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ORIGINAL PAPER

Treatment-related gonadotoxicity in young male cancer survivors: a comparative cross-sectional study

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ABSTRACT

Introduction: Male gonads are susceptible to the deleterious effect of anticancer therapy (chemotherapy, radiation to the pelvis, central nervous system, or total body irradiation). Hormonal dysfunction after anticancer treatment was evaluated in young male cancer survivors.

Material and methods: In 153 male adolescent cancer survivors divided into three risk groups (low-LR, moderate-MR, and high-HR) and 24 controls, gonadal and pituitary hormones were analysed. FSH, LH, and testosterone levels were assessed in all the studied patients using immunoenzymatic techniques, dimeric inhibin B – by ELISA method.

Results: All cancer survivor groups had lower mean values of inhibin B (86.87 ±69.07 ng/l vs. 161.07 ±60.64 ng/l; $p < 0.001$), and higher FSH (10.23 ±13.35 mIU/l vs. 4.38 ±2.39 mIU/l; $p < 0.001$) and LH (5.0 ±3.43 IU/l vs. 3.58 ±2.17 IU/l; $p = 0.016$); testosterone levels were comparable to the controls. Abnormal values of inhibin B were found: in 15.2% of survivors in LR, 47.6% in MR, and 94.1% – in the HR group. Elevated FSH levels were seen in 20.4% of survivors in LR, 47.4% in MR, and 92.2% in the HR group. The inhibin B: FSH ratio

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was lowered in MR and HR risk groups. We did not observe any influence of the age at treatment and the time since treatment termination on the analysed hormonal values.

Conclusions: Anticancer treatment increases the risk of gonadal damage, particularly in the HR group. Patients and parents ought to be informed about the risk of lowered reproductive function, and pretreatment semen cryopreservation should be recommended.

KEY WORDS:

childhood cancer survivors, late effect, fertility, gonadal function, inhibin B.

INTRODUCTION

Currently more than 80% of patients treated for cancer during childhood achieve long-term survival. However, more than 60% present at least one late effect of the treatment. Some of them are serious and result in higher mortality (cardiac or lung dysfunction, second cancers), whereas others are the cause of augmented morbidity, organ dysfunction, and lower quality of life [1–3]. Endocrine disturbances are the most frequent complications after anticancer treatment affecting nearly half of childhood cancer survivors. Dysfunction of the hypothalamic pituitary axis, thyroid disorders, abnormal growth and pubertal development, glucose metabolism, as well as gonadal dysfunction can be observed [2, 3]. Male gonads are more susceptible to the deleterious effect of anticancer treatment than female ones. The gonadal function can be affected by the type of chemotherapy, administration of higher doses of gonadotoxic cytostatics such as alkylating agents, radiation to the pelvic area, and total body irradiation, leading to oligospermia and deleterious changes in sperm quality [4, 5]. Anticancer protocols include some cytostatics that exert various effects on the gonads [6–8]. Wallace *et al.* divided all the most frequent paediatric cancers into three groups according to their gonadotoxicity [9]. Treatment protocols for acute lymphoblastic leukaemia (ALL), Wilms' tumour, soft tissue sarcoma, germ-cell tumour, retinoblastoma brain tumour after surgery, and cranial irradiation < 24 Gy were classed into a low-risk group (LR); for acute myeloblastic leukaemia (AML), hepatoblastoma, osteosarcoma, non-metastatic Ewing's sarcoma, neuroblastoma (NBL), non-Hodgkin's lymphoma (NHL), and brain tumour after irradiation > 24 Gy were classed into a medium-risk group (MR); and the patients after total body irradiation (TBI), radiotherapy of the areas located in the pelvis or testes, megachemotherapy before bone marrow transplantation (BMT), Hodgkin's lymphoma treated with alkylating agents, stage IV of soft tissue sarcoma (STS), or Ewing's sarcoma were referred to a high-risk group (HR). The probability of infertility in the low-risk group was less than 20%, in the medium-risk group it was between 20% and 80%, and in the high-risk group it was above 80% [9].

Semen analysis is the gold standard for determining male fertility. Inhibin B, a glycoprotein hormone and the product of Sertoli cells, plays an important role in the regulation of the hypothalamic-pituitary-gonadal action. In younger prepubertal boys or when sperm analysis is impossible to make (e.g. lack of patient consent), inhibin B is used as an indirect marker of spermatogenesis [10]. In our previous study, we analysed male gonadal function in small groups [11], whereas in the current study the hormonal status was assessed in a large group of adolescents and young adults, cancer survivors, from Polish Departments of Paediatric Oncology.

MATERIAL AND METHODS

We included 153 adolescents and young men who visited the outpatient clinics belonging to the Departments of Paediatric Oncology and Haematology of the Medical Universities of: Bialystok, Poznan, Wroclaw, Gdansk, Warszawa, Bydgoszcz, Zabrze, Olsztyn, Lublin, and Szczecin, and the Children's Hospital in Kielce. All survivors were at least two years after cancer treatment termination. All patients were classified according to the risk of subfertility and infertility proposed by Wallace *et al.* [9]. Details concerning diagnosis, age at the time of therapy, the time since the end of therapy, and hormone levels are presented in Table 1, taking into consideration the risk groups proposed by Wallace *et al.* [9].

Total body irradiation was received by four survivors, 14 received irradiation to infradiaphragmatic areas, and 24 received cranial irradiation.

The control group included 24 males of similar age (18.69 ±2.29 years; median 18.5 years), healthy students and older patients from an outpatient clinic (in Bialystok), admitted for lymphadenopathy, pigmented nevus, or benign tumours (younger).

Blood was collected in the morning, and serum was separated and stored at –80° until study assay. All analyses were performed in the Department of Paediatric Laboratory Diagnostics of the Medical University of Bialystok. Follicular stimulating hormone (FSH), luteinising hormone (LH), and testosterone levels were assessed in all the studied patients using immunoenzymatic techniques (Siemens Diagnostic Product Corporation); inhibin B- by ELISA method with double-labelled antibodies against beta B and alpha subunits. A set of antibodies produced by Oxford Bio-Innovation, UK was used for determinations.

The study was approved by the Local Ethical Committee. Written, informed consent was obtained from all the participants and/or their parents.

TABLE 1. The risk group characteristics

Diagnosis	N			Age of diagnosis (years)	Age of follow-up (years)	Time from diagnosis (years)
ALL	33	**LR**	***N***	60	60	53
Wilms tumour	12		**X**	7.41	17.86	11.12
Germ cell tumour (without orchidectomy)	15		**SD**	4.83	3.39	4.45
			Median	5.25	17.50	11.00
			Min.	0.50	12.00	2.00
			Max.	17.00	25.00	23.50
Non-Hodgkin lymphoma	21	**MR**	***N***	40	40	40
			X	10.04	16.53	6.49
STS (II–III stages)	12		**SD**	3.86	3.81	3.91
Neuroblastoma	7		**Median**	10.00	16.00	5.25
			Min.	1.50	11.00	0.50
			Max.	16.50	25.00	15.00
		HR	***N***	53	53	53
Hodgkin lymphoma	31		**X**	11.23	17.98	6.79
STS IV stage	10		**SD**	4.45	3.08	4.90
SCT (stem cell transplantation) (including total body irradiation)	10 4		**Median**	12.50	17.00	5.50
			Min.	1.50	11.40	0.50
Supradiaphragmatic radiotherapy	14		**Max.**	17.50	25.00	17.50
		Total	***N***	153	153	146
			X	9.42	17.55	8.28
			SD	4.74	3.44	4.95
			Median	10.00	17.00	8.00
			Min.	0.50	11.00	0.50
			Max.	17.50	25.00	23.50

STATISTICS

Statistical analysis was carried out using Statistica software. The mean values, standard deviations, median, minimum, and maximum were calculated. Student's t-test was used for normally distributed variables, whereas Mann-Whitney *U*-test was performed otherwise. Correlations between the features studied were defined using the Spearman's coefficient. Analyses were performed at $\alpha = 0.05$ significance level.

RESULTS

All cancer survivors group (taken together), compared to the control group, presented lower mean inhibin B values (86.87 ±69.07 ng/l vs. 161.07 ±60.64 ng/l; $p < 0.001$), and higher FSH (10.23 ±13.35 mIU/l vs. 4.38 ±2.39 mIU/l; $p < 0.001$) and LH (5.0 ±3.43 IU/l vs. 3.58 ±2.17 IU/l; $p = 0.016$). Testosterone levels were comparable to the controls.

Considering the risk of gonadotoxicity, we observed elevated mean FSH levels in the three subgroups (LR group: 9.35 ±19.92 mIU/l, MR group: 8.45 ±7.4 mIU/l, HR group: 12.4 ±7.69 mIU/l vs. control group 4.38 ±2.39 mIU/l), the highest values were in the HR group ($p < 0.05$). Inhibin B values were comparable to the controls (161.06 ±60.64 ng/l) in the LR group (129.98 ±77.08 ng/l), and were lower in the MR (91.25 ±48.58 ng/l; $p = 0.003$) and HR groups (37.19 ±30.54 ng/l; $p < 0.001$) with differences between the MR and HR group ($p = 0.003$) and between LR and HR group ($p < 0.001$). Mean serum LH values were normal in the LR group (5.25 ±4.9 IU/l) and HR group (4.36 ±2.25 IU/l), whereas they were elevated in the MR group (5.55 ±2.14 IU/l; $p = 0.002$). However, no differences were noted between all study groups and controls in testosterone values. Testicular volumes were comparable in all risk groups and controls (Fig. 1A–E).

Abnormal levels of inhibin B (< 100 ng/l; < 1 SD compared to the control group) were found in 53.7% of

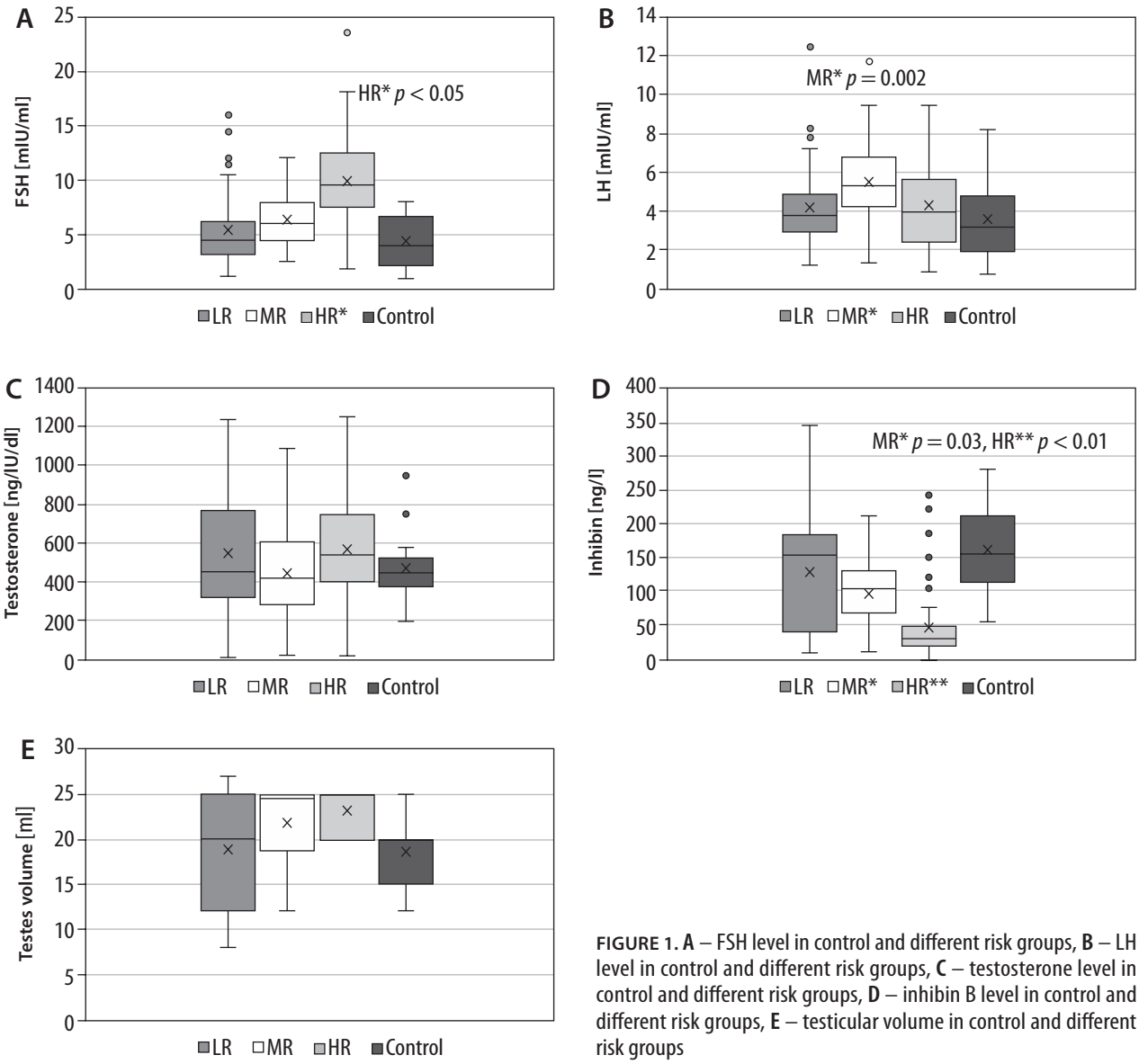

FIGURE 1. **A** – FSH level in control and different risk groups, **B** – LH level in control and different risk groups, **C** – testosterone level in control and different risk groups, **D** – inhibin B level in control and different risk groups, **E** – testicular volume in control and different risk groups

survivors. When we took into consideration the risk groups, lowered levels of inhibin B were observed in 15.2% in the LR group, 47.6% in the MR group, and 94.1% in the HR group. Elevated FSH levels (> 1 SD) were observed in 54.3% of the survivors, including 20.4% in the LR group, 47.4% in the MR group, and 92.2% in the HR group.

The inhibin B : FSH ratio in the control group was 52.56 ±35.94 in all cancer survivor groups: 20.39 ±27.47 ($p < 0.001$), in the LR group: 41.7 ±36.57 (NS), in the MR group: 16.42 ±11.39 ($p = 0.002$), and in the HR group 4.12 ±4.8 ($p < 0.001$). The testosterone : LH ratio was 186.37 ±119.87 in controls and 143.55 ±152.74 in all analysed group ($p = 0.03$); the lowest in the MR group (83.40 ±52.28, $p = 0.001$) and comparable to controls in the LR group (145.08 ±90.01) and HR group (185.71 ±221.85) (Table 2).

We found positive correlation between FSH and inhibin B, but there was no influence of the age at diagnosis, age at follow-up, and length of the follow-up on hormonal values.

DISCUSSION

The current study was the first Polish multicentre analysis of male gonadal/hormonal function after anticancer treatment during childhood. The government monitoring program concerning the health status of childhood cancer survivors was created in 2008. Currently, more than 2000 children and adolescents participate in this program. In our first analysis, we found gonadal dysfunction as the most frequent endocrinopathy [12]. We have decided to perform more accurate analysis of the hormonal status in male cancer survivors using classification proposed by Wallace *et al.* [9], based on the type of disease and kind of treatment affecting the gonads. Due to the rarity of childhood cancers (< 1% of all cancers) and differences in protocols, it is impossible to form large homogeneous groups of cancer survivors. In our opinion, this classification seems useful in the assessment of frequency of subfertility and degree of gonadotoxic treatment.

Because we were not able to include sperm analyses in all survivors (a majority of males in our study did not accept this method), our study was based on the hormonal status. We assessed inhibin B, a product of Sertoli cells, as an indirect marker of spermatogenesis to be better than FSH evaluation. A large number of studies have presented the usefulness of inhibin B in the determination of Sertoli cell dysfunction and correlation between inhibin B levels and sperm concentration [10, 13]. Previously, in a small group of cancer survivors, we found not only a lowered sperm count but also qualitative changes in spermatocytes [11]. Although recently Green *et al.* in a large cohort of cancer survivors did not confirm the utility of inhibin B and FSH in spermatogenesis assessment, other studies performed in large groups proved the usefulness of inhibin B and FSH in the determination of male reproductive status [14–16]. We found a negative correlation between inhibin B and FSH in males in all risk groups. In healthy males, this correlation appears at puberty and persists into adulthood [10]. Similar observations were made by Lahteenmaki *et al.*, who found strong correlations between testicular size or FSH and inhibin B in postpubertal survivors [17].

In all study groups the mean levels of inhibin B were lower, whereas FSH was higher (except for the LR group) than in the control group. Similar results were obtained by Cicognani *et al.* and Wallace *et al.* [18, 19]. Not surprisingly, abnormal values were most frequent in the high-risk group, in which patients received the most vulnerable treatment, e.g. for Hodgkin lymphomas or soft tissue sarcomas, and underwent myeloablative chemotherapy or total body irradiation prior to bone marrow transplantation. The lowest inhibin B values (< 1 SD, < 100.0 ng/l) were found in 94.1% of survivors from the HR group, while in the LR group abnormal inhibin B levels were presented only in 15.2% of survivors. The results obtained in our control group were lower than in studies performed by van Dorp *et al.* (reference values between 150 and 400 ng/l) and van Casteren *et al.* (176.5 ng/l) [20, 21]. However, the boys from our control and study groups were younger than in the studies mentioned above. Similarly, we observed the highest percentage of abnormal FSH values in the HR group (92.2%) compared to the MR group (47.4%) and LR group (20.4%). In a study by Brignardello *et al.*, symptoms of primary hypogonadism were found in 13.33% and abnormal sperm analysis in 42.2% of 310 adult childhood cancer survivors [22]. Tromp *et al.*, in a large (565 survivors) cohort treated for all types of cancers, showed elevated FSH levels in 33% [15]. In an analysis by van Casteren *et al.* inhibin B was decreased in 67% of adults treated for cancer during childhood [21]. Laporte *et al.* received similar results of abnormal testicular function in 74% of survivors after haematopoietic cell transplantation [23]. This was confirmed by Anserini *et al.* in a group of 64 males after bone marrow transplantations – 70.3% presented azoospermia, especially after myeloablation with cyclophosphamide – 85.4% of survivors had azoospermia [24]. In our HR group, the most numerous were the survivors after HL treatment. Although the percentage of long-term survivors after HL is the highest, the late-effects are numerous. In Poland, protocols containing procarbazine were used until 2010. Patients with HL were treated with MOPP (mustargen, vincristine, procarbazine, prednisone) combined with B-DOPA (bleomycin, dacarbazine, vincristine, prednisone, doxorubicin), and in advanced clinical stages, additionally with infradiaphragmatic radiotherapy. Previously, we demonstrated that this kind of treatment had a damaging effect on gonadal function [11]. The use of six or more cycles of MOPP deteriorated spermatogenesis significantly. The most gonadotoxic was procarbazine. Currently, dacarbazine is used in HD treatment [25, 26]. In a study conducted by Relander *et al.*, the most visible gonadal dysfunctions were observed in HL survivors and after treatment with cyclophosphamide [27]. In German Trials based on the Hodgkin Study Group, abnormal FSH values were found in 93% of survivors treated with BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen

TABLE 2. The inhibin B : FSH ratio and the testosterone: LH ratio in control group and risk groups

Risk group		Testosterone/LH ratio	Inhibin/FSH ratio
Control	*N*	24	24
	X	186.37	52.56
	SD	119.87	35.94
	Median	160.22	46.30
LR group	*N*	49	46
	X	145.08	41.70
	SD	90.01	36.57
	Median	123.90	36.45
MR group	*N*	37	38
	X	83.40	16.42
	SD	52.28	11.39
	Median	77.21	15.35
HR group	*N*	51	51
	X	185.71	4.12
	SD	221.85	4.80
	Median	132.40	2.60
Control-LR		ns	ns
Control-MR		0.001	0.002
Control-HR		ns	ns
LR-HR		ns	$p < 0.001$
LR-MR		0.006	ns
MR-HR		0.001	$p < 0.001$

[28]. Recently, Behringer *et al.*, in a cohort containing 761 male adult HL survivors, found normal FSH and inhibin B values in nearly half of the patients treated with less intensive chemotherapy, whereas 88.8% of males after advanced-stage treatment presented the hormonal signs of azoospermia [29].

The inhibin B : FSH ratio was lowered in all groups of cancer survivors, being lowest in the HR group. Schmiegelow *et al.* found a decreased inhibin B : FSH ratio in males after treatment of brain tumours [30], similarly to Bordallo *et al.* [31], and Lahteenmaki *et al.* [16] who suggested the utility of this parameter in the estimation of spermatogenesis. Although in same exceptional cases they observed no correlation between inhibin B, FSH, and sperm counts.

Fertility was impaired in more than 60% of patients treated for solid tumours [32, 33]. The protocols used for their treatment consisted most often of alkylating agents, such as cyclophosphamide, ifosfamide, or cisplatinum in higher cumulative doses, and radiotherapy directed to the abdominal/pelvic areas had the most deleterious impact on gonadal function [7, 34, 35].

The function of steroidogenesis is less affected than spermatogenesis due to lower sensitivity of Leydig cells to radio- and chemotherapy. In all our study groups, LH levels were elevated and testosterone values were normal, indicating a compensated increase in LH due to insufficient testosterone production by Leydig cells. In the study made by van Casteren *et al.*, elevated LH was found in 2% and testosterone in 10% of adult childhood cancer survivors [21]. Tromp *et al.* found decreased testosterone levels in 12% and increased LH in 3% of adult childhood cancer survivors [15]. Sieniawski *et al.* observed, in a group of HL survivors treated with BEACOPP regimen, abnormal testosterone in 57%, LH in 21%, and FSH in 93% of survivors [28]. Romerius *et al.* showed more deteriorated effect of anticancer treatment on Leydig cell function. They found a seven-fold increased odds ratio (OR) for hypogonadism (low testosterone values and/or elevated LH) in adult childhood-cancer survivors [36].

In the present study, we did not observe a protective role of younger age. In comparable risk groups, patients treated in younger age presented similar hormone values to those seen in survivors treated during puberty. This shows that prepubertal gonads present the same sensitivity to gonadotoxic treatment. This was confirmed by the observations of van Casteren *et al.*, Ben Arush *et al.*, Hobbie *et al.*, and Soriano *et al.* [21, 26, 37, 38].

The hormonal status in the LR group was generally comparable to the controls, although 15.2% had lowered inhibin B level. The most representative were the boys treated for acute lymphoblastic leukaemia (33 patients). The treatment for acute lymphoblastic leukaemia (ALL) is not significantly deteriorating for gonads (cyclophosphamide doses are lower than in other protocols) but some patients – derived from the HR group – presented lower inhibin B values. In studies by Soriano *et al.* and van Casteren *et al.*, normal testicular function was shown in ALL survivors [21, 38].

In conclusion, our study indicates increased risk of gonadal damage with a particularly high percentage observed in survivors from the HR group. Since the process of spermatogenesis is more affected than steroidogenesis, puberty and secondary sexual characteristics may be normal. Men having undergone more intensive chemotherapy present the hormonal symptoms of disturbed spermatogenesis and require follow-up in the future. They also should be informed about the impact of the treatment on gonadal function and possibilities of fertility preservation. The patients and parents should be informed about the possibility of lowered reproductive function, and pretreatment semen cryopreservation should be recommended.

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DISCLOSURE

The authors declare no conflict of interest.

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