EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Sex Steroid-Binding Globulin in Sera of Children with Psoriasis

V. N. Grebenyuk, E. P. Burova, and N. E. Kushlinskii

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Radioimmunoassay of sex steroid-binding globulin (SSBG) in sera of 37 girls with psoriasis aged 7-15 years and in age-matched controls showed a decrease in its concentration in all patients. Serum concentration of SSBG in patients depended on clinical stage, form, and duration of the disease. SSBG levels negatively correlated with age and body weight in patients with psoriasis and in healthy girls. The role of endocrine disorders in the pathogenesis of psoriasis is discussed.

Key Words: *psoriasis; sex steroid binding globulin*

The incidence of severe forms and relapses of refractery psoriasis in children increased in recent years [5,7]. It was suggested that many systems of the organism are involved in this process, including the hepatobiliary, cardiovascular, urinary, immune, and endocrine [5]. There are few reports devoted to endocrinological disorders in children with psoriasis, and all of them are based on just few cases. Endocrinological parameters were studied in adult patients: total 17β estradiol and testosterone, pituitary (luteinizing, follicle-stimulating, somatotropic hormones and prolactin) and thyroid hormones (thyrotropic hormone, triiodothyronine, and thyroxin) [1,4,6]. Estrogenism or androgyny can be detected only by measuring free fractions, but not total concentrations, of sex steroid hormones in blood serum [8,11]. Free steroid is believed to enter target cells and cause early or delayed biochemical response in them [12, 15]. Blood concentration of free steroid fraction, specifically, testosterone is 2-5% [8,15]. The remaining testosterone is bound to albumin and sex steroid-binding globulin (SSBG) in the plasma [14]. In adolescents the relative content of free testosterone is inversely related to SSBG level in the blood [13]. The testosterone-SSBG relationship is covalent, while the albumin-SSBG relationship is labile [11]. Therefore, SSBG concentration determines the level of free testosterone fraction. It is inversely related to SSBG concentration, and therefore, testosterone measurements can help detect changes in the relative content of bioactive testosterone in the blood of patients with psoriasis.

Our purpose was to measure SSBG concentrations in the blood of children of different ages with different clinical forms of psoriasis.

MATERIALS AND METHODS

Thirty-seven girls aged 7-15 years with psoriasis were examined. The majority of them were repeatedly hospitalized for exacerbations of the disease. The disease duration was 1 month to 14 years. 59.4% patients were presented with the progressive stage, 35.2% with stable regressive stage, and 5.4% with remission. Common psoriasis was diagnosed in 43.2%, exudative form in 54%, involvement of the joints, nails, local psoriasis of the hairy part of the head, palms and soles in 2.8% cases. Psoriasis was a hereditary disease in 43.2% patients. Concomitant dis-

Central Institute of Skin and Sexually Transmitted Diseases, Ministry of Health of Russia; N. N. Blokhin Oncology Research Center, Russian Academy of Medical Sciences, Moscow

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eases were hypothyrosis in one patient, a history of renal tumor (Wilms' tumor) 6 years before hospitalization in one patients, and Werlhoff's disease (thrombocytopenic purpura) in one patient.

SSBG was radioimmunoassayed in sera of 37 patients and 37 controls using a Farmos Diagnostica kit. Blood was collected after an overnight fast at 8:00-9:00 from the cubital vein with due consideration for the cycle phase (on days 5-7 and 22-25 at 25-27-day cycle). Physical development of girls was assessed as described elsewhere [3]. Twenty-two girls were prepubertal and early pubertal (7-11 years), fifteen pubertal (12-16 years).

Control group consisted of 37 healthy age-matched girls of similar physical development.

The data were statistically processed using software for medical data.

RESULTS

Basal secretion of SSBG in girls with psoriasis is shown in Table 1. SSBG concentrations in the sera of patients and controls varied within a wide range and depended on age, physical development, and disease form, stage, and duration. SSBG level in the blood of patients was significantly lower than in the controls, irrespective of age. In patients of prepubertal and early pubertal age its concentration was 65.0± 5.4 nM *vs.* 100.8±15.6 nM in the controls ($p<0.05$).

Analysis of correlations in the patients and controls showed a negative correlation between age and serum SSBG concentration (in patients and controls $r=-0.5$, $p<0.01$). Study of correlation between patients' ages and serum SSBG level in prepubertal and early pubertal *vs.* pubertal and late pubertal periods showed some regularities. This correlation was significant in the former group (7-11 years) but not in the latter: there was no relationship between SSBG level and patient's age in the pubertal and late pubertal periods. The same regularity was observed in controls. A negative correlation between body weight and SSBG concentration was established in both age groups of patients and in controls.

The concentration of SSBG was significantly lower in prepubertal and early pubertal patients with exudative psoriasis (61.4±9.4 nM) than in common psoriasis (86.3±9.2 nM, $p<0.05$). By contrast, at the age of 12-15 years there was a tendency toward an increase of SSBG concentration in the patients with exudative form (68.7±12.2 nM) *vs.* common psoriasis (53.0±7.3 nM, $p<0.05$, Table 1). The levels of SSBG were virtually the same in patients with stable regressive (65.4±8.2 nM) and progressive (81.0±10.7 nM, $p<0.05$) stages, aged 7-11 and 12-15 years (58.6± 16.7 and 56.4±6.5 nM, respectively). SSBG concentrations were decreased in younger girls suffering from psoriasis for two years and longer (62.0±12.9 nM). In patients of the same age but with a shorter disease (less than 2 years) the level of SSBG was higher (83.6±8.5 nM). However, the differences between these two groups are statistically insignificant because of a wide range of SSBG values. The concentration of SSBG in patients of prepubertal and pubertal age was different in patients with the disease lasting two and more years, but there was a trend to its increase in older patients (Table 1).

Table 1. Serum Concentrations of SSBG in Girls with Psoriasis (*M±m*)

Patients' characteristics	7-11 years	12-15 years
Disease stage:		
Progressive	81.0±10.07	56.4±6.5
stable regressive	65.4±8.2	58.6±16.7
Disease form:		
common	86.3±9.2	53.0±7.3
exudative	61.4±9.4*	68.7±12.2
Disease duration:		
up to 2 years	83.6±8.5	48.8±6.1
nore than 2 years	62.0±12.9	63.0±8.8
Family history:		
present	84.4±9.8	52.0±9.5
none	63.3±9.7**	67.7±10.9

Note. $p<0.05$: *in comparison with common form, **in comparison with patients with a family history of psoriasis.

Results of measuring SSBG levels in girls with hereditary psoriasis are of special interest. SSBG levels were higher in prepubertal and early pubertal patients with a family history of psoriasis than in those without family history of disease (84.4±9.8 *vs.* 63.3±9.3 nM). By contrast, a decrease of SSBG was observed in older patients with family history of disease: 52.0±9.5 nM, while in age-matched patients without family history of the disease no tendency of this kind was observed: 67.7±10.9 nM.

The concentration of the main human blood protein, SSBG, binding 17β-estradiol and testosterone with high affinity and low capacity directly depends on age, disease form, stage, duration, and family history in girls with psoriasis. The differences in SSBG levels in patients with psoriasis and controls indicate a probable contribution of the sex steroid main transport protein to pathogenetic mechanisms of disease. Endocrine disorders in patients with psoriasis have attracted the attention of scientists because of pronounced changes in the endocrine system (in the pituitary, adrenal cortex, gonads, and thyroid) in this patient population [2,4,6].

It is hardly possible to draw a final conclusion about the role of sex steroid hormones in the pathogenesis of psoriasis, although the level of steroid secretion is genetically determined [8,15]. In addition, an important role of hereditary factor may indicate a relationship between endocrine changes in the organism and mechanisms of psoriasis development. However, this hypothesis can be verified only in large populations in an epidemiological survey. Our data demonstrate changes in an important endocrinological parameter, SSBG, in the blood of girls with psoriasis. Fundamental studies of blood steroid transport proteins have been recently started, although their importance for clinical endocrinology today is undoubted. Blood SSBG level permits a judgment on the absolute and relative content of bioactive free steroids, which enter target cells, including skin cells, and modify their metabolic processes [15]. Previously, skin was shown to be the target for sex steroid hormones, whose binding to skin receptor proteins is more intense [8]. Changes in the levels of free and SSBG- and albumin-bound sex steroids and pituitary, thyroid, and other hormones modify the metabolic processes in skin cells [2,4].

Changes in the endocrine system in healthy prepubertal girls and during various periods of puberty are characterized by specific features [3]. Endocrine glands, whose hormones and bioactive substances are related to SSBG production, are successively triggered and function at each stage of a child's development. Moreover, the mechanisms of central regulation of the hypothalamo-pituitary system are changing, which reflects on sex steroid hormone secretion. Secretion of SSBG by hepatocytes at prepubertal and early pubertal age is regulated by the main androgen of adult age: testosterone in children of both sexes [10,13].

In prepubertal age, the concentration of SSBG is virtually the same in healthy children of both sexes, and in early puberty, when gonads start active functioning, its secretion gradually decreases [13]. The majority of scientists attribute the decrease in SSBG at this period to increased testosterone and androstenedione production by the ovaries and adrenal cortex. A significant decrease in blood SSBG concentration in girls with psoriasis indicates androgyny. The same was observed in adult women with psoriasis [2]. This regularity was observed in all age groups. Possible androgyny of adolescent girls during the pubertal period is caused by intense secretion of androgens by sex glands or adrenal cortex and increased androgen metabolism in skin cells because of increased activity of the key enzyme of testosterone metabolism 5α-reductase. In addition, intense secretion of growth hormone starts in early puberty, which is inversely related to serum level of SSBG [15]. A decrease in SSBG concentration in prepubertal and early pubertal patients can be caused by other factors, for instance, changed secretion of thyroid hormones (specifically triiodothyronine), level of polypeptide growth factors, and percentage of fatty tissue [15].

Many unknown factors modify the production of SSBG in children. Analysis of SSBG levels with consideration for psoriasis form and stage yielded interesting results (Table 1). SSBG level is increased in common *vs.* exudative and in progressive *vs.* stable regressive stages of psoriasis in prepubertal and early pubertal girls. In girls at the pubertal and late pubertal periods the concentration of SSBG did not depend on disease form and stage. These data may be indicative of a variety of factors regulating the production of SSBG during the prepubertal and pubertal periods. A long duration of disease (more than 2 years) in 7-11-year-old girls was also associated with a notable decrease in SSBG concentrations. It cannot be explained by chronic stress, because psoriasis is a chronic stress, and later, at the age of 12-15 years, the level of SSBG had a trend to increase in patients suffering from the disease for a long time. A similar regularity of SSBG fluctuations was observed in girls with a family history of psoriasis. Higher levels of SSBG were observed in girls aged 7-11 years with a family history of the disease, while in girls aged 12-15 years the correlation was negative.

The results obtained permit the following conclusions: serum SSBG concentration is decreased in girls with psoriasis irrespective of age in comparison with healthy controls. SSBG concentration depend on stage, form, and duration of psoriasis. SSBG levels negatively correlate with age and body weight in patients with psoriasis and in healthy girls.

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Significance of Adenylate Cyclase System of the Liver in Its Chronic Diseases

R. A. Vysotskaya, A. S. Loginov, G. G. Varvanina, and A. Yu. Pilenitsyn

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The activity of adenylate cyclase in the hepatocyte plasma membranes, content of cAMP, and cAMP/cGMP ratio in the liver and blood plasma are decreased in patients with chronic liver diseases (fatty dystrophy, chronic hepatitis, and cirrhosis). This decrease depends on the disease severity and is most pronounced in cirrhosis. The sensitivity of liver adenylate cyclase to insulin and glucagon is changed. It is concluded that disorders in the adenylate cyclase system are an important molecular mechanism in the pathogenesis of chronic liver diseases.

Key Words: *adenylate cyclase; cyclic nucleotides; chronic diseases of the liver*

The significance of the adenylate cyclase system for functional activity of the liver in health and disease has not been evaluated. Cyclic nucleotides, primarily cyclic adenosine monophosphate (cAMP), actively participate in biochemical processes regulated by the liver: regulation of cell metabolism, realization of hormone effects on lipid and carbohydrate metabolism, protein production, and modification of cell growth and differentiation [8,10]. There are some contradictory reports about changes in the activity of membrane-bound cAMP adenylate cyclase (AC) and the levels of cyclic nucleotides in the liver during chronic diseases in rats [11]. Patients with chronic diseases of the liver develop metabolic and hormonal disorders whose biochemical mechanisms are still unknown.

Our purpose was to investigate AC system of the liver in man in health and chronic disease and to elucidate the role of this system in the disease development.

Central Institute of Gastroenterology, Moscow

MATERIALS AND METHODS

A total of 125 patients with chronic diseases of the liver (fatty dystrophy, chronic hepatitis, and cirrhosis of different etiology and severity) were examined. The diagnosis was made on the basis of comprehensive examinations including general clinical biochemical, morphological, x-ray, and ultrasonic studies. Control group consisted of 12 subjects without gastrointestinal disease or liver involvement, according to morphological studies. Adenylate cyclase (EC 4.6.1.1) activity in plasma membranes of liver cells was assayed by the radioisotope method [4]. The incubation medium contained 50 mM Tris-HCl (pH 7.5), 30°C, 5 mM $MgCl_2$, 0.5 mM cAMP, 0.5 mM isobutylmethylxanthine, 0.1 mM ATP (0.5 μCi ^{32}P-ATP), 20 mM creatine phosphate, 0.2 mg/ml creatine kinase, 0.1 mM GTP. The reaction was triggered by adding 10-50 mg protein. The duration of incubation was 20 min at 30°C. cAMP and cGMP in liver homogenates and blood plasma were radioimmunoassayed

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