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THE ROLE OF PROINFLAMMATORY CYTOKINES INTERLEUKIN 1-B AND TUMOR NECROSIS FACTOR-A IN DIAGNOSTICS OF PUBERTAL MENORRHAGES AGAINST THYROID PATHOLOGY

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Summary

Introduction. *During puberty, the reproductive system is vulnerable to the influence of any adverse factors that lead to a disorder of its functional state and to menstrual disorders in particular. Among the numerous factors that provoke menstrual dysfunction is the pathology of the thyroid gland.*

Cytokines are known to be involved in all aspects of innate and acquired immunity, including the activation of growth and differentiation of immunocompetent cells, inflammation and restoration of the function of the affected organ. Cytokines are characterized by the action of preventing the interaction of cells of the immune, hematopoietic, endocrine and nervous systems. Cytokines of the first generation are conditionally distinguished, which are produced by cells of nonspecific anti-infective protection. The main pro-inflammatory cytokines are IL-1β, IL-2, IL-6, interferons, TNF-α and others. The main factor of inflammatory reactions is multifunctional IL-1β. Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine, one of the central regulators of factors and mechanisms of innate resistance. It has many biogenic effects, most of which are similar to the action of IL-1β.

Considering the above exactly IL-1β and TNF-α to study their concentration in the blood of adolescent girls with pubertal menorrhagia has been the basis of immunological studies.

The aim of the study. *Assessment of cytokine status in girls of pubertal age against the background of concomitant thyroid pathology.*

Material and methods. *We examined 70 adolescent girls with pubertal menorrhagia who were treated in the gynecological department of the Chernivtsi Regional Perinatal Center. The girls were divided into two groups: I (main) included 30 adolescent girls diagnosed with pubertal menorrhagia on the background of concomitant thyroid pathology, II group (comparison) - 40 adolescent girls diagnosed with pubertal menorrhagia. Control group III - 25 practically healthy adolescent girls. Pro-inflammatory cytokines, namely interleukin 1-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) were studied once, after inclusion of patients in the study, by enzyme-linked immunosorbent assay based on a solid-phase 'sandwich' variant using mono- and polyclonal antibodies to IL-1β and TNF-α. The tubes with the serum samples were closed with lids and stored in the freezer until analysis at -20 °C.*

Statistical processing of the material was carried out using the computer program STATISTICA and Microsoft Exel Windows, StatSoft® Inc.

The design of the study and all methods used in this study were reviewed and approved by the Bioethics Committee of the Higher Educational Institution "Bukovinian State Medical University" (protocol No. 1, dated 24.01.2011). Research work "Prevention, diagnostics and treatment of perinatal and reproductive system disorders of women and adolescent girls" (№ 201110H state registration number 0111U006499. Term of realization: 02.2011-12.2015.)

Results of the study. *The obtained results of the study of the cytokine cascade showed that upon admission to inpatient treatment and examination in the blood of adolescent girls with pubertal menorrhagia without concomitant pathology, the concentration of IL-β increases significantly (by 60.61%) and a tendency to increase (4.09 times) the concentration of TNF-α in the peripheral blood of the examined patients is formed. However, the results of clinical and laboratory examinations obtained during admission for inpatient examination and treatment of adolescent girls with pubertal menorrhagia associated with thyroid pathology showed that patients have a steady tendency to decrease the concentration of IL-1β by 6.96% and TNF-α - by 1.48 times. It was found that the pathology of the thyroid gland contributes to the inhibition of immunocompetent cells production of IL-1β by 1.66 times, TNF-α by 6.04 times.*

Conclusion. *Pathology of the thyroid gland leads to a decrease in immunoregulatory function due to a decrease in the concentration of some important proinflammatory cytokines (IL-1β and TNF-α).*

Key words: *girls of pubertal age, pro-inflammatory cytokines, thyroid gland, pubertal menorrhagia.*

Introduction

Preserving the health of girls of puberty is an important medical and national task. Pubertal menorrhagia is one of the urgent problems of modern pediatric gynecology. Today, science has achieved certain results in the correction of these disorders, but the frequency of reproductive disorders in women who had endocrine-dependent gynecological diseases in puberty remains high [1,2].

Their future reproductive health depends on the functional state of the reproductive system of girls in childhood and adolescence. During the period of formation, the reproductive system is vulnerable to the influence of any adverse factors that lead to a disturbance in its functional state and to menstrual disorders in particular. The numerous factors that provoke menstrual disorders include pathology of the endocrine system, namely the thyroid gland [3,4]. In recent years, there has been an increase in menstrual disorders among girls of puberty and insufficient effectiveness of their treatment in adolescence, including pubertal uterine bleeding [5]. It is known that most endocrine-related gynecological diseases are formed during puberty. The result of pathology of

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the endocrine system during puberty is a pathological puberty in girls, the frequency of which has been steadily increasing in recent years [5, 6]. This is due to a complex of medical, social problems that arise in modern adolescents and affect the formation of the reproductive system in puberty. The increase in the number of young patients with pubertal menorrhagia on the background of endocrine pathology can be explained by several reasons:

- unstable ecological situation on the territory of Ukraine, in particular in Chernivtsi region;
- the suppressive impact of environmental factors on the endocrine status of girls in puberty;
- inadequate nutrition of adolescent girls of certain social categories and, as a consequence, deficiency of vitamins and microelements that come with food, due to the low financial situation of their parents [10,11].

The problem of changes in the reproductive system of an adolescent girl suffering from various thyroid diseases is especially important in Ukraine and in particular in the Chernivtsi region, which is an iodine-deficient region [12]. The growth of abnormalities in the formation of the menstrual cycle in girls, delayed sexual development in the structure of gynecological pathology among this category of patients, insufficient effectiveness of conventional treatments stipulate the need for further research to determine the influence of various factors on the course of puberty and the possibility of taking into account in order to improve the treatment of menstrual pathology in pubertal girls with thyroid pathology [12,13]. Dysfunctional uterine bleeding occupies a significant place in the structure of menstrual dysfunction in puberty. Uterine bleeding in puberty reflects the physiological immaturity and imperfection of the mechanisms of regulation of the reproductive system during its maturation.

Cytokines (interleukins, lymphokines, etc.) synthesized by lymphoid and non-lymphoid cells, have a direct effect on the functional activity of immunocompetent cells. They can't independently induce a specific immune response. They regulate it. Thus, interleukin-1 (IL-1), among other important functions, activates the proliferation of antigen-sensitized T- and B-lymphocytes; IL-2 accelerates the proliferation and functional activity of T- and B-lymphocytes [23]. Cytokines are characterized by hormone-like action, which is to prevent the interaction of cells of the immune, hematopoietic, endocrine and nervous system. Cytokines of the first generation (preimmune cytokines) are conditionally distinguished, which are produced by cells of nonspecific against infection protection (innate immunity). These include IL-1β, IL-6 and TNF-α, which induce the biosynthesis of IL-2, which acts as a central regulatory cytokine, as well as IL-3, IL-4, IL-5 and gamma interferon (second generation cytokines) [26]. In turn, secreting cytokines of the second generation have a corrective effect on the biosynthesis of cytokines of the first generation (early cytokines). This principle of interaction contributes to the constant involvement of an ever-increasing number of immunocompetent cells in the immune response. Cytokines by their function are divided into pro-inflammatory and anti-inflammatory. The main pro-inflammatory cytokines are IL-1β, IL-2, IL-6, interferons, TNF-α and others [26,27]. The main factor of inflammatory reactions is multifunctional IL-1β. It induces the production of IL-2, causes the production of acute phase proteins by hepatocytes, acts on the CNS (drowsiness, anorexia), and induces the production of IL-3, IL-6, IL-8 and colony-stimulating factors. Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine, is one of the central regulators of factors and mechanisms of innate resistance. It has many biogenic effects, most of which are similar to the action of IL-1β. Prolonged circulation of TNF-α in the blood system leads to depletion of muscle and adipose tissue (cachexia) and suppression of hematopoiesis. The molecular stimulator of TNF-α production by macrophages and activated killer cells are polysaccharides of gram-negative bacteria (enterobacteriaceae, etc.) [28,29].

The aim of this work was to assess the cytokine status in adolescent girls with concomitant thyroid pathology.

Material and methods of the study

We examined 70 adolescent girls with pubertal menorrhagia who were treated in the gynecological department of the Chernivtsi Regional Perinatal Center. The girls were divided into two groups: I (main) included 30 adolescent girls diagnosed with pubertal menorrhagia on the background of concomitant thyroid pathology, II group (comparison) comprised 40 adolescent girls diagnosed with pubertal menorrhagia. Control group III was 25 practically healthy adolescent girls.

The inclusion criteria for the study were:
age (from the beginning of menarche to 18 years);
menstrual irregularities at the time of examination;
absence of somatic pathology;
concomitant thyroid pathology.

The exclusion criteria from the study were:
age over 18 years;
absence of menarche;
secondary amenorrhea;
presence of an infectious factor;
concomitant extragenital pathology (except for thyroid pathology).
diagnosis of hyperprolactinemia;
girls with Stein-Leventhal syndrome.

Considerable attention was paid to the period of puberty, the period of establishment of the girl's menstrual function, the nature of vaginal discharge not associated with menstruation were analyzed in detail.

The main indicators of physical development of the girl were determined considering age (height, weight, chest circumference, pelvic size), then a general examination of all organs and systems was carried out. During the examination of girls, attention was paid to height and body weight, constitution, development of adipose tissue and features of its distribution. The assessment of the body structure, especially in case of significant deviations from the basic sizes, allowed to retrospectively assess and determine the course of puberty. Examination of external genitalia was performed in the presence of parents, relatives or caretakers (parents/caretakers). The type of hair growth, symmetry, labia minora,

structure of labia majora and labia minora, nature of discharge, presence of pathological discharge, were determined. We examined the perineum and anus, vaginal entrance, color of mucous membranes, condition of the external opening of the urethra and the excretory ducts of the bartholinium glands, the shape of the hymen (or its glands), the nature of discharge.

The concentration of interleukin 1-beta (IL 1-β) and tumor necrosis factor-alpha (TNF-α) was determined by enzyme-linked immunosorbent assay. The method of determination based on solid-phase 'sandwich'-variant with the use of mono- and polyclonal antibodies to IL 1-β and TNF-α. Blood of the subjects was taken in the morning, on an empty stomach, from the ulnar vein, in a volume of 5 ml. The tubes with serum samples were closed with lids and stored in a freezer at -20 °C until analysis. The samples were incubated at 37 °C for 120 min in an air-bath shaker at 700 rpm. The optical density was measured using a spectrophotometer in two-wave mode: the main filter - 450 nm, the reference filter - in the range of 620-655 nm (for 10 minutes).

Statistical processing of the material was carried out using the computer program STATISTICA and Microsoft Exel Windows, StatSoft® Inc.

The design of the study and all methods used in this study were reviewed and approved by the Bioethics Committee of the Higher Educational Institution "Bukovinian State Medical University" (protocol No. 1, dated 24.01.2011). The study meets all the requirements of the Declaration of Helsinki.

The work is a fragment of the research work of the department UDC 618.1-053.34 + 618.1-0536 /.8] -07-084-08 "Prevention, diagnosis and treatment of disorders of the perinatal period and reproductive system of women and adolescent girls" (№ 201110H, state registration number 0111U006499. Term of implementation 02.2011-12.2015).

Table 1

Distribution of adolescent girls in the survey groups by age (M±m)

Survey groups	n	Average age, years	p
M±m	p	14,93±0,37	<0,05
Group I (main)	n=30	14,93±0,37	<0,05
Group II (comparison)	n=40	14,40±0,28	<0,001
Group III (control)	n=27	15,85±0,28	

Note: *p - probability, comparison with the control group.*

Results of the study and their discussion

Girls with thyroid pathology were consulted by a pediatric endocrinologist, with mandatory ultrasonographic examination of the thyroid gland. All girls had menstrual disorders in the form of pubertal menorrhagia or hyperpolymenorrhea.

The average age of girls in both groups was almost the same as shown in Table 1, compared to the control. There was no significant difference between the three groups in the average age category (12 to 17 years) ($p<0.05$). The average age of onset of menarche in group I (n=30) was 11.83±0.20 years, in group II (n=40) 13.05±0.29 years ($p<0.05$), in control group (n=27) 11.44±0.42 years.

Considering the above, the immunological studies were based on the indicators of IL-1β and TNF-α to study their concentration in the blood of adolescent girls with pubertal menorrhagia.

The results of studying the concentration of IL-1β and TNF-α in the peripheral blood of adolescent girls with pubertal menorrhagia (PM) are shown in Table 2.

The results of the study of the cytokine cascade obtained and presented in Table 1 showed that upon admission to inpatient treatment and examination the blood concentration of IL-β was significantly higher (by 60.61%) and a tendency to increase (4.09 times) the concentration of TNF-α in peripheral blood was formed in adolescent girls with pubertal menorrhagia.

Chernivtsi region and the city of Chernivtsi belong to the iodine-deficient region and is an area of endemic Bukovinian goiter. Therefore, a significant number of residents suffer from thyroid pathology. The deterioration of reproductive health among adolescent girls is closely linked to the deterioration of the environmental situation. Deficiency of vital elements, such as iodine, creates unfavorable conditions for the development of the reproductive system, negatively affects the formation of menstrual function and the ovarian-menstrual cycle in particular. Iodine deficiency has a negative impact on the reproductive system of not only adult women, but also adolescent girls.

Therefore, we studied the concentration of certain pro-inflammatory cytokines (IL-1β and TNF-α) in the peripheral blood of 30 adolescent girls with pubertal menorrhagia associated with thyroid pathology. The results of studying the concentration of IL-1β and TNF-α in the peripheral blood of adolescent girls with pubertal menorrhagia associated with thyroid pathology are shown in Table 3.

The results of clinical and laboratory examinations obtained and presented in Table 2 upon admission to inpatient examination and treatment of adolescent girls with pubertal menorrhagia associated with thyroid pathology showed that patients have a steady tendency to reduce the concentration of IL-1β by 6.96% and TNF-α - by 1.48 times.

To establish the influence of thyroid gland pathology on the course of pubertal menorrhagia in adolescent girls, a comparative study of cytokine concentrations in the peripheral blood of adolescent girls with pubertal menorrhagia and pubertal menorrhagia combined with thyroid pathology was conducted. The results of these comparisons are shown in Table 4.

Analysis and synthesis of the results obtained and presented in Table 3 showed that the pathology of the thyroid gland contributes to the inhibition of

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immunocompetent cells production of IL-1β by 1.66 times, TNF-α - by 6.04 times.

Thus, the pathology of the thyroid gland leads to a decrease in immunoregulatory function due to a decrease in the concentration of some important pro-inflammatory cytokines (IL-1β and TNF-α).

Table 2

Concentration of pro-inflammatory cytokines (IL-1β and TNF-α) in peripheral blood of adolescent girls with pubertal menorrhagia (M±m)

Cytokines	Patients with pubertal menorrhagia (n=40)	Practically healthy peers (n=27)	P
Interleukin 1- β (pcg/ml)	0,530±0,08	0,330±0,07	>0,05
Tumor necrosis factor-alpha (pcg/ml)	4,050±2,80	0,990±0,24	>0,05

Note: p - probability, comparison with the control group

Table 3

Concentration of IL-1β and TNF-α in peripheral blood of adolescent girls with pubertal menorrhagia associated with thyroid pathology (M±m)

Cytokines	Patients with pubertal menorrhagia associated with thyroid pathology (n=30)	Practically healthy adolescent girls, (n=27)	P
Interleukin 1- β (pcg/ml)	0,320±0,12	0,330±0,07	>0,05
Tumor necrosis factor-alpha (pcg/ml)	0,670±0,23	0,990±0,24	>0,05

Note: *p - probability, comparison with the control group.*

The results of retrospective studies show that the incidence of menstrual dysfunction with concomitant thyroid pathology among 221 adolescent girls was observed in 49 (22.17%) patients who were on inpatient treatment. Among them, diffuse non-toxic goiter of Ia degree in patients with pubertal menorrhagia occurred eight times more often than thyroiditis. Also, we found that diffuse non-toxic goiter of Ia degree was observed in 32 (65.31%) inpatients, diffuse non-toxic goiter of Ib degree was observed in nine patients (18.37%), and diffuse non-toxic goiter of II degree was observed in four (8.16%) inpatients who were treated for pubertal menorrhagia at the Chernivtsi Regional Perinatal Center.

Table 4

Comparative characteristics of pro-inflammatory cytokines in the peripheral blood of adolescent girls with pubertal menorrhagia and pubertal menorrhagia associated with thyroid pathology, (M±m)

Cytokines	Patients with pubertal menorrhagia associated with thyroid pathology (n=30)	Patients with pubertal menorrhagia (n=40)	P
Interleukin 1- β (pcg/ml)	0,320±0,09	0,530±0,08	>0,05
Tumor necrosis factor-alpha (pcg/ml)	0,670±0,15	4,05±2,80	>0,05

Note: *p - probability, comparison with the control group.*

During the study of the mechanism of development of pubertal uterine bleeding, various pathogenetic theories of development have been put forward. In addition to the classical 'hormonal' concept of menstrual bleeding, there is an 'inflammatory' hypothesis, which is based on certain changes in the endometrium in the phase of late secretion: tissue edema, leukocyte migration and the presence of decidual cells that have signs of tissue fibroblasts. There is also a concept according to which uterine bleeding is an active process that is under the control of matrix metalloproteinases and depends on their activity. The decrease of progesterone concentration in the late secretory phase is the key point that changes the balance in the ratio of metalloproteinase inhibitors and matrix metalloproteinases (MMPs) towards the latter. These proteolytic enzymes (MMP-1, MMP-3, MMP-9) destroy the extracellular matrix and contribute to the rejection of the upper two-thirds of the endometrium. Indirectly, pro-inflammatory cytokines (interleukins types 1 and 8, tumor necrosis factor - alpha) are involved in this process, affecting the processes of angiogenesis, endometrial remodeling and leukocyte involvement, which also produce MMPs [10,11]. The occurrence of pubertal menorrhagia is determined not only by the

level of sex steroid hormones, but also by the local production of other biologically active molecules: prostaglandins, cytokines, growth factors.

As we can see, the theories of pubertal menorrhagia development are diverse, which requires further study of the immunological features of individual pro-inflammatory cytokines in girls with menstrual irregularities in thyroid pathology before and after treatment.

The data obtained indicate that the pathology of the thyroid gland promotes immunosuppression and suppresses the activity of the hypothalamic-pituitary-ovarian system, namely, leads to a decrease in immunoregulatory function by reducing some of the most important proinflammatory cytokines (IL-1β and TNF-α).

Conclusion

Thyroid pathology in girls with pubertal menorrhagia contributes to the inhibition of IL-1β production by immunocompetent cells by 1.66 times, TNF-α by 6.04 times and causes immunosuppression and suppresses the activity of the hypothalamic-pituitary-ovarian system.

Prospects for further research

In the future, it is planned to continue to clarify the place and role of cytokines in the development of menstrual disorders in modern gynecology and human reproduction.

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РОЛЬ ПРОЗАПАЛЬНИХ ЦИТОКІНІВ ІНТЕРЛЕЙКІНА 1-В ТА ФАКТОРА НЕКРОЗУ ПУХЛИН-А В ДІАГНОСТИЦІ ПУБЕРТАТНИХ МЕНОРАГІЙ НА ТЛІ ПАТОЛОГІЇ ЩИТОПОДІБНОЇ ЗАЛОЗИ

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Резюме

Вступ. У пубертатний період репродуктивна система є уразливою до впливу будь-яких несприятливих чинників, що призводять до порушення її функціонального стану та до розладів менструальної функції зокрема. До численних чинників, що провокують порушення становлення менструальної функції, варто віднести патологію щитоподібної залози.

Цитокіни, як відомо, беруть участь у всіх аспектах вродженого і набутого імунітету, включаючи активацію росту і диференціацію імунокомпетентних клітин, запалення і відновлення функції враженого органу. Цитокінам властива дія, що полягає у запобіганні взаємодії клітин імунної, кровотворної, ендокринної та нервової системи. Умовно виділяють цитокіни першого покоління, які продукуються клітинами неспецифічного проти інфекційного захисту. Основними прозапальними цитокінами є ІЛ-1β, ІЛ-2, ІЛ-6, інтерферони, ФНП-α та інші. Основним фактором запальних реакцій є багатофункціональний ІЛ-1β. Фактор некрозу пухлин-альфа (ФНП-α) прозапальний цитокін, є одним із центральних регуляторів факторів і механізмів вродженої резистентності. Він проявляє багато біогенних ефектів, значна частина з яких аналогічна дії ІЛ-1β.

Враховуючи перераховане вище в основу імунологічних досліджень взято саме ІЛ-1β та ФНП-α для вивчення їх концентрації у крові дівчат-підлітків, хворих на пубертатні менорагії.

Мета дослідження. Оцінка цитокінового статусу у дівчат пубертатного віку на тлі супутньої патології щитоподібної залози.

Матеріал та методи. Обстежено 70 дівчат-підлітків, хворих на пубертатні менорагії, які лікувались у гінекологічному відділенні Чернівецького обласного перинатального центру. Дівчата були розподілені на дві групи: I (основна) – 30 дівчат-підлітків з діагнозом пубертатні менорагії на тлі супутньої патології щитоподібної залози, II група (порівняння) – 40 дівчат-підлітків з діагнозом пубертатні менорагії. Контрольна група – 25 практично здорових дівчат-підлітків. Прозапальні цитокіни, а саме інтерлейкіна 1-бета (ІЛ-1β) та фактор некрозу пухлин-альфа (ФНП-α) вивчали один раз, після включення пацієнтів у дослідження, шляхом методом імуноферментного аналізу, що оснований на твердофазному «сендвіч»-варіанті з застосуванням моно- і поліклональних антитіл до ІЛ 1-β та ФНП-α. Пробірки з сироватками закривали кришками зберігали в морозильній камері до проведення аналізу при температурі -20 ºС.

Статистичну обробку матеріалу проводили за допомогою комп¢ютерної програми «STATISTICA» та «Microsoft Exel» Windows, компанії StatSoft® Inc.

Дизайн дослідження та всі методики, які були нами використані в даному дослідженні, розглянуті та схвалені комісією з біоетики закладу вищої освіти «Буковинський державний медичний університет» (протокол №1, від 24.01.2011). НДР «Профілактика, діагностика та лікування порушень перинатального періоду і репродуктивної системи жінок та дівчат підліткового віку» (державний реєстраційний номер 0111U006499. Термін виконання 02.2011-12.2015 рр.

Результати дослідження. Одержані результати вивчення цитокінового каскаду показали, що при поступленні на стаціонарне лікування та обстеження у крові дівчат-підлітків, хворих на пубертатні менорагії без супутньої патології суттєво (на 60,61%) зростає концентрація ІЛ- β і формується тенденція до зростання (у 4,09 раза) концентрації ФНП-α у периферичній крові обстежених пацієнток. Проте, одержані результати клінічно-лабораторних обстежень при поступленні на стаціонарне обстеження та лікування дівчат-підлітків, хворих на пубертатні менорагії, асоційовану з патологією щитоподібної залози показали, що у пацієнток формується стійка тенденція до зниження концентрації ІЛ-1β на 6,96 % та ФНП-α – в 1,48 раза. Встановлено, патологія щитоподібної залози сприяє інгібуванню продукції імунокомпететними клітинами ІЛ-1β в 1,66 раза, ФНП-α –у 6,04 раза.

Висновок. Патологія щитоподібної залози призводить до зниження імунорегуляторної функції через зниження концентрації окремих важливіших прозапальних цитокінів (ІЛ-1β та ФНП-α).

Ключові слова: дівчата пубертатного віку,прозапальні цитокіни, щитоподібна залоза, пубертатна менорагія.

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