Gynecomastia — a difficult diagnostic problem

Ginekomastia — trudny problem diagnostyczny

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Abstract

Gynecomastia is a benign, abnormal, growth of the male breast gland which can occur unilaterally or bilaterally, resulting from a proliferation of glandular, fibrous and adipose tissue. Gynecomastia is characterised by the presence of soft, 2–4 cm in diameter, usually discus-shaped enlargement of tissues under the nipple. It is estimated that this pathology occurs in 32–65% of men over the age of 17. Gynecomastia is a psychosocial problem and may lead to a perceived lowering of quality of life.

The main cause of gynecomastia is a loss of equilibrium between oestrogens and androgens. Increased sensitivity for oestrogens of the breast gland, or local factors (e.g. an excessive synthesis of oestrogens in breast tissues or changes in oestrogen and androgen receptors) may cause gynecomastia. Also, prolactin, thyroxine, cortisol, human chorionic gonadotropin, leptin and receptors for human chorionic gonadotropin, prolactin and luteinizing hormone localised in tissues of the male breast may participate in the etiopathogenesis of gynecomastia.

Usually three types of gynecomastia are distinguished: physiological, idiopathic and pathological gynecomastia. The latter is the consequence of relative or absolute excess of oestrogens. In this paper, frequent as well as casuistic causes of gynecomastia will be described.

A diagnosis of gynecomastia is usually possible after a palpation examination. Ultrasonographic, mammographic or histopathological examinations are useful in aiding diagnosis. The five degree scale devised by Tanner and Marshall is useful in estimating disease progression. **(Pol J Endocrinol 2011; 62 (2): 190–201)**

Key words: *gynecomastia, etiopathogenesis, diagnosis, psychosocial problem*

Streszczenie

Ginekomastia jest łagodnym, nieprawidłowym, występującym jedno lub obustronnie wzrostem objętości gruczołów piersiowych u mężczyzn, wynikającym z rozrostu tkanki gruczołowej, włóknistej i tłuszczowej. Zmiany charakteryzują się obecnością miękkiego, zwykle dyskoidalnego powiększenia tkanek o średnicy 2–4 cm, zlokalizowanego pod brodawką sutkową. Szacuje się, że występuje u 32–65% mężczyzn powyżej 17. roku życia. Ginekomastia stanowi problem psychospołeczny i prowadzi do pogorszenia jakości życia mężczyzn.

Główną przyczyną ginekomastii są zaburzenia równowagi pomiędzy estrogenami a androgenami. Do jej rozwoju może prowadzić również zwiększona wrażliwość tkanki gruczołu piersiowego na estrogeny i/lub czynniki miejscowe (takie jak np. nadmierna produkcja estrogenów w tkankach gruczołu piersiowego, a także zmiany dotyczące receptorów dla estrogenów i androgenów). Również prolaktyna, tyroksyna, kortyzol, ludzka gonadotropina kosmówkowa, leptyna oraz receptory dla β-hCG, prolaktyny i luteotropiny zlokalizowane w tkance męskich gruczołów sutkowych mogą brać udział w rozwoju ginekomastii.

Wyróżnia się ginekomastię fizjologiczną, idiopatyczną i patologiczną, będącą wynikiem bezwzględnego lub względnego nadmiaru estrogenów. W pracy opisano zarówno częste, jak i kazuistyczne przyczyny ginekomastii.

Rozpoznanie stawiane jest zwykle na podstawie badania palpacyjnego. W diagnostyce wykorzystywane są techniki obrazowe, takie jak ultrasonografia czy mammografia lub badanie histopatologiczne. W ocenie zaawansowania ginekomastii przydatna jest 5-stopniowa skala Tannera i Marshalla. **(Endokrynol Pol 2011; 62 (2): 190–201)**

Słowa kluczowe: *ginekomastia, przyczyny, diagnostyka, aspekty psychospołeczne*

Introduction

The term gynecomastia (Greek: gyne = woman, mastos = breast) was introduced in the first century A.D. by Galen. Gynecomastia is marked by a benign, abnormal, unilateral or bilateral volumetric increase in men's breast glands as a result of the proliferation of glandular, fibrous, and adipose tissue. Changes are characterised by a soft, usually discoidal tissue enlargement two to four centimetres in diameter, located below the nipple. The enlargement of the glands is usually bilateral and symmetrical; however, gynecomastia may also occur unilaterally, usually on the left side [1]. The enlarged volume of the breast glands in some cases may be accompanied by tenderness and pain, the cause of which is usually the rapid growth of glandular tissue. Its occurrence among men over the age of 17 is estimated at 32–65%. In some age groups, such changes may

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occur in up to 72% of men [2–4]. Diagnoses are often made on the basis of palpation exams: the diameter of the palpable lesion should then exceed 2 cm. In diagnosing gynecomastia, visual techniques such as ultrasonography or mammography may prove useful. It may also be diagnosed on the basis of a histopathology exam, which necessitates invasive diagnostic methods [2]. In the assessment of gynecomastia, Tanner and Marshall's five-stage scale evaluating the proper development of the breast glands is useful [5].

The causes of gynecomastia

The commonest cause of gynecomastia is disturbance of the balance between oestrogens (exhibiting a stimulatory action on the breast gland) and androgens (which have an inhibitory function) [6–8]. The changes frequently occur in response to an increased production and//or activity of oestrogens and a decreased production and/or activity of testosterone. Increased sensitivity of the breast tissue to oestrogen may also lead to the development of gynecomastia, at which time the development of changes occurs despite the proper concentration of these hormones in the blood. A major role in the pathogenesis of changes seems to be played by local factors, such as excessive production of oestrogens in the breast tissues, being a result of increased activity of aromatase, their decreased degradation, and also changes concerning oestrogen and androgen receptors [9]. Likewise, prolactin (PRL), thyroxin, cortisol, human chorionic gonadotrophin (β-hCG), leptin, and receptors for β-hCG, prolactin, and luteotropin localised in the tissue of men's mammary glands may play a part in the development of gynecomastia [10–12].

Hyperprolactinaemia, once considered to be the primary cause of gynecomastia, in fact plays a less significant role in its origination. In most patients with gynecomastia, the level of PRL in the blood is within the normative range [12]. An elevated level of PRL may however inhibit the secretion of gonadotropins, evoking secondary hypogonadism, although gynecomastia does not occur in all patients with hyperprolactinaemia. Enlargement of the breast glands is also affected by an excess of growth hormone (GH) and insulin-like growth factor (IGF). The major impact of these substances on the growth of breast gland size, and the increase of the proliferation index of the epithelium, have been demonstrated in experimental studies [13] (Table I).

Types of gynecomastia
Physiological gynecomastia
Physiological gynecomastia is most often defined as symptomless gynecomastia occurring in three periods of life [3]:

Table I. *Gynecomastia — causes and frequency of their occurrence [2]*

Tabela I. *Ginekomastia — przyczyny i częstość ich występowania [2]*

Cause	Frequency of occurrence
Idiopathic	25%
Sexual maturity	25%
Medications	10–20%
Hepatic cirrhosis or poor nourishment	8%
Primary hypogonadism	8%
Orchidoncus	3%
Secondary hypogonadism	2%
Hyperthyreosis	2%
Kidney diseases	1%
Others	6%

Infancy
Transient gynecomastia is observed in 60–90% of infants, being a result of the activity of maternal oestrogen found in the child's organism. Changes usually give way to idiopathic regression within a few months.

Adolescence
Gynecomastia as a result of excessive production of oestrogen and its precursors in relation to testosterone is found in 20–70% of pubertal boys. The peak of symptom occurrence is experienced at 13–14 years of age. Changes usually give way to spontaneous regression in six months to three years. It seems that in the pathogenesis of gynecomastia, besides the upsetting of the hormonal balance, a major role may be played by an elevated level of leptin, which has been observed in boys with pubescent gynecomastia. This compound increases the activity of aromatase in the fatty tissue as well as other tissues of the breast gland. This leads to a rise in the concentration of oestrogens and/or the oestrogen//androgen relation. The impact of leptin on the development of gynecomastia is also probably connected to its direct functional stimulation of the growth of mammary gland cells or the increase of sensitivity of these cells to oestrogen with concurrent functional activation of oestrogen receptors in the breast gland tissue [14]. A significant overgrowth of glandular tissue persisting beyond 17 years of age usually requires the application of the appropriate treatment. Cases of gynecomastia (often occurring unilaterally) are observed among adolescent boys in the course of neurofibromatosis [15].

Senescence
About 30–85% of cases of physiological gynecomastia occur in men aged 50 to 80. The cause of the changes is

most often a relative excess of oestrogens resulting from an age-related reduced production of testosterone and intensification of its peripheral aromatisation to oestrogen, which in turn leads to an upset of the androgen/ /oestrogen balance. Gynecomastia occurring in the andropause period usually does not give way to idiopathic regression. Decreased range of testosterone levels, and in some cases an increased level of LH, occurs among patients [16]. The fall in testosterone levels results from a decreased efficiency of testicular hormones, and their intensified aromatisation connected with excessive accumulation of fatty tissues, being an important centre of aromatisation of androgens and oestrogens.

Idiopathic gynecomastia

Idiopathic gynecomastia (of unknown origin) rivals physiological gynecomastia as the most commonly diagnosed type of gynecomastia, and constitutes 25% of all cases. Making such a diagnosis requires ruling out all other known causes of overgrowth of the breast glands. Proper concentrations of gonadotropin, sex hormones, and SHBG (sex-hormone-binding-globulin) are often observed in patients [17]. However, according to Zgliczyński et al., increased concentrations of SHBG occur among men diagnosed with idiopathic gynecomastia [18]. In response, clinical studies by Ernsos et al. confirm the existence of a correlation between idiopathic gynecomastia, obesity, and decreased concentrations of testosterone and LH, which may be a result of increased conversion of testosterone into oestradiol in excessively developed fatty tissues [19]. It is assumed that impaired tissue response, which may be an effect of a diminished number of androgen receptors, may also lead to the proliferation of glandular tissue in this type of gynecomastia [20]. It seems that the developmental basis of idiopathic gynecomastia may also lie in a local increase in activity of aromatase [21].

Pathological gynecomastia

In the United States over the course of the last 50 years, gynecomastia has been reported as an unwanted side-effect of more than 300 pharmaceutical drugs. According to various sources, drug-induced gynecomastia constitutes 10–25% of all cases of gynecomastia [2, 22]. It is often a consequence of chronic application of hormonal drugs, antibiotics, preparations for the treatment of cardiovascular diseases, ulcers, chemotherapeutics, retroviral drugs and some psychiatric medications. These medications induce gynecomastia through various mechanisms, mainly direct or indirect increasing of the oestrogen/androgen relation, the result of which is the disturbance of the activity of the hypothamalic-hypophyseal-nuclear axis. Therapeutic agents may also exert an oestrogenic effect, dislodge oestrogens from the con-

nection with SHBG, increase activity of aromatase, act anti-androgenously and increase PRL secretion [2, 17, 22]. Enlargement of the breast glands among those treated for arterial hypertension often testifies to the existence of a secondary cause of arterial hypertension or undesirable effects of applied hypertensive medications [23, 24]. Abuse of alcohol, marijuana, heroin and amphetamines also increases the risk of gynecomastia [25]. It may also be evoked by teratogenic substances acting on the foetus in the prenatal period, the effect of which may cause subsequent hypogonadism in the foetus [26] (Tables II, III).

As previously mentioned, the cause of gynecomastia is an imbalance between oestrogens and androgens. The upsetting of the oestrogen/androgen relation may also result from both actual and relative excess of oestrogens.

Gynecomastia in the course of actual excess of oestrogens

Exogenous oestrogens, substances of oestrogenic and anti-androgenic function

The common occurrence in a person's environment of compounds of oestrogenic function carry with them the risk of development of gynecomastia. There are several categories of these substances, in the composition of which are included compounds of weak oestrogen function (xenoestrogens) capable of affecting a person's health [55]. Among these, it is possible to distinguish diet composition, such as meat and some fitoestrogen-containing edible plants, which when consumed (long-term and in large quantities) may increase the risk of the development of gynecomastia [56]. Examples of fitoestrogens are genistein contained in soy and other leguminous plants, and 8-prenylnaringenin contained in hops. Martinez et al. described a case of gynecomastia as the result of high consumption of soy products [57]. However, the effect of a diet rich in soy on the development of gynecomastia is not unambiguous. Experiments conducted on monkeys excluded the effect of a several-year-long soy-rich diet on the development of gynecomastia [58, 59]. There were no demonstrated differences in the structure and mass of breast glands of individuals subsisting on a soy diet and a normal diet. Nor did the soy diet have an effect on the concentration of oestradiol and testosterone in the serum of the animals studied in the experiments. Histopathological and histomorphometric studies on mammary glands have not demonstrated irregularities or gynecomastic features [59].

Numbered among xenoestrogens are also synthetic compounds applied as additives to fodder. Moreover, oestrogenic effects are displayed by substances applied in agriculture such as plant-protecting agents. Compounds of a weakly oestrogenic nature are also found in

Table II. *Selected drugs and substances capable of inducing gynecomastia on the basis of [2, 22, 27–54]*

Tabela II. *Wybrane leki i substancje mogące wywoływać ginekomastię; na podstawie [2, 22, 27–54]*

Antiandrogens/Androgen synthesis inhibitors	Bicalutamide, Cyproterone, Finasteride, Flutamide
Antibiotics/Chemotherapeutics/Antifungal drugs/ /Anti-retroviral drugs	Didanosine, Efavirenz, Ethionamide, Isoniazid, Ketoconazole, Metronidazole, Stavudine, Zidovudine
Drugs applied in the treatment of peptic ulcer disease	Cimetidine, Omeprazole, Ranitidine
Drugs applied in the treatment of cardiovascular diseases	Amiodarone, Amlodipine, Captopril, Digitoxin, Diltiazem, Enalapril, Methyldopa, Nifedipine, Reserpine, Spironolactone, Verapamil
Hypolipidemic drugs	Atorvastatin , Fenofibrate, Rosuvastatin
Psychiatric drugs	Diazepam, Phenothiazines, Haloperidol, SSRI (Fluoxetine, Paroxetine, Venlafaxine), Mirtazapine, Risperidone, Tricyclic antidepressants
Hormones	Androgens and anabolic steroids, Oestrogens and agonists of oestrogens, Chorionic gonadotrophin, Growth hormone
Drugs applied in chemotherapy	Vinca alkaloids (e.g. Vincristine, Vinblastine), Imatinib, Alkylating drugs, Methotrexate, Polychemotherapy
Addictive drugs/Narcotics	Alcohol, Amphetamine, Heroin, Marijuana, Methadone
Others	Auranofin, Buspirone, Dasatinib, Diethylpropion, Domperidone, Etretinate, Phenytoin, Marinol, Metoclopramide, Penicillamine, Saquinavir, Sulindac, Theophylline

Table III. *Mechanism of pharmacological action of selected drugs capable of inducing gynecomastia [17]*

Tabela III. *Mechanizm działania farmakologicznego wybranych leków mogących wywoływać ginekomastię [17]*

Drugs	Mechanism of action
Diazepam, Digoxin, Phenytoin, hCG, Clomiphene, Anabolic steroids, , Conjugated and synthetic oestrogens	Are metabolized to oestrogens, possess intrinsic oestrogenic activity or stimulate synthesis of oestrogens
Bicalutamide, Cimetidine, Flutamide, Isoniazid, Ketoconazole, Cytotoxic drugs (Busulfan, Vincristine, Vinblastine), Marijuana, Methotrexate, Metronidazole, Omeprazole, Penicillamine, Ranitidine, Spironolactone	Exhibit anti-androgenic properties or inhibit synthesis of androgens
Domperidone, Haloperidol, Metoclopramide, Phenothiazines	Induce hyperprolactinemia
Alcohol	Increase metabolism and clearance of androgens
Diazepam, Phenytoin	Increase concentration of SHBG

industrial products, for example in paint and cleaning products. An influence on a person's hormonal management may also be exerted by pharmaceutical drugs, such as contraceptive drugs and other hormonal medications, of which a small amount makes its way into the water supply via the sewage system.

In literature there are described cases of the occurrence of gynecomastia among prepubertal boys as a result of indirect exposure to preparations containing oestrogens in their composition [60, 61]. In the blood of children whose mothers applied creams with oestrogen additives, Felner et al. revealed heightened levels of oestradiol [60]. Edidin et al. also described a case of gynecomastia in a boy, of which the cause was the application of hair cream containing in its composition substances of oestrogen function [61]. Similar cases have occurred as the result of the application of hygiene preparations containing lavender oil and tea tree oil [62]. In vitro studies using isolated human breast cancer cells have confirmed the weakly oestrogenic and anti-androgenic properties of these substances [62]. There have also been cases of the development of gynecomastia in the aftermath of consumption of nettle teas and Chinese 'Dong Quai' tablets, popularly known as 'women's Ginseng', and containing in their composition pulverised roots of Chinese Angelica *(angelica sinensis)* [63–65]. The overgrowth of mammary glands among men has been observed after the consumption of Burra Gokharu (tribulis terrestris), used by body-builders and athletes as an alternative to steroids [66]. Brody et al. described a case of an epidemic of gynecomastia among refugees as a result of the application of specimens used in

the treatment of lice infestation (pediculosis) which contained in their composition phenothrin, a compound with anti-androgenic properties [67].

Taking into consideration the universal presence of compounds in a person's environment which may increase the risk of the development of gynecomastia, it seems that precise determination of a person's eating habits and susceptibility to exogenous oestrogens/anti-androgens is called for. This especially pertains to those afflicted in whom all known causes of gynecomastia have been ruled out.

Holiday gynecomastia
In the early 1990s, Heufelder et al. described a case of gynecomastia which appeared in a man after his return from a long vacation in the Virgin Islands. The authors of this research, after excluding other known causes, recognised that the cause of breast gland enlargement was a 'vacationary' lifestyle, consisting of daily consumption of large amounts of alcohol and a significant intake of poultry containing in its composition oestrogens [68]. It seems that the risk of developing holiday gynecomastia may be particularly increased by certain kinds of alcohol, for example phytoestrogen-containing bourbon [69]. Chronic alcohol consumption or occasional binge-drinking may lead to the impairment of testicular function, resulting in a decrease of testosterone production. Ethanol also inhibits the conversion of androgen precursors (androstenedione and dehydroepiandrosterone- DHEA) into androgens in the liver. Through a stimulatory effect on aromatase and adenylate cyclase, peripheral conversion of precursors of androgens into oestrogens may also be intensified [70]. In turn, the inhibitory effect on dopaminergic activity in the brain stimulates PRL production in the pituitary gland. This may induce the growth of breast gland tissue [71].

In scientific literature as far back as the 1970s, cases of consumption of poultry containing in its composition diethylstilbestrol, an oestrogen-like structure compound applied as a growth stimulator to animal fodder, have been described [72]. According to Dardick, an additional factor which may increase the risk of holiday gynecomastia could be smoking large amounts of marijuana [73]. This seems to confirm the work of other authors concerning the application of narcotics and their effect on the breast gland [74, 75]. There are no reports excluding the effects of cannabis on the development of gynecomastia among men [76]. As Heufelder et al. say, holiday gynecomastia syndrome should be taken into consideration in every case of reversible gynecomastia prior to a diagnosis of idiopathic gynecomastia [77].

Oestrogen-producing tumours of adrenal glands
Oestrogen-producing tumours of adrenal glands are in most cases benign. They are characterised by their large

size and in roughly half of cases are accessible in palpation exams of the abdominal cavity [78]. They are marked by a tendency to secrete large amounts of substances such as androstenedione, DHEA and DHEA sulphate (DHEA-S), being the precursor of oestrogens. Some of these produce oestradiol and oestrone [2]. According to Bembo et al., there is an increased level of 17-ketosteroids detected in urine analysis in two thirds of those afflicted. In some cases, there is an increased level of DHEA-S in the serum [3]. According to Lanigan et al., gynecomastia may sometimes be the sole symptom of the presence of a feminising tumour of the adrenal cortex [79].

Gynecomastia in the course of β-hCG-producing tumours
Some of the tumours secreting β-hCG possess the capacity for the uptake of oestrogen precursors and their aromatisation to active oestrogens [3]. Human chorionic gonadotrophin in its structure and function resembles LH. Increased levels of β-hCG stimulate Leydig cells to secrete oestradiol. Mentioned among tumours producing β-hCG are, among others, embryonic tumours of the testicles, liver, and stomach [80]. There have also been cases published of painful gynecomastia occurring among patients with clear cell renal cell carcinoma, lung neoplasms and β-hCG secreting tumours of the urinary tract. After surgical treatment, the levels of β-hCG diminished, reaching undetectable levels in standard tests, and gynecomastia underwent regression [81–84].

Aromatase Excess Syndrome (AEXS)
Aromatase Excess Syndrome, also called familial gynecomastia, is a familial, genetic, heterogenic disease of autosomal dominant inheritance [85–87]. It is characterised by an increased concentration of oestrogens in the blood serum, as a result of an augmentation of peripheral conversion of C-19 androgens into oestrogens.

Probably the first documented occurrence of AEXS originates from the 14th century B.C. and was discovered in the tomb of the Pharaoh Tutankhamun. This documentation confirms evidence of the occurrence of familial gynecomastia in the Pharaoh, his brother, father and grandfather [88–90]. In 2005, Tiulpakov et al. described a five-generational Russian family in which the occurrence of gynecomastia was documented in 16 family members. Symptoms of AEXS affected both sexes and began developing in early childhood in the form of breast enlargement, rapid growth, and accelerated bone age. In the case of the adults, the following features were observed: short stature and gynecomastia among the men, and macromastia and more frequent gynaecological diseases related to oestrogen excesses, such as cancer of the endometrium, uterus myomas or the inflammation of menstruation, among the women

[91]. The mutation causing the occurrence of AEXS has not been defined. Presumably it may concern the P450 gene for aromatase [92]. The mutation causing the occurrence of AEXS may reveal itself as early as in the period of increased secretion of androgens of the adrenal cortex in the time preceding sexual maturity, or also in its early stage [17, 93].

Gynecomastia in the course of 11β-hydroxylase and 21-hydroxylase deficiencies

There have been published cases of gynecomastia occurring in boys caused by an increased peripheral conversion of androstenedione, resulting from deficiencies of 11-β-hydroxylase (11-β-OHD) and 21-hydroxylase (21-OHD) [94,95]. In the case of 21-OHD deficiency, there has been observed regression of symptoms as a result of glucocorticoid replacement therapy. As Waśniewska et al. say, 21-OHD deficiency may be a more frequently supposed cause of gynecomastia in both the prepubertal and pubertal periods. The earliest possible diagnosis is essential because prolonged gynecomastia is resistant to pharmaceutical treatment [95].

Gynecomastia in the course of other genetic diseases

The occurrence of gynecomastia is more frequent among men with karyotype 47, XXY (Klinefelter's syndrome) and among subjects with masculine phenotype possessing karyotype 46, XX (MEN [Multiple endocrine neoplasia] syndrome). According to Korenman, gynecomastia may accompany Klinefelter's syndrome in approximately 80% of cases, and its primary cause is primary hypogonadism [96]. Changes are accompanied by elevated concentrations of LH and FSH, with concurrent lowering of total and free testosterone and proper levels of E2 and SHBG. Men with an additional X chromosome are also marked by smaller gonad volume [97]. Klinefelter's syndrome is accompanied by a 10-20-fold increased risk of the development of breast cancer, something which is not found in cases of gynecomastia of other etiologies [96, 98]. Painful gynecomastia may also be one of the endocrinological complications in patients suffering from myotonic dystrophy (Steinert's disease) [99]. Occurrence of gynecomastia is also described in the course of pseudomyopathic spinal muscular atrophy [100]. Gynecomastia may also occur in persistent Mullerian duct syndrome, a rare disease consisting of, among other disturbances, the presence of fallopian tubes, uterus or upper vaginal fragments among individuals of the male sex [101–103].

Gynecomastia in the course of prostate cancer

The tolerance of hormonal therapy administered for prostate cancer is usually good. Gynecomastia or tenderness and pain of breasts are potential side effects of this therapy. The occurrence of side effects depends on the mechanism of action of the administered substance. Among other drugs, nonsteroidal anti-androgens which block androgenic receptors (bicalutamide, flutamide or nilutamide) are used in the treatment of prostate cancer. In up to 90% of cases, these drugs may cause mild to moderate gynecomastia, in contrast to steroidal androgen-cyproterone, which has a significantly lower occurrence of gynecomastic changes [104, 105]. Gynecomastia and breast pain are observed on average in 50% of men treated with bicalutamide and nilutamide (24–76% of patients respectively). Treatment with flutamide has been connected with occurrence of these symptoms in 30–79% of patients [106]. However, treatment with one LHRH agonist, leuprolide, induced gynecomastia and breast pain in only in 3–12.7% of cases [106].

Gynecomastia after spinal cord injury

Gynecomastia is a well-known medical phenomenon among patients with spinal cord injuries [107, 108]. Therefore it can be assumed that the disorders of the diencephalon play an important role in its etiology. Heruti et al. described several cases of the occurrence of gynecomastia after spinal cord injury. Enlargement of the breast glands was observed one to six months after trauma. As the authors say, diagnostics excluding gynecomastia should be conducted in every patient after a spinal cord injury [108].

Stress-induced gynecomastia

There are published cases of the occurrence of transient gynecomastia in response to stress. At the time of stress, increased concentrations of cortisol and oestradiol, with an accompanying decrease in the level of testosterone in the blood serum, are observed, though the level of hormones was still found to be within the proper range. According to Gooren et al., the adrenal gland may increase secretion of oestrogen precursors in response to stress, which among other things may be a cause of periodically occurring gynecomastia [109].

Gynecomastia in the course of relative oestrogen excess
Primary hypogonadism

Primary hypogonadism is hormonal underactivity occurring in the aftermath of testicular injury. Its cause may be genetic factors (e.g. Klinefelter's syndrome) often occurring in the course of testicular inflammation (i.e. mumps), mechanical injuries, pharmaceutical treatment, chemo- or radiotherapy, and also in the course of serious diseases as well as overdose of stimulants. It also occurs as an after-effect of surgical operations or poisoning, for example by heavy metals [2, 110–113].

Among patients with gynecomastia in the course of primary hypogonadism, the presence of a testicle-da-

maging factor has been asserted in medical histories. In physical examinations in some cases somatic features resulting from lowered testosterone levels are present. In laboratory research, the lowering of total and free testosterone levels in particular are asserted. A rise in the LH level stimulates aromatase in Leydig cells of the testicles to produce a large amount of oestrogens and peripheral aromatisation of androgenic androstenedione to oestrogen does not give way to change. Gynecomastia is also observed among castrated men [114, 115]. As Biglia et al. say, gynecomastia occurring among carriers of the HIV virus tends to be induced by hypogonadism, and is not, as some researchers believe, a side-effect of retroviral therapy [116].

Secondary hypogonadism (hypothalamus-pituitary)
Gynecomastia may also be an effect of androgen deficiency in the course of secondary hypogonadism, being a result of underactivity of the hypothalamus and/or pituitary gland. Because of a lack or decrease in secretion of pituitary gonadotropin, the testicles do not produce a proper amount of testosterone, and peripheral aromatisation of adrenal androgens to oestrogens remains unperturbed and ensures normal oestrogen levels in the serum [3]. Secondary hypogonadism is characterised by low levels of gonadotropin and testosterone. This form of hypogonadism is usually conditioned by organic illness of the hypothalamus or pituitary. The cause of hypogonadism may also be a genetic defect, for example the disturbance of synthesis of gonadotropin with accompanying anosmia (Kallmann syndrome). Tumours and abscesses of the hypothalamus or pituitary gland, inflammation processes, skull injury, vascular change, haemochromatosis and tuberculosis may also lead to secondary hypogonadism. It may arise as a complication from a surgical procedure, occur in the course of severe constitutional illnesses, and also be a reaction to extreme overexertion. The cause of hypogonadism may also be rapid and excessive reduction of body mass. All of these causes may be related to the risk of hypogonadism often accompanying gynecomastia.

Refeeding gynecomastia
Gynecomastia occurring a few weeks after resumption of a normal diet among persons extremely malnourished was observed for the first time among prisoners of war after World War II. The symptoms usually gave way to idiopathic regression after one or two years. The exact mechanism of inflammation was not recognised, although Carlson suggests that it may be similar to that which occurs in gynecomastia in the period of sexual maturity [9]. Appreciable weight loss secondary to malnourishment is often associated with hypogonadism due to decreased gonadotropin secretion. Together with body growth, secretion of gonadotropin and gonad

function return to normal, the effect of which may be a so-called second puberty [9].

Gynecomastia in the course of liver disease
Gynecomastia occurs commonly among patients suffering from alcohol-induced cirrhosis of the liver, often associated with hypogonadism [117, 118]. Liver disease leads to the intensification of the peripheral process of aromatisation of androgens to oestrogens. In some cases, heightened levels of SHBG are also claimed, which is a cause of reduction of free testosterone [9, 119]. Farthing et al. observed a significantly higher level of progesterone among men with non-alcohol-related cirrhosis and gynecomastia compared to men without features of overgrowth of the breast glands. No such dependence was confirmed in the group of men with alcohol-induced fatty degeneration of the liver or cirrhosis in the course of alcoholism [120]. Progesterone displays a synergistic effect with oestrogen on the mammary gland, stimulating growth of the glandular alveolus and the end-epidermis of canals. Among women, it appears with expression of receptors vital to lactation. In the researched group, hyperprolactinaemia was observed among 14% of those tested with liver disease; however, this level did not correlate with the presence of gynecomastia [120]. In turn, as Van Thiel et al. suggest, alcoholics with a fatty liver and without features of gynecomastia are characterised by a decreased level of PRL and excessive response to TRH. In contrast, alcoholics with both cirrhosis and gynecomastia are characterised by an elevated level of PRL and a decreased response to TRH [121]. There are also published cases of bilateral gynecomastia occurring in the course of primary liver cancer (hepatocarcinoma) or in the form of malignant hepatoma (fibrolamellar carcinoma) producing oestrogens. The symptoms of gynecomastia subsided after surgical removal of the tumours [122–124].

Gynecomastia in the course of chronic kidney failure
In the course of chronic kidney failure, gynecomastia has been observed in around 18% of patients [125]. Men with chronic kidney failure are marked by a number of hormonal disturbances including a low level of testosterone in the blood serum, elevated levels of oestradiol and LH, together with a slightly increased level of PRL in the blood serum. Hormonal disturbances often regress after kidney transplantation, but dialysis does not affect them [126, 127]. Dialysis-related gynecomastia usually regresses idiopathically after one or two years. The pathogenesis of change is similar to that occurring in the course of refeeding gynecomastia. Prior to the initiation of dialysis, patients with kidney failure usually have a low body mass resulting from the necessity

of adhering to a strict diet. In the course of dialysis, the diet is expanded and patients usually gain weight [3].

Gynecomastia in the course of hyperthyroidism
The occurrence of gynecomastia with an overactive thyroid is estimated at around 10–40% [3]. Thyroid hormones increase synthesis of SHBG in the liver [77]. The effect of this is a rise in the concentration of total testosterone, a lowered level of free testosterone and a rise in the concentration of oestradiol in the blood. The effect of weakly-bonded oestradiol with SHBG in those suffering from hyperthyroidism is an elevated level of free oestradiol alongside proper levels of testosterone in the blood serum. Hyperthyroidism also leads to increased peripheral conversion of androgens to oestrogens through aromatase [9]. Hyperthyroidism leads to the intensification of the adrenal process of steroidogenesis. A rise in production of androstenedione leads to increased peripheral synthesis of oestrone. After achieving a state of euthyroidism, there have been seen decreases and even complete reversals of gynecomastic change and a subsidence of painful ailments [3, 128–130]. In some undiagnosed patients, gynecomastia may be the first symptom of an overactive thyroid [131]

Gynecomastia as a manifestation of testicular disease
Castro-Magana et al. showed that varices of the spermatic cord may inflame the activity of dehydrogenase 17β-hydroxysteroidal, thereby reducing the production of testosterone and leading to the development of gynecomastia [132]. Gynecomastia may also be an endocrinological manifestation of testicular cancer. Testicular cancer is among the commonest tumours occurring in men in their twenties and thirties. Each year, 3-6 new cases are documented per 100,000 men. It is estimated that around 7–11% of men in the initial phase of the illness develop gynecomastia which may precede the presence of a palpation-detectable testicular lump and the occurrence of hormonal disturbances [133, 134]. In around 9% of patients, the development of gynecomastia is preceded by the application of chemo- or radiotherapy in the treatment of testicular cancer [134]. In cases of Leydig cell tumours, where the cause of gynecomastia is increased concentration of oestradiol, the symptoms may be present even in 20% of cases. Only 1-3% of all testicular tumours are Leydig cell tumours. Leydig cell tumours can occur at any age, but most often concern boys aged 5 to 10 and men aged 25 to 35. The presence of a tumour may be connected with gynecomastia and the lack of a palpation-detectable testicular lump, but noticeable during ultrasonographic examination. About 90% of tumours are benign [126, 135–137]. Increased oestradiol concentration inhibits LH secretion, resulting in a decrease of testosterone level. An elevated oestradiol

level also stimulates synthesis of SHBG, which preferentially binds testosterone leading to a decrease of the free testosterone level associated with normal or elevated free oestradiol level. There are published cases of the regression of bilateral gynecomastia and hormonal disturbances (decreased gonadotropin level and decreased testosterone/oestradiol ratio) in groups of men after orchidectomy due to Leydig cell tumour [138–140].

The occurrence of gynecomastia has been observed in the course of testosterone treatment of men suffering from hypogonadism. The reason for this type of gynecomastia is peripheral conversion of testosterone to oestradiol through aromatase [141]. Gynecomastia may be also one of the reasons for withdrawing from hormone treatment.

Gynecomastia occurs in about 50% of body-builders who are long-term users of high doses of anabolic steroids [142].

Other pathologies of the male mammary

Changes of mastopathic character are described in cases of long-term diabetes type 1 which are estimated to constitute less than 1% of mild illnesses of the mammary. The pathogenesis of the changes is unknown, although the involvement of extracellular deposition of collagen, and inflammatory processes with the involvement of B lymphocytes, have been suggested [143, 144].

Diagnostics and differential diagnosis

Establishing the cause of gynecomastia requires the gathering of a patient's complete medical history, the conduction of a thorough physical examination and precise assessment of the breast and testicular glands, and also of hormone levels such as: LH, FSH, PRL, testosterone, oestradiol, B-hCG and TSH. Assessment of liver and kidney function is also essential [10, 145]. Ultrasonographic exams and core needle biopsy are also safe and effective methods of diagnosing cases of unilateral enlargement of the mammary gland among men. According to Janes et al., the cause of about 93% of cases of unilateral enlargement of the mammary gland among men is gynecomastia. The remaining cases are due to the occurrence of primary breast cancer, metastasis of lymphoma to the breast gland, and chronic inflammation of the breast gland [146].

Overgrowth of fat tissue (pseudogynecomastia, false gynecomastia, lipomastia, steatomastia)

In clinical practice, simple overgrowth of fat tissue located in the area of the nipples is often mistaken for

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Table IV. *Diagnostic assessment of gynecomastia according to Czajka and Zgliczyński [159]*
Tabela IV. *Diagnostyczna ocena ginekomastii według Czajki i Zgliczyńskiego [159]*

Relevant data from medical history	Physical examination	Laboratory tests	Visual examinations *
— Duration of symptoms	— Close examination of breasts	— Total and free testosterone	— USG of breasts or mammography
— Presence of pain/t/enderness	— Close examination of testicles (assessment of size and possible pathological changes)	— LH, FSH, PRL — TSH, fT_4, — β-hCG	— Ultrasonographic or thermographic examinations of testicles
— Applied drugs/stimulants	— Evaluation of abdominal cavity including possible changes in suprarenal glands and enlargement of liver	— DHEA-S or 17 ketosteroids in urine — Liver enzymes — Creatinine	— CT of adrenal glands — MRI of pituitary gland
— Presence of sexual dysfunctions	— Thyroid gland examination and the presence of symptoms suggesting hyperthyroidism		
— Changes in body mass	— Degree of virilisation		
— Presence of virilisation	— Pilosity		
— Symptoms of hyperthyroidism	— Timbre of voice — Musculature		

*ordering of visual examinations should concern justified cases confirmed by clinical examination and laboratory tests

gynecomastia. Susceptible to pseudogynecomastia are obese persons as a result of rapid body mass reduction [147]. A palpation exam is a useful means of differentiating between lipomastia and gynecomastia. In the case of gynecomastia, after applying fingertip pressure on the nipple, glandular tissue is perceptible. In the case of obesity (and in healthy subjects), no resistance is felt, with only the ribcage being detectable. Ultrasonographic exams of the mammary glands constitute a more precise method of differentiation.

Breast cancer

In contrast to other pathologies of the mammary glands, changes of a malignant nature must be taken into consideration with gynecomastia. Breast cancer, a rare disease among men, mainly affects the elderly. The illness occurs roughly 125 times more commonly among women than men. Breast cancer constitutes only 0.2% of all cancerous tumours in men and 0.5–1% of all cases of cancer of that gland in both sexes [9, 148, 149]. A centrally positioned, hard, painless, immovable lump is often detected during palpation exams. The change is usually grounded in a base which consists of the skin and/or breast muscle. In some cases it may also lead to deformity of the nipple and the so-called 'orange peel' symptom. In around one quarter of those afflicted, a bloody leakage from the nipple, which may be accompanied by ulceration, is seen [150]. Among the patients, lymphadenopathy is often observed occurring on the tumorous side [151]. According to Krause, breast can-

cer among men is diagnosed in less than 5% of cases of surgically removed changes concerning that gland [152]. The literature contains very rare cases of the occurrence of ductal carcinoma among 15 and 16 year old boys with unilateral gynecomastia [153, 154].

An important role in visual diagnostics is played by mammography and ultrasonography of the breast gland, whose sensitivity in the case of cancer approaches 100%. Mammography, as opposed to ultrasonography, is marked by a somewhat greater specificity: about 90% compared to 74% in the case of USG [155]. In mammographic examinations, the presence of an irregular mass positioned under the lid of the nipple is most often observed, with unpronounced or 'spike-like' borders. The changes may be accompanied by calcification and gynecomastia. In the regional assessment of lymph nodes, an important role is played by ultrasonography [156]. With respect to the technical difficulties involved in conducting mammography on men, ultrasonographic examinations are recommended as a method serving the evaluation of the pathology of the mammary [157]. In distinguishing gynecomastia from breast cancer, alongside visual examinations a very important role is played by the biopsy. In a case when these methods do not allow for an unequivocal assertion of benign change, the conducting of a mid-operation biopsy should be considered [158].

Hyperprolactinaemia

In differential diagnostics of gynecomastia, it is also necessary to reflect on hyperprolactinaemia, which ac-

companies either spontaneous or under-pressure leakage of milk from the nipple. Elevated levels of PRL concentrations and the presence of pituitary tumours are found in supplementary examinations. Elevated levels of PRL inhibit the secretion of LH, which leads to the reduction of synthesis of testosterone and an excessive impact of oestrogens on the breast gland. As previously mentioned, gynecomastia does not occur in all patients with hyperprolactinaemia. Hyperprolactinaemia may also be induced by the application of dopamine secretion-affecting medications (Table IV).

Psychosocial aspects of gynecomastia

Although gynecomastia does not constitute a threat to health or life in and of itself, the enlargement of the breast glands and concomitant pain and tenderness do lead to a deterioration in the quality of life [160]. Gynecomastia can bring with it feelings of shame, low self-esteem, dissatisfaction with one's body, a sense of loss of masculinity, and a feeling of not being accepted in one's environment. Men suffering from gynecomastia usually avoid social contact, fear showing their bodies in public places such as pools and saunas, and are in fear of developing breast cancer. Gynecomastia is also one of the commonest reasons for withdrawing from hormone treatment applied due to prostate cancer.

Considering the pervasive effect gynecomastia has on the psychosocial functioning of some of those affected, it seems prudent to draw attention to this aspect of their lives, and when the need arises, surround them with the appropriate psychological care.

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