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Thyroid disorders after oncologic treatment in children

Zaburzenia czynności tarczycy po leczeniu onkologicznym u dzieci

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Słowa kluczowe
leczenie onkologiczne choroby tarczycy, dzieci

Abstract

The length of patient survival after cancer treatment is increasing and, in some cases, does not differ from the average life span in healthy individuals. **The aim of the study** is to evaluate thyroid function after oncologic treatment in children. **Patients and methods.** A group of 158 patients aged 16–25 who underwent oncologic treatment in childhood and the control group 66 children and young adults were examined. The prospective study was conducted in the period between 4 and 19 years after the diagnosis. After physical examination,the levels of TSH, fT4, and fT3 (Abbott), as well as TPO Ab and Tg Ab (DAKO Denmark) were assayed and TSI Ab (BRAHMS Germany) levels were measuredin patientswith hyperthyroidism. The ultrasound of the thyroid gland was done using a Siemens-2000 device. **Results.** The prevalence of hypothyroidism in the group of patients was statistically significantly higher than in the control group (27.2% versus 6.1%. p=0.001). The occurrence of primary hypothyroidism was correlated with the total anthracycline dose and with the total X-irradiation (XRT) dose. The incidence of autoimmune thyroid diseases was statistically significantly higher in children after BMT. There was a statistically significantly higher prevalence of thyroid nodules in children after oncologic treatment. The nodules developed more frequently after XRT anticancer therapy and their prevalence was

Streszczenie

Choroby nowotworowe mogą wpływać na czynność tarczycy poprzez sam rozwój procesu chorobowego, konieczność stosowania leczenia operacyjnego, cytostatycznego lub naświetlania promieniami X. Coraz dłuższy jest okres przeżycia pacjentów po leczeniu nowotworów i w części przypadków nie różni się on od średniego okresu przeżycia osób zdrowych. **Cel pracy:** ocena czynności tarczycy po leczeniu onkologicznym u dzieci. **Pacjenci i metody.** Zbadano 158 pacjentów w wieku 16–25 lat po leczeniu onkologicznym w okresie dzieciństwa. Grupę kontrolną stanowiło 66 zdrowych dzieci i młodych dorosłych. Badania prospektywne były prowadzone w okresie 4 do 19 lat od postawienia diagnozy. U pacjentów i dzieci z grupy kontrolnej wykonywano badanie fizykalne i oznaczano poziomy TSH, fT4 i fT3 (Abbot), przeciwciała Tg Ab i TPO Ab (DAKO) i TSI (Brahms). Badanie ultrasonograficzne tarczycy wykonano przy użyciu aparatu Siemens 2000. **Wyniki.** Częstość występowania niedoczynności tarczycy w grupie pacjentów była statystycznie istotnie wyższa niż w grupie kontrolnej (27,2% versus 6,1%, p=0,001). Występowanie pierwotnej niedoczynności tarczycy było skorelowane z całkowita dawką antracykliny i z całkowitą dawka promieniowana X (XRT). Występowanie autoimmunizacyjnych chorób tarczycy było statystycznie istotnie wyższe u dzieci po przeszczepie szpiku (BMT). Po leczeniu onkologicznym u dzieci statystycznie istot-

correlated with the total XRT dose. **Conclusions.** 1. Primary and secondary hypothyroidism is more prevalent in patients who have received oncologic treatment than in healthy individuals. 2. Cytostatics, especially anthracycline, and XRT have an effect on the development of primary hypothyroidism. 3. BMT in children has a significant effect of development of hypothyroidism in the course of AITD. 4. Cytostatic treatment and XRT contribute to development of potentially neoplastic thyroid nodules.

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nie częściej występowały guzy tarczycy. Rozwijały się one częściej po radioterapii i ich występowanie było skorelowane z całkowitą dawką promieniowania X. **Wnioski.** 1. Pierwotna i wtórna niedoczynność tarczycy występuje częściej u pacjentów leczonych onkologicznie niż u zdrowych dzieci. 2. Leczenie cystostatyczne, zwłaszcza antracyklina i naświetlania promieniami X, wpływa na rozwój pierwotnej niedoczynności tarczycy. 3. Przeszczep szpiku (BMT) ma wpływ na rozwój autoimmunizacyjnych chorób tarczycy. 4. Leczenie cytostatyczne i naświetlanie promieniami X mają udział w rozwoju potencjalnie złośliwych guzów tarczycy.

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Introduction

Cancer diseases can affect the thyroid function through the necessity of surgical, cytostatic, or X-radiation treatment(XRT) or incidentally through the development of the neoplastic process itself. The length of patient survival after cancer treatment is increasing and, in some cases, does not differ from the average life span in healthy individuals. The effects of XRT and chemotherapy appear and progress at a slow rate within a few next years after the cytostatic treatment. Hypothyroidism caused by damage to the hypothalamic-pituitary area is another problem.

The most common cancers in children include acute lymphoblastic leukaemias (26%), lymphomas (15%),central nervous system tumours (15%), bone and soft tissue tumours (14%), neuroblastoma (7%), and Wilms'tumour (6%) [1]. Targeted therapies and individual chemotherapy regimens have yielded substantial improvement in the effectiveness of cancer therapy. The following cure rates (5-year remission) were observed: 92% in Hodgkin's lymphoma, 95% in Wilms'tumour, 80% inacute lymphoblastic leukaemia, and 56% in rhabdomyosarcoma. Gonads, thyroid, hypothalamus, and pituitary are most sensitiveto oncologic treatment.

Acute lymphoblasticleukemia (ALL) is the most common malignancy in children, accounting for 30% of all cancers and 80% of all leukaemias. ALL is a rapidly progressive disease that involves proliferating immature lymphocytes including B- or T-cell progenitors. The diagnosis of acute leukaemia (ALL) can be established when the bone marrow examination reveals a lymphoid blast cell content in excess of 20% of total cellularity. The mechanisms underlying the induction of ALL include aberrant expression of proto-oncogenes, chromosomal translocations, and hyperdiploidy [2].

Hodgkin's lymphoma (HL) is a disease mainly affecting young adults and with a good prognosis for survival since more than 80% of HL patients can expect to live free of disease five years after diagnosis. Classical Hodgkin's lymphoma (HL) includes nodular sclerosing, mixed cellularity, lymphocyte-rich and lymphocyte-depleted subtypes, and represents about 95% of all HL cases [3]. It is distinguished from nodular lymphocyte predominant Hodgkin's lymphoma (NLPHL), which accounts for about 5% of all HL cases [3]. Chest X-ray and a computed tomography (CT) scan of the neck,chest, and abdomen are mandatory as well as bone marrow aspiration and histology [3].

NHL is a malignant disorder characterized by an uncontrolled growth of monoclonal lymphocytes, observed most commonly within the lymph nodes. NHL is a heterogeneous condition and comprises several different morphologic subtypes with distinct clinical behaviours and outcomes. Chemotherapy, immunotherapy, and XRT have been the main modalities of treatment in this disease [4].

The Ewing's family of tumours are a group of nonhereditary small, blue, round-cell tumours occurring in bone and soft tissues, characterized as a group by the presence of the translocation t (11; 22) (q24; q12). They typically occur in children

and young adults, and the majority are of osseous origin [5].

Nephroblastoma now is recognized as the most common malignant renal tumour of childhood and is known more commonly as Wilms' tumour. Most commonly, patients present with a palpable abdominal mass accidentally noted by parents or in the course of a routine clinical examination. However, about one-third of patients present with abdominal pain, anorexia, vomiting, malaise, or a combination of these symptoms. Gross or microscopic haematuria is found in 30% of patients [6]. The treatment consist of chemotherapy and surgery.

Rhabdomyosarcoma (RMS) is a malignant tumour of mesenchymal origin thought to arise from cells committed to a skeletal muscle lineage. It is the most common soft-tissue sarcoma of childhood. RMS is one of the small round blue cell tumours that occur in children and it must be distinguished from neuroblastoma, Ewing's sarcoma, and lymphoma. Common sites of primary disease include the head and neck region, genitourinary tract, and extremities. The treatment includes chemotherapy and XRT [7].

Paediatric germ cell tumoursrepresent a diverse group of tumours that present from in utero through adolescence at many nongonadal locations, from the neck to the sacrococcygeal region. Paediatric germ cell tumours are relatively rare tumours accounting for approximately 3% of paediatric malignant tumours and include teratomas, choriocarcinomas, seminomas, or dysgerminomas. Several interesting features distinguish these tumours from other malignancies: the abnormal migration of primordial germ cells which explains the frequent occurrence of extragonadal germ cell tumours in children, and the existence of serum markers that allow evaluation of the extent of resection and development of recurrent tumour [8]. The chemotherapy and surgery is the treatment of choice.

The aim of the study

The aim of the study is to evaluate thyroid function in children after oncologic treatment with cytostatics (chemotherapy), bone marrow transplant (BMT), or after XRT.

Patients and methods

A group of 158 patients aged 16–25 years who underwent oncologic treatment in childhood in the Department of Paediatric Hematology and Oncology in Lublin from 1992 to 2007 and remained in complete remission (CR) of oncologic disease were included into the prospective study. All the patients were diagnosed and treated as well as qualified for specific risk groups in

Table I. The structure of the patient group

	n	Disease	n	The age of start oncologic treatment	Chemotherapy	XRT	Surgery	BMT
Total	158		158	0–18	146	75	34	37
Hematooncologic leukaemias and lymphomas	118	Acute leukaemia	75	0–16	75	10	0	10
		Lymphoma	43	1–18	43	43		14
Solid tumours	40	Brain tumours	10	0–12	6	8	9	2
		Bone tumours	6	3–17	6	2	6	1
		Germ cell tumours	5	6–16	5	1	5	1
		Nephroblastoma (Wilms' tumour)	7	3–11	6	2	7	0
		Miscellaneous	12	1–18	5	9	7	9

accordance with the diagnosis with currently used chemotherapy protocols. The structure of patient groups is presented in table I.

None of the subjects had previously been diagnosed with thyroid disease or had been treated for thyroid dysfunction. The median time interval from the diagnosis was 10 years and ranged from 4 to 19 years. The data were obtained byprospective investigation and analysis of database of the Department of Endocrinology and Diabetology, Medical University in Lublin.

After physical examination of the children and the young adults, the levels of TSH, fT4, and TT3 (Abbott) and the levels of anti-thyroid antibodies TPO Ab and Tg Ab (DAKO Denmark) were assayed in each patient every year; in patients with hyperthyroidism, the levels of TSI Ab (BRAHMS Germany) were measured. Additionally, an ultrasound of the thyroid gland was done using a Siemens-2000 device.

The same parameters were determined in the control group consisting of 66 children and young adults aged 10–25.

The research was approved by the Bioethics Committee, Medical University of Lublin.

The statistical analysis was conducted using Statistica 9.0.

Results

Hypothyroidism was diagnosed more frequently (with statistical significance) in the group of the patients after oncologic treatment 27.2% (21.5% primary and 5.7 secondary hypothyroidism) than in the control group – 6.1%. p=0.001. The occurrence of primary hypothyroidism was statistically significantly higher in children treated for hemato-oncologic diseases, i.e. leukaemias and lymphomas (15.2%. p=0.001), and solid tumours (25%. p=0.0002), in comparison with the control group (table II). Primary hypothyroidism in children after hemato-oncologic treatment was diagnosed less frequently than in children treated for solid tumours, but the differences were not statistically significant (p=0.071). The occurrence of the disease was correlated with the total anthracycline dose (Spearman's correlation coefficient 0.52, p=0.012) and with the total X-irradiation dose (Spearman's correlation coefficient 0.72, p=0.001). No correlations with other cytostatic treatment and hypothyroidism were observed.

Secondary hypothyroidism occurred after surgical treatment of solid tumours of the central nervous system. It was not observed in any child from the control group (table II, III).

Hyperthyroidism occurred sporadically in children after oncologic treatment and in one child from the control group.

Primary hypothyroidism was most prevalent after BMT and XRT, but after cytostatic treatment the prevalence of primary hypothyroidism was statistically significant in comparison withthe control group. The secondary hypothyroidism was connected with XRT of brain,especially in children after brain tumour treatment.

Analysis of the incidence of autoimmune thyroid diseases (AITD) in patients after oncologic treatment demonstrated that autoimmune thyroid diseases occurred more frequently (with statistical significance) in children and adolescents with a history of cancer (Pearson's Chi-square 8.95.

Table II. Thyroid hormone disorders after oncologic treatment

	n	Primary hypothyroidism	p	Secondary hypothyroidism	p	Hyperthyroidism
Patients after oncologic treatment	158	34 (21.5%)	0.001	9 (5.7%)	0.023	2 (1.3%)
Hematooncologic leukaemias and lymphomas	118	24(15.2%)	0.011	0	1.0	1 (0.6%)
Solid tumours	40	10(25%)	0.003	9(22.5%)	0.001	1(2.5%)
Control group	66	4(6.1%)	–	0	–	1(1.5%)

p – in comparison with the control group

Table III. Primary and secondary hypothyroidism after oncologic treatment

	Patients n	Primary hypothyroidism	p	Secondary hypothyroidism	p
Cytostatic treatment	146	34 (23,2%0	0.001	1 (0,6%)	–
XRT	75	19 (25,3%)	0.001	9 (12%)	0.001
BMT	37	15 (40,5%)	0.001	1(2,7%)	–
Control group	66	4(6.1%)	–	0	–

p – in comparison with the control group

Table IV. Autoimmune thyroid diseases after oncologic treatment

	n	AITD	p	Hashimoto's thyroiditis (positive thyroid autoantibodies)	p	Graves' disease (positive TSH receptor autoantibodies)	p
Patients after oncologic treatment	158	18 (11.3%)	0.001	16 (10.1%)	0.001	2 (1.3%)	0.086
Hematooncologic disease	118	7 (5.9%)	0.073	6 (5.1%)	0.047	1 (0.6%)	0.986
Solid tumours	40	5 (12.5%)	0.001	4 (10%)	0.001	1(2.5%)	0.978
Control group	66	5 (7.5%)	–	4 (6.1%)	–	1(1.5%)	–

p – in comparison with the control group

p=0.03) than in the control group. AITDs were more prevalent in patients treated for solid tumours than in those treated for hematologic diseases (table IV).

The Mann-Whitney U test showed that elevated TPO Ab and TG Ab levels ($p<0.01$) were detected more frequently in the group of patients after oncologic treatment than in the control group. In patients after oncologic therapy, autoimmune thyroid diseases developed in children treated for Wilms' tumour, NHL, CNS, and other cancers. The highest levels of anti-TG antibodies were found in children and adolescents after treatment of various solid tumours. Statistically significantly higher TG Ab levels were observed in patients after Wilms' tumour treatment 187.36±459.34 IU/ml).

No correlation was found between the total X-irradiation dose applied in radiotherapy and presence of anti-thyroid antibodies(Spearman's coefficient 0.23. p=0.73).

The highest X-irradiation doses were applied in children with HD and NHL, which however did not result in a change in the level of anti-thyroid antibodies and development of AITD in these patients.

The autoimmune reactions developed especially after BMT (table V). Allogeneic or autogenic BMT hasapositive effect on the level of thyroid autoantibodies (Spearman's correlation coefficient 0.63 p=0.01 at allogeneic BMT, and Spearman's correlation coefficient 0.78 p=0.001 at autogenic BMT).

The frequency of occurrence of thyroid nodules was increased, with statistical significance, in children after anticancer therapy (tableVI and VII) They were more common in patients treated with radiotherapy. The frequency of development of thyroid nodules was correlated with the X-irradiation dose (Spearman's correlation coefficient 0.68 p=0.001), but neither with the anthracycline dose (Spearman's correlation

Table V. Thyroid autoantibodies in children after oncologic treatment

	Patients n	Average TPO Ab [IU/ml]	SD	p	Average TgAb [IU/ml]	SD	p
Cytostatic treatment	146	13.2	34.5	0.051	41.6	151.7	0.059
XRT	75	13.3	27.09	0.067	23.8	69.4	0.043
BMT	37	57.5	2.4	0.023	90.4	4.6	0.003
Control group	66	23.18	61.32	–	64.92	290.3	–

p – in comparison with the control group

Table VI. Nodular goitre in children after oncologic treatment

Disease	Number of patients	Decreased thyroid volume <3 percentile	Enlarged thyroid volume >97 percentile	Nonhomogenous decreased echogeneity	Nodules of the thyroid diameter >5.0mm
All patients	158	2 (1.3%)	0	7	20 (12.7%)
Hematooncologic disease	118	0	0	5	14 (11.9%)
Solid tumours	40	2	0	2	6 (15.0%)
Control group	66	0	2 (3.0%)	5 (7.6%)	0 (0%)

p– in comparison with the control group

Table VII. Ultrasonography of the thyroid in children after cytostatics, XRT, and BMT

	Patients n	Decreased thyroid volume <3 percentile	Enlarged thyroid volume >97 percentile	Nonhomogenous decreased echogeneity	Nodules of the thyroid diameter >5.0mm	p
Cytostatic treatment	146	2	0	4	15 (10,3%)	0,001
XRT	75	2	0	5	20 (26,7%)	0,001
BMT	37	0	0	7	2 (5,4%)	0,048
Control group	66	0	2 (3.0%)	5 (7.6%)	0 (0%)	–

p – in comparison with the control group

coefficient 0.23 p=0.5) or application of bone marrow transplant therapy (Spearman's correlation coefficient 0.31 p=0.7).

Most frequently, thyroid nodules developed in patients treated for Wilms' tumour, NHL, and TGM. They were usually thyroid adenomas or neutral nodular goitre. In one patient, a secondary papillary thyroid cancer developed after treatment of NHL. No tumours developed in the patients from the control group.

Discussion

Development of cancer disease, cancer treatment, or both these factors can be the causes of thyroid dysfunction.

By exerting pressure and destruction of the hypothalamus and pituitary glands, brain tumours of the hypothalamic-pituitary area suppress release of TSH and/or TRH, which leads to secondary hypothyroidism. Debilitating cancer diseases are frequently the cause of a low T3/T4 level.A separate analysis of the influence of cytostatic treatment, XRT and BMT is very difficult, because all methods of therapy are used in the same patients.

Effect of cytostatic drugs on thyroid function

Chemotherapeutics often affect thyroid function and the results of laboratory thyroid examinations. Application of the MOPP chemotherapy protocol without radiotherapy is the cause of primary hypothyroidism in nearly 50% of patients. L-asparaginase irreversibly inhibits the synthesis of albumin and TBG, which results in a low T4 level at a normal fT4 level [9]. Anthracyclines are very important antineoplastic agents used as broad-spectrum cytostatic treatment of a wide variety of malignancies. Cardiotoxicity is a well-recognized side effect of anthracycline limiting the total amount of drug doses [10]. Hearth failure in some patients is dose related: 4% are caused bycumulative dose 500 mg/m^2, 18% by cumulative dose 551–600 mg/m^2, and 36% by a dose over 601 mg/m^2 [10]. Anthracyclines caused alteration in iron homeostasis and deregulation of calcium homeostasis in endoplasmatic reticulum and in mitochondria. The increased oxidative stress and mitochondrial dysfunction lead to DNA damage and apoptosis of cells (especially cardiomyocytes) [10,11]. The effect of anthracyclines on thyroid cells has been poorly investigated.

In our investigations, we found a correlation between the development of hypothyroidism and the total anthracycline dose; this was primary hypothyroidism, in most cases unrelated to development of autoimmune reaction.

Interferon stimulates development of autoimmune reactions in the thyroid, leading to hypo- or hyperthyroidism, particularly in patients with an elevated level of antithyroid antibodies [12].

The level of thyroid hormones can also be affected by other drugs and agents used in diagnostics and adjuvant therapy. Large quantities of iodinated contrast, used e.g. in computed tomography, can impair thyroid function through the Wolff-Chaikoff effect or induce autoimmune reactions. Chronic administration of low molecular weight heparin may raise the level of fT3 and fT4 [13].

Impairment of the hypothalamus-pituitary-thyroid axis caused by X-irradiation

Our observations indicate that primary and secondary hypothyroidism is connected with treatment of solid tumours. In a majority of cases,hypothyroidismis compensated by an increase in the TSH level. The total dose of irradiation of the CNS in the range of 18–24 Gydoes not play a significant role as a cause of post-treatment pituitary and thyroid dysfunction. Clinical observations indicate that total irradiation doses increasing the risk of hypothalamus-pituitary axis dysfunction are within the range of 18–20 Gy. Secondary hypothyroidism is observed at doses exceeding 36 Gy [14]. Recent reports reveal a 1% prevalence of overt or subclinical hypothyroidism in patients that have been treated by CNS irradiationwith a total dose of 18 Gy. In the case of applying treatment with a total dose of 24 Gy, the risk of thyroid diseases is higher. Scattered radiation can lead to irradiation of the thyroid with 7.5% of the dose applied in the radiotherapy. This corresponds with our observations of the prevalence of hypothyroidism correlated with the total X-irradiation dose applied in therapy.The risk of hypothyroidism reaches 30–40% in the case of children treated with cranial and spinal irradiation for brain tumours without chemotherapy. A similar risk is found in patients treated with total body irradiation (TBI), even 5–10 years after the therapy. Radiotherapy applied to body areas located above the diaphragm, which is used in Hodgkin's disease at a total dose of 36–44 Gy, poses a risk of thyroid

dysfunction in 37–88% patients [14]. In our patient group,hypothyroidism was less prevalent and associated with damage to the thyroid gland caused by irradiation or cytostatic treatment and not with induction of autoimmune reactions. The impairment of TSH release by the pituitary gland and TRH release from the hypothalamus was associated with cancer development and neurosurgery of this area.

Ionising radiation is known to havea carcinogenic effect, which combined with chronically increased TSH stimulation elevates the risk of thyroid cancer development. Observations of children after the Hiroshima bombing or Chernobyl disaster indicate an increased risk of development of thyroid papillary cancer and, less frequently, follicular thyroid carcinoma [15,16]. One from our patient group developed follicular thyroid cancer.

Benign changes in the thyroid, e.g. focal hyperplasia, single or multiple adenomas, chronic lymphocytic thyroiditis, colloid nodular goitre and fibrosis can be observed in 20–30% of patient after radiotherapy [17]which corresponds with our results.

Effect of allogeneic bone marrow transplantation (BMT) on thyroid function

Patients treated with allogeneic bone marrow transplantation may develop an immune response of the graft-versus-host disease (GvHD) type or autoimmune response against own organ cells. The development of autoimmune thyroid disease (AITD) as a common long-term complication following bone marrow transplantation (BMT) is frequently associated with total body irradiation (TBI) given in the pre-BMT conditioning protocol [18]. The progress of treatment methods has contributed to reduction of thyroid complications after BMT. Short-term changes in thyroid function after BMT can indicate euthyroid sick syndrome rather than tertiary hypothyroidism [19]. Sanders et al. describes that thyroid dysfunction was more likely if patients were less than 10 years of age [20].

Within 20 years after allogeneic BMT, thyroid dysfunction may occur in 47% of patients. Low levels of T3 are detected at the time of preparation and after transplantation accompanied by chronic thyroiditis (36%), and transient clinical or subclinical hyperthyroidism (2.4%), or hypothyroidism (8.2%) [21]. The risk of thyroid dysfunction is higher in children after total body irradiation TBI). In few patients,bone marrow transplantation from a donor with ongoing or past autoimmune thyroid disease can trigger reactions of donor lymphocytes against recipient thyreocytes, which may lead to Graves' disease or Hashimoto's thyroiditis immediately after allogeneic transplantation [22,23]. Our study indicated a high prevalence of AITD and thyroid antibodies in patients after allo- and auto-BMT in comparison to the control group,similar to previous investigations [21] and comparable to patients with other autoimmune disorders [24,25].

Endocrine care after oncologic treatment

In children after oncological treatment, assessment of the structure and thyroid functionshould be performed every 6 month in the endocrinology outpatient clinic and, where necessary, thyroid diseases should be treated in a standard way. Each thyroid nodule should be regarded as a potential cancer change; therefore, careful diagnostics should be carried out and surgical treatment if necessary.

Conclusions

Primary and secondary hypothyroidism develops more frequently in patients after oncologic treatment than in healthy individuals.

The anthracycline dose and the dose of X-irradiation have an effect on development of primary hypothyroidism.

Bone marrow transplantation in children has a significant effect on the occurrence of hypothyroidism in the course of AITD.

Cytostatic treatment and radiotherapy contribute to development of thyroid nodules with a potential for neoplasia.

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