation.

Thirteen of the 14 GH deficient patients belonged to the irradiated group, and 10 of them had significant height loss predictions. The 2 patients who had the most severe short stature (Bayley-Pinneau) were girls irradiated with 24 Gy before 8 years of age. Some authors have concluded that the severe late sequelae of radiation therapy are dose related. However, there is no consensus about the correlation between the dose of 18 Gy or 24 Gy of irradiation and the sequelae. In this study, in spite the fact that 16 patients had low GH levels in 2 stimulating tests, only 6 of them had a loss of predicted height, probably because they were exposed to lower doses (18 or 24 Gy) of cranial irradiation. Nevertheless, it is well known that the hypothalamus appears to be more radiosensitive than the pituitary gland, and the GH deficiency seems to result from disruption of the GHRH/somatostatin feedback mechanisms[14]. Evidence suggests that of all the pituitary hormones, GH is the most radiosensitive, showing impaired 24-hour profiles[14]. Some of these children can benefit from GH therapy. The success of the therapy depends on the age and puberty stage of these children.

The MRI showed some alterations in 13 patients: small pituitary (9 patients), stalk deviation, pineal cyst, bulgy pituitary, and basal nucleus calcification (1 each). Eight of these patients had been exposed to 24 Gy.

After treatment for ALL with low doses of cranial irradiation, girls appear to be particularly susceptible to the development of precocious puberty. The earlier growth spurt at puberty can mask the growth impairment in these children.

Ovarian development in girls treated for ALL may be affected by cytotoxic agents[15]. Girls treated with either craniospinal or abdominal irradiation for ALL may develop abnormalities of both LH and FSH[16]. They can experience precocious or delayed puberty. Two boys presented low testosterone responses to hCG, and 1 of them presented calcification of the epididymis, delayed puberty, and delayed bone age without growth impairment. One girl had an enlarged uterus and LH peak level of 35UI/mL. Two girls showed clinical signs of early puberty.

In conclusion, the groups that underwent RT showed significant growth impairment irrespective of the dose of irradiation (18 or 24 Gy). The impact on pubertal development was apparently less pronounced. It is important to remember that the group that needed RT had the most severe form of disease, and we cannot rule out the impact of the disease itself on these hormonal dysfunctions. It is important to keep in mind that since leukemia is a treatable disease, dysfunctions, especially on growth, cannot be underestimated, and short stature is an important sequelae that needs treatment whenever detected.

RESUMO

ALVES CHB da S e col. - Crescimento e puberdade após tratamento da leucemia linfoblástica aguda. **Rev. Hosp. Clín. Fac. Med. S. Paulo 59**(2):67-70, 2004.

Nos últimos 20 anos, após o tratamento de pacientes portadores de leucemia linfoblástica aguda, com quimioterapia e radioterapia, houve melhora na taxa de sobrevivência e cura em torno de 70%. Crianças portadoras da doença foram envolvidas em protocolos de tratamento internacionais que visavam melhorar a sobrevida e minimizar os graves e irreversíveis efei-

tos tardios. A nossa unidade utiliza o protocolo internacional GBTLI LLA-85 e 90, com as drogas metrotexate, citosina, arabinoside, dexametasona e radioterapia .Entretanto, estes tratamentos podem causar insuficiências gonadais e prejuízo no crescimento.

PACIENTES E MÉTODO: Os autores analisaram 20 crianças fora de terapia a fim de determinar o papel das várias doses de radioterapia sobre alterações endocrinológicas. Foram divididos em três grupos baseados na profilaxia do sistema nervoso central: o grupo A foi submetido à quimioterapia, o grupo B à quimioterapia mias radioterapia (18Gy) e o grupo C à quimioterapia mais radioterapia (24 Gy). Foram avaliadas as concentrações séricas de LH, FSH, GH e testosterona. Os estudos de imagem incluiram idade óssea, ultrassonografia pélvica, escrotal e ressonância nuclear magnética do crânio.

RESULTADOS: Houve diferenças significativas nas respostas do hormônio de crescimento e prejuízo na estatura final (Bayley-Pinneau) entre os dois grupos irradiados e o grupo que não foi irradiado, mas não houve diferenças quando se compararam as doses de radiação utilizadas (18 ou 24 Gy). A previsão da altura final (Bayley-Pinneau) foi menor (p= 0,0071) nos dois grupos tratados com radioterapia. Duas meninas apresentaram puberdade precoce e um menino teve atraso puberal associado a calcificação do epidídimo.

CONCLUSÃO: A radioterapia é responsável por efeitos colaterais especialmente quanto ao crescimento e puberdade.

UNITERMOS: **Disfunção endócrina na leucemia linfoblástica. Crescimento e leucemia aguda. Puberdade na leucemia linfoblástica.**

REFERENCES

1. Sklar CA. Overview of the effects of cancer therapies: the nature, scale and breadth of the problem. Acta Paediatr 1999; (Suppl 433):1-4.

2. Groot-Loonen JJ, Van Setten P, Otten Bj, Van't Hof Ma, Lippens RJJ, Stoelinga GBA. Shortened and diminished pubertal growth in boys and girls treated for acute lymphoblastic leukemia. Acta Paediatr 1996; 85:1091-1095.

3. Brito VN, Batista ML, Borges MF, Latronico AC, Kohek MBF, Thirone ACP et al. Diagnostic value of fluorometric assays in the evolution of precocious puberty. J Clin Endocrinol Metab 1999; 84:3539-3544.

4. Reiter OE, Rosenfeld RG. Normal and aberrant growth. In Wilson J D, Foster DW, Kronenberg Hm, Larsen Pr eds. Williams Textbook of Endocrinology W B Saunders Company; Philadelphia USA 1998; 1427-1507 .

5. Siris ES, Leventhal BG, Vaitukaitis JL. Effects of childhood leukemia and chemotherapy on puberty and reproductive function in girls. N Engl J Med 1976; 294:1143-1146.

6. Lannering B, Rosberg S, Marky C, Möellt C, Albertsson-Wikland K. Reduced growth hormone secretion with maintained periodicity following cranial irradiation in children with acute lymphoblastic leukemia. Clin Endocrinol 1995; 42:153-159.

7. Cicognani A, Cacciair E, Rosito P, Mancini AF, Caarla G, Mandini M, Paoluci, G. Longitudinal growth and final height in long-term survivors of childhood leukemia. Eur J Pediatr 1994;153:726-730.

8. Ochs J, Mulhern R. Long-term sequelae of therapy for childhood acute lymphoblastic leukemia. Bailliers Clin Haematol 1994; 7:365-376 .

9. Adan L, Souberbielle J C, Blanche S, Leverger G, Schaison G, Brauner R. Adult height after cranial irradiation with 24 Gy: factors and markers of height loss. Acta Paediatr 1996; 85:10996-1101.

10. Ahmed SF, Wallace WHB, Kelanl CJH. An anthropometric study of children during intensive chemotherapy for acute lymphoblastic leukemia. Horm Research 1997; 48:178-183.

11. Leiper A, Grant DB, Chessells JM. Gonadal function after testicular radiation for acute lymphoblastic leukemia. Arch Dis Child 1986; 61:53-56.

12. Davies H A, Didcock E, Didi M, Ogilvy-Stuart A, Wales J K, Shalet S M - Disproportionate short stature after cranial irradiation and combination chemotherapy for leukemia. Arch Dis Child 1994; 70:472-475.

13. Holm K, Nysom K, Hertz H, Müller, J - Normal final height after treatment for acute lymphoblastic leukemia without irradiation. Acta Paediatr 1994; 83; 1287-1290.

14. Shalet SM, Clayton PE, Price DA. Growth and pituitary function in children treated for brain tumors or acute lymphoblastic leukemia. Horm Res 1988; 30:53-61.

15. Shalet SM. Disorders of gonadal function due to radiation and cytotoxic chemotherapy in children. Adv Intern Med Pediatr 1989; 58:1-21.

16. Leung W, Hudson M, Zhu Y.Rivera GK, Ribeiro RC, Sandllund JT et al. Late effects in survivors of infant leukemia. Leukemia 2000; 14:1185-1190.