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Long-term follow-up of hormonal function and growth in patients who received hematopoietic stem cell transplantation in their childhood or adolescence

Późne powikłania ze strony układu endokrynnego, wzrastanie i rozwój pacjentów po przeszczepieniu komórek hematopoetycznych

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ABSTRACT/*STRESZCZENIE*

The aim of this paper is to present the long-term impacts of HSCT procedures on the hormonal functions, the growth and development of pediatric patients after HSCT. **Material and methods.** We analyzed 57 patients (M=30, F=27). At the HSCT and annually during the follow-up period, visits at the endocrinology department were carried out according to EBMT recommendations for screening for late complications of HSCT: anthropometrics and pubertal status were assessed and hormonal tests performed. **Results.** There were no significant differences in mean HtSDS at HSCT and follow-ups in first three years post transplant. In the group of patients with follow-up period > 4 years, an average increase in HtSDS was noticed. Mean HVSD did not change during follow-up period. GHD was confirmed in 3/57 patients. Obesity and overweight was diagnosed in 8/57 patients. Gonadal dysfunction was diagnosed in 40,74%girls and 13,34% boys, presenting as hypergonadotropic hypogonadism with elevated FSH and LH or delayed pubertal development. The prevalence of gonadal dysfunction did not depend on conditioning regimen. There was no evidence of gonadal recovery in any of the patients during the follow-up period. 3,51% patients were found to have thyroid dysfunction: hypothyroidism (1 patient) and thyrotoxicosis (1 patient). An adrenal dysfunction was observed in 15,78% patients and in 8,77% subjects the glucose metabolism was impaired. **Conclusions**. In pediatric patients after HSCT endocrine disorders with growth and development impairment occur frequently post transplantation. In our study gonadal dysfunction in girls was a prominent complication of this procedure. Pediatr. Endocrinol. 11/2012;1(38):9-16.

Celem pracy była ocena odległych następstw leczenia przeszczepieniem komórek hematopoetycznych (HSCT) w dzieciństwie w zakresie układu hormonalnego, wzrastania i dojrzewania. **Materiał i metody.** Do badania włączono 57 pacjentów (M=30, F=27). Przed HSCT i corocznie w ciągu okresu obserwacji prowadzono konsultacje endokrynologiczne wg zaleceń EBMT: przeprowadzano pomiary antropometryczne, oceniano stopień dojrzewania płciowego i wykonywano badania hormonalne. **Wyniki.** Nie odnotowano istotnej statystycznie różnicy pomiędzy średnim HtSDS w czasie pierwszego badania (HSCT) i w ciągu pierwszych trzech lat obserwacji. W grupie pacjentów z okresem obserwacji przekraczającym 4 lata obserwowano wzrost HtSDS. Średnia HVSD nie zmieniła się w ciągu obserwacji. Somatotropinową niedoczynność przysadki rozpoznano u 3/57 pacjentów. Otyłość i nadwaga występowała u 8/57 pacjentów. Dysfunkcję gonad rozpoznano u 40,74% dziewcząt i 13,34% chłopców, głównie był to hipogogonadyzm hipergonadotropowy z podwyższonym stężeniem FSH i LH oraz opóźnione dojrzewanie płciowe. Częstość występowania dysfunkcji gonad nie zależała od schematu kondycjonowania. W czasie obserwacji u żadnego pacjenta nie zaobserwowano regeneracji gonad. U 3,51% pacjentów rozpoznano dysfunkcję tarczycy: niedoczynność tarczycy u jednego pacjenta i nadczynność tego gruczołu w jednym przypadku. Dysfunkcję kory nadnerczy stwierdzono u 15,78% badanych, natomiast nieprawidłową tolerancję glukozy u 8,77%. **Wnioski.** Częstość występowania zaburzeń endokrynologicznych, a także wzrostu i dojrzewania płciowego u pacjentów, którzy w wieku rozwojowym przeszli przeszczepienie komórek hematopoetycznych, jest duża. W naszej obserwacji najczęstszym późnym powikłaniem HSCT była dysfunkcja jajników u dziewcząt. Endokrynol. Ped. 11/2012;1(38):9-16.

Introduction

Hematopoietic stem cell transplantation (HSCT) has improved the prognosis of patients with fatal diseases – both malignancies and nonmalignant disorders. As the number of long-term survivors is increasing, and patients recover from their primary disease, it is important to evaluate the impact of treatment-related toxicity on other organs. Cancer therapy and pre-HSCT preparative regimens consist of cytotoxic drugs as well as irradiation, particularly affecting the endocrine function. In consequence, growth and development disorders may occur [1–3].

In this study we analyzed 57 patients who underwent HSCT for various diseases in one of HSCT center in Wrocław. The aim of this paper is to present the results of the above study and the impacts of HSCT procedures on the hormonal functions, as well as the growth and development of these patients.

Patients and methods

We investigated 57 patients (30 males, 27 females) who underwent HSCT at the Department of Pediatric Bone Marrow Transplantation, Oncology and Hematology, Medical University of Wrocław between 1996 and 2006 and survived at least one year after HSCT. During the follow-up period, all studied patients were scheduled for several visits at the Department of Endocrinology and Diabetology for Children and Adolescents, Medical University of Wrocław. These were carried out according to EBMT recommendations for screening for late complications of HSCT [4].

None of the patients was either diagnosed or treated for any hormone and/or growth and/or development disorder before HSCT.

Patient characteristics are shown in Table I.

Anthropometrics and pubertal status assessment

Height (Ht) and weight (Wt) measurements were assessed at diagnosis, at HSCT and during each follow-up visit using a Harpenden stadiometer and a electronic scales. The body mass index (BMI) was calculated with the following formula: Wt/Ht^2 [kg/m^2]. The measurements were converted to SDS values standardized for a given age and sex using Polish reference charts of Palczewska and Niedźwiedzka. Moreover, the height velocity (HV) was calculated using the following formula: -365,25*(Ht2-Ht1)/(No. of Days: Visit 2-Visit1) [cm/yr], all values were converted to SD using Prader charts [5, 6].

The pubertal status was assessed clinically according to Tanner and Whitehouse. [7] In males, testicular volumes were measured with Prader's orchidometer.

Endocrine testing

Hormonal function tests included examination of thyroid function (TSH, fT3, fT4, ATPO), the insulin like growth factor 1(IGF-1), the insulin like growth factor binding protein 3 (IGFBP-3), the secretion status of a growth hormone (GH), estradiol in females and testosterone in males,

Table I. Patients characteristics
Tabela I. *Charakterystyka pacjentów*

Characteristics	No of patients
Sex;	
Males	30
Females	27
Age at HSCT (yr):	
Min	1,21
Max	17,82
Median	9,86
Pubertal stage at HSCT:	
Prepubertal	28
Pubertal	29
Primary Disease:	
Malignant diseases:	
ALL	23
AML	6
CML	7
Others	12
Nonmalignant diseases:	
SAA	6
Others	3
Type of transplant:	
MUD	34
HLA ID SIB	20
HLA MM REL	2
SYNG	1
Follow-up duration after HSCT (yr):	
Min	0,30
Max	11,43
Median	1,85

gonadotropins – follicle stimulating hormone (FSH) and luteinizing hormone (LH), cortisol, insulin, peptide-C, HbA1c concentrations, blood glucose levels were recorded and/or WHO oral glucose tolerance test (OGTT) was performed. If needed, additional hormonal function tests as well as e.g. ACTH and DHEAS levels were examined. All tests were performed using commercially available assays.

Statistical methods

The mean SDS for Ht, Wt and BMI as well as HVSD of the entire group were calculated at HSCT and at follow-up visits annually. Afterwards the results were compared with each other using Student t-test for independent variables.

All statistical analysis was performed using Medcalc statistical software.

Results

Growth and body mass

The group as a whole showed a fall-off in growth after diagnosis with a little evidence of catch-up growth in the following HSCT years. Ten patients (17,54%) (six boys and four girls) had a HtSDS more than -2,0; six of them underwent HSCT in the pre pubertal age. In two boys the short stature was present before initial diagnosis, one of them was diagnosed with X-linked adrenoleukodystrophy (X-ALD). In three patients (one female, two males) with Ht, an efficient catch-up growth of >10th percentile for age and sex was observed at the last follow-up visit. However there were no significant differences in mean HtSDS at HSCT and follow-ups on first, second and third year. The patients were significantly higher after fourth year post

transplantation. Mean HVSD did not change. The data are presented in table II.

The growth hormone secretion status was performed in twenty one patients – all patients with HtSDS <-2,0, and eleven patients with Ht and HV within normal ranges. In eleven patients, the concentration of GH in this test was below norm (<10 ng/ml), in three patients (14,28%) a growth hormone deficiency (GHD) was confirmed with two more diagnostic tests and a low concentration of IGF-1 (<-2,0 SD). GHD was a temporary finding in one patient, and the symptoms withdrew without treatment. IGF-1 and IGFBP-3 levels were within normal ranges in 48/57 patients.

In eight patients (14,03%) (four females, four males) obesity and overweight were found during follow-up visits, with a tendency to body mass reduction.

Detailed data on anthropometric measurements are presented in table III.

Gonadal function

In 15/31 pubertal and post-pubertal patients (48,38%) (eleven girls (40,74%) and four (13,34%) boys) a gonadal dysfunction was present. All patients in that group had clinical symptoms of hypergonadotropic hypogonadism (ovarian or testis failure). In addition, two girls and two boys were diagnosed with a delayed pubertal development. Secondary amenorrhea and symptoms typical for a menopause were identified in eight girls. In males, testicular volumes were within normal ranges for age and pubertal status.

Nine girls and three boys had shown elevated gonadotropin levels (FSH and LH) with lowered estradiol or testosterone respectively. In all cases, a hormone replacement therapy was required.

There was no evidence of gonadal recovery in any of the patients. Two patients underwent orchidectomy, due to primary disease relapse, and before the testosterone replacement therapy.

Prolactin levels in 56/57 studied patients were within normal ranges. In one female patient PRL of 33,7 IU/ml was recorded, however it was asymptomatic.

The prevalence of gonadal dysfunction did not depend on conditioning regimen, as shown in table IV.

Thyroid and adrenal function, glucose metabolism

Among the 57 patients of our study group, two patients (3,51%) were found to have thyroid dysfunction with clinical symptoms. One girl presented with hyperthyroidism with thyroid inflammation with present anti thyroid antibodies

Table II. Results of growth curve model showing the annual change in mean HtSDS and mean HVSD for the whole group (p-values)
Tabela II. *Coroczne zmiany wzrostu i tempa wzrastania (wartości p)*

	At HSCT	1st yr post	2nd yr post	3rd yr post	≥ 4th yr post
HtSDS	–	0,91	0,25	0,35	0,04231
HVSD	–	0,65	0,97	0,28	0,45

Table III. Overall anthropometric measurements referring to different criteria
Tabela III. *Pomiary antropometryczne*

		HtSDS	HVSDS	BMI-SDS
Conditioning regimen:	BUCY vs controls	-1,01 ± 2,48 *vs* -0,49 ± 1,56, $p = 0,36$	-0,09 ± 3,19 *vs* 0,24 ± 2,79 $p = 0,79$	-0,84 ± 1,67 *vs* -2,05 ± 5,77, $p = 0,27$
	TBI vs controls	-0,47 ± 1,58 *vs* -0,86 ± 2,28, $p = 0,55$	-1,06 ± 2,35 *vs* 0,35 ± 3,12 $p = 0,36$	1,27 ± 2,31 *vs* - 1,20 ± 2,89, **$p = 0,015777$**
Disease:	Malignant vs Nonmalignant	-0,72 ± 2,13 *vs* -1,04 ± 2,04, $p = 0,66$	-0,75 ± 2,19 *vs* 3,84 ± 3,61 **$p = 0,0026315$**	-0,15 ± 2,14 *vs* -0,94 ± 2,29, $p = 0,13$

Table IV. Gonadal disorders referring to conditioning protocol
Tabela IV. *Dysfunkcja gonad w zależności od schematu kondycjonowania*

	n	*p*-value
BUCY vs others	10/25 *vs* 5/32	0,45
TBI vs others	3/13 *vs* 12/44	0,16
BUCY vs TBI	10/25 *vs* 3/13	0,082
Others vs BUCY+TBI	2/19 *vs* 13/38	0,081

(aTPO Ab, TgAb, TRAb) two years after HSCT. She was administered antithyroid drugs, glucocorticoids and propranolol. At the last follow-up visit she still required antithyroid drugs. The HSCT was conducted in her 6,5yrs of age due to SAA. She was conditioned with TREO, CY and ATG protocol. A second patient, also a female, presented with secondary hypothyroidism, and was administered levothyroxine. She had two HSCT procedures done in her 17 and 17,8yrs of age due to AML M4. She was conditioned with following protocols: BU, MEL and TREO, FLU, MEL, ATG. Moreover, in five patients (9,61%) aTPO antibodies were present in measurable concentration, however only one was clinically significant.

An adrenal dysfunction was observed in nine patients (15,78%). In one patient it was connected to the primary disease (X-ALD). The adrenal dysfunction in this boy presented with low cortisol, dehydroepiandrostendione sulfate (DHEAS) and 17-OH-progesterone levels with high ACTH and needed steroid replacement therapy. In seven patients, an adrenal dysfunction was observed probably due to graft versus host disease treatment with a high dose of glucocorticoids. It presented itself with irregular cortisol and ACTH profiles and low DHEAS concentrations, but withdrew without treatment.

In five patients (8,77%) the glucose metabolism was impaired: in one patient post steroid diabetes was diagnosed. Two cases involved impaired glucose tolerance with OGTT. Hyperinsulinemia (fasting insulin >15,0 IU/ml or >75 in 120' of OGTT) was found in all five cases. An insulin treatment was indicated for the patient who had been diagnosed with diabetes. A diet with limited simple carbohydrates was initiated in all other cases, with a good outcome. All five patients were obese/overweight.

Discussion

As HSCT is becoming a common therapeutic option for both malignant and non-malignant diseases, it is important to reduce the risk of long-term treatment complications. Several studies documented endocrinal HSCT late side-effects in children adolescents and adults.

Growth retardation has been a consistent finding in patients who undergo HSCT treatment. The etiology of this problem is considered as a combination of multiple factors: patient's individual characteristics (e.g. age, sex), the underlying disorder and its primary treatment method/s, and the subsequent HSCT, GVHD [8].

There are several studies that prove conditioning regimens, such as irradiation, both cranial or TBI, result in greatest height impairment in children. Sanders et al. found all their subjects who had been treated with irradiation had HtSDS more than two below the mean, five years post transplantation [9]. Bushhouse et al. reported HtSDS of more than 1,5 below the mean four years post transplantation [10]. A greater growth impairment was observed in patients who had received a single dose TBI than those treated with fractionated TBI [11, 12].

On the other hand, some therapeutic regimens, such as Busulfan-Cyclophosphamide (BUCY) conditioning regimen for acute myeloid leukemia (AML), are believed to have no effect on growth [13, 14]. Whereas, in Bakker's study, GHD was diagnosed in 4/10 BUCY patients who were evaluated for GH secretion [15].

In our population, 2/9 patients with short stature are AML patients. The levels of GH in night profile were low, however GHD was not confirmed in dynamic tests and IGF-1 concentration was normal.

Li et al. reported that in thalassemia major, HtSDS improves after HSCT. In our study a similar effect of this treatment was observed [16].

Late side-effects of stem cell transplantation include hypogonadism with infertility and sexual dysfunction [17–19]. Again, this problem can be attributed to both chemo- and radiotherapy [15, 20]. As pediatric patients are not at the age to consider pregnancy, the indirect signs of gonadal dysfunction have to be inquired, such as elevated gonadotropins. In males elevated serum FSH levels reflect germinal epithelium damage and impaired spermatogenesis. The higher FSH levels, the more reduced testicular volumes are observed. Elevated LH levels reflect Leydig cell insufficiency. Testosterone level is usually in low normal. Gynaecomastia is less frequent [13, 21]. Young women are at higher risk of premature menopause.

The risk of a permanent gonadal failure depends on the treatment regimen: high dose irradiation usually results in ovarian/testicular dysfunction, whereas chemotherapy regimens differ in gonadal risk [17, 18, 22]. According to some studies the prepubertal status of patients at the time of transplantation cannot be considered as a protective factor against a treatment-induced gonadal damage [20, 23]. Other investigators suggest the opposite [24, 25]. Therefore long-term monitoring of gonadal function in children who were treated with HSCT at prepubertal age is an important issue. Some researchers suggest that male subjects tended to recover more quickly after BMT than females [17]. That would agree with our observation that only 13,34% boys presented clinically significant gonadal dysfunction, in contrast to 40,74% girls. Moreover, most of the girls had a complete gonadal failure and most of the boys had spontaneous puberty but a germinal epithelial failure.

Thyroid dysfunction occurs in both children and adults after HSCT, particularly in those after TBI [26]. The most frequent type of thyroid dysfunction in long term survivors is hypothyroidism, both overt and clinically compensated. Hyperthyroidism is a rare condition [27]. Recent studies demonstrated that the thyroid gland was especially sensitive to irradiation at very young age [28]. In our study, two female patients presented with thyroid dysfunction: one girl was nearly 18 when she underwent two HSCT procedures. Hypothyroidism occurred one year after her second HSCT. A second girl, who underwent HSCT at the age of 6,5yrs, presented with thyrotoxicosis 30 months post-transplantation. Tatevossian reported a similar case in 2004 [29]. Neither of these patient had TBI.

Taskinen, Mohn and d'Annuzio reported a higher risk of diabetes mellitus, impaired glucose tolerance and insulin resistance in patients after HSCT. Those conditions gradually resolved [30–32]. Similar cases were observed in our study group.

Conclusions

In children and adolescents who undergo hematopoietic stem cell transplantation, growth impairment and the endocrine system disorders have been observed to occur frequently post transplantation. We have demonstrated that gonadal dysfunction is a prominent adverse effect of the HSCT procedure, especially in girls.

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