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New perspectives on the pathogenesis and treatment of hair disorders

Nowe horyzonty patogenezy i terapii chorób włosów

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Summary

In recent years, along with the progress of balding has been on the rise, which is reflected both in the prevalence of the problem and in the persistently low treatment efficacy. The leading causes of diffuse hair loss and a badly balanced diet, anaemia, zinc, copper or iron deficiency, same types of medication, heavy metal poisoning, smoking, chronic stress and neurosis. Diseases responsible most frequently for hair loss are systemic lupus erythematosus contagious diseases, diabetes, hormonal imbalances and some types of cancer. In today's world, where the advancement of medicine is enormously fast and the pharmaceutical industry has been introducing numerous treatment agents with multiple side effects a problem of medication – induced balding has occurred. The overall prevalence of the problem in humans is not known, but has been established for some types of medication.

Key words: hair disease, pathogenesis, treatment

Streszczenie

W pracy przedstawiono nowe horyzonty patogenezy i terapii chorób włosów. W ostatnich latach równoległe z postępowaniem cywilizacji narasta problem łysienia zarówno w aspekcie częstości występowania, jak i ciągle mało skutecznego leczenia. Najczęstsze przyczyny łysienia rozlanego to: niezbilansowana dieta, niedokrwistość, niedobór cynku, miedzi, żelaza, zatrucie metalami ciężkimi, palenie papierosów, stresi, nerwica. Do najczęstszych chorób powodujących łysienie rozlane należą: toczeń rumieniowaty układowy, choroby zakaźne, cukrzyca, zaburzenia hormonalne, niektóre choroby nowotworowe. We współczesnym świecie, gdzie postęp medycyny jest ogromny a przemysł farmaceutyczny wprowadza liczne środki lecznicze posiadające wiele działań niepożądanych pojawia się problem łysienia polekowego. Częstość występowania łysienia polekowego u ludzi w skali ogólnej nie jest znana, ale została określona w stosunku do niektórych leków.

Słowa kluczowe: choroby włosów, patogeneza, leczenie

Hair on the head is primarily a subtle sensory organ. The scalp may protect against sunburn and constitute some form of insulation. Hair has a powerful ornamental function (1) and acting as a sensory organ it also transfers and receives sexual stimuli (2). Apart from having the above functions, hair is also important in areas of medicine such as physiology and forensic medicine, as well as other fields of science such as archeology. Examination of the hair of Egyptian mummies, which provided data important to archeologists and historians, could be noted here as an example. A change in hair density, colour, thickness and lustre

may be indicative of an abnormal process in the body. Sudden hair loss disturbs the psychological balance of an individual and their social functioning as well as reducing their self-esteem (being a source of frustration) (3).

In recent years, along with the progress of civilization, the problem of balding has been on the rise, which is reflected both in the prevalence of the problem and in the persistently low treatment efficacy (3). The scalp may frequently be affected by metastases, especially from breast cancer. Cancer cells infiltrating the area can damage hair follicles, leading to hair loss (1).

Balding as a reaction of anagen hair follicles to harmful agents manifests itself in three different forms.

Firstly, the hair matrices may react with a sudden significant reduction in the number of mitoses in the cells or their complete suppression, which causes atrophy of the hair bulbs and the reduction, to varying degrees, of hair thickness, leading to hair breaking in the narrowest portion and to the loss of the so-called dystrophic hair. This type of hair loss is called anagen or dystrophic effluvium. Hair loss is usually observed within a few days up to less than 20 days after the harmful agent occurred.

Secondly, hair matrices may react to a harmful agent with a premature onset of hair follicle involution, which means an early entry of hair into the resting stage. This type of hair loss is called telogen effluvium. Hair shedding ensues after a long period of latency, which in humans is usually 2-4 months after the (onset of) exposure to the cause.

Thirdly, the anagen hair follicles may be affected by both types of hair loss mentioned above – anagen and telogen (2, 3).

Excessive hair loss may be determined by counting all individual hairs shed, both by themselves and during combing, per 24 hours over a period of a few days. This problem is present when one loses over a hundred hair per 24 hours over a period of a few weeks with cutting and shaving causing no improvement (4).

In order to establish the cause of hair loss, the following laboratory tests need to be carried out: full blood count, glycemia, the level of protein, iron, ferritin, alkaline phosphatase as well as tests of such hormones as FT3, FT4, TSH, prolactin, progesterone and testosterone. It is always necessary to administer a trichogram (hair root condition test), conduct a histopathologic examination of a scalp sample (not routinely conducted, indicated in alopecia areata and its varieties), as well as the gentle pull test.

Scalp biopsy should always be conducted in the direction of hair growth and in alopecia areata the sample is to be taken from the lesion's rim. In the case of massive hair loss, biopsy should be taken from the parietal and occipital areas (1).

One of the modern diagnostic techniques for hair disorders is trichoscopy. In order to diagnose and monitor hair conditions, a dermatoscope with suitable computer software and a digital camera (videodermatoscope) is used. The application of an optical system allows lesion examination in magnification of up to 70x. This technique is non-invasive, painless, easy to handle and it allows objective assessment of the disease intensity. It does not require the hair to be shaved off or dyed. The only requirement for the use of this technique is abundant experience of the examiner. Non-invasiveness and the possibility of image preservation constitute major advantages of this technique. The use of trichoscans and phototrichograms, in contrast, requires special software as well as shaving and dyeing of the hair. These techniques are not very precise, have little clinical value and are labour-intensive (5-7).

Balding may be congenital or acquired, reversible or irreversible, and- depending on its scale and development – limited, diffuse or complete.

The leading causes of diffuse hair loss are a badly balanced diet (slimming, low in calories and protein, leading to deficient levels of essential unsaturated fatty acids, vitamins B, biotin and minerals), anaemia, zinc, copper or iron deficiency, some types of medication, heavy metal poisoning (involving lead, thallium and mercury), smoking, chronic stress and neurosis.

Diseases responsible most frequently for hair loss are systemic lupus erythematosus, contagious diseases (e.g. typhoid fever, meningitis, tuberculosis or syphilis), diabetes, hormonal imbalances (hypo- and hyperthyroidism) and some types of cancer (e.g. gastric and liver cancer).

The extent of chemotherapy-induced alopecia depends on the dose of the agent and the length of treatment. Hair loss in this case affects mainly the top of the head, while the peripheral parts are spared (8).

Systemic lupus erythematosus involves mainly diffuse reversible hair loss, whose intensity depends on the course of the underlying condition.

In contagious diseases, the intensity and length of fever are the predominant factors causing hair loss.

Diabetic patients are affected by hair loss or thinning at the top of the head. Insulin, as opposed to oral anti-diabetic medication, increases the proportion of hair in the stage of growth. Hair loss takes place between 30 and 40 years of age (usually accompanied by seborrhea), mainly in patients with badly managed diabetes.

Hypothyroidism causes hair thinning, dryness, roughness and brittleness. Hertoghe sign may occur, which involves the loss of the outer 1/3 (one third) of eyebrows. Hyperthyroidism, on the other hand, causes hair to be thinner, silky, with increased shine, while hair loss is of diffuse character or can be limited to the forehead.

In some types of cancer, especially gastric cancer and in heavy liver damage, the so-called Schridde hair may occur at the temples, eyebrow arches and the chin area. Such hair is dark, thick and lustreless. Male pattern pubic hair may adopt the female pattern. This phenomenon is called Chvostek sign. Apart from that thinning or lack of armpit or chest hair may be found in both sexes (9).

In today's world, where the advancement of medicine is enormously fast and the pharmaceutical industry has been introducing numerous treatment agents with multiple side effects, a problem of medication-induced balding has occurred. The overall prevalence of this problem in humans is not known, but has been established for some types of medication.

Chemotherapeutic agents cause hair loss in the majority of patients and the extent of balding depends on the type, dosage and length of exposure to the agent used (10). The treatment affects exclusively hair in the stage of growth, while eyebrow, pubic, armpit and terminal hair is spared due to a shorter hair cycle in those areas.

Anticoagulants cause balding in 50% of the patients, which occurs 1-12 weeks after the last dose is administered. Originally unfractionated heparin was mainly blamed for this condition, however it has recently been demonstrated that low molecular weight heparins and warfarin have the same side effect.

Anticoagulants belonging to the vitamin K antagonist group involve hair thinning usually between 3 and 20 weeks after the onset of the therapy. Most cases of hair loss are of benign nature and only 20% of patients display pronounced clinical symptoms, initially present on the scalp and later occurring in the eyebrow, armpit and pubic areas (10, 11).

Retinoids also are reported to damage the hair follicle as hair loss occurs in up to 20-30% of patients admitted to the therapeutic regimen.

Alopecia, due to Vitamin A intake in a daily dose of 500.000 IU, occurs after several months of treatment. In contrast, hair loss starts after 3-8 weeks of administration of II generation monoaromatic retinoids. The hair loss is usually severe and affects not only the scalp but also the eyelashes, eyebrows and genital hair. The condition usually is reversible and hair regrows after discontinuation of the drug, within 2-3 months (12).

The relation between DMARD (disease-modifying antirheumatic drugs) intake and hair loss have also been proven. Drugs that belong to this group are: gold salts, methotrexate, leflunamide, sulfasalazine, takrolimus, mofetile mycophenolan. The hair loss varies and may be due to the toxic effect of the drug on the hair follicle matrix (methotrexate) or skin damage (gold salts) (13).

Drugs used in psychiatry, neurology and cardiology are also responsible for drug induced alopecia.

Carbimazole and karbamazepine induce hair loss in up to 10.0% of individuals. Valproic acid in 2.6-12%, lithium salts in 12-17% and dopaminergic drugs in up to 30% of patients submitted to the therapeutic regimen (13,14).

In addition, cardiology patients may report hair loss due to: lipid lowering agents, angiotensin converting enzyme inhibitors, β -blockers and calcium channel blockers (15).

Lipid lowering agents such as statins and fibrates are responsible for alopecia in 1-5% of the patients admitted to the therapeutic regimen. The hair loss is usually transient, and affects not only the scalp but also other body regions (16, 17).

Other toxic effects of drugs used in a therapy of hypertension, ischemic disease and cardiovascular insufficiency vary, however they are usually transient.

Alopecia, due to angiotensin converting enzyme inhibitors, occurs in up to 5% of the treated patients, and depends on the type of drug. Hair loss affects usually the scalp, is reversible after discontinuation of the treatment and occurs both in adults and children (18).

Azole antifungal drugs are also reported to produce transient hair loss that affects the scalp. It depends on the type of drug and time of exposure.

Sometimes hair loss is very severe, affects other body hair and leads to malignant alopecia. The loss of

hair is probably due to hormonal changes during the antifungal therapy.

It is known that endocrine system is involved in hair cycling and indicates other drugs responsible for hair loss that results from impaired systemic hormonal homeostasis (19).

The group of drugs that induce changes in hair growth related to hormonal changes is very wide. Drugs used in thyroid gland diseases, such as propylthiouracyl, carbimazole, metizole, may be responsible for iatrogenic hypothyroidism and therefore lead to alopecia.

Oral contraceptives may also induce changes in the hair cycle. Hair loss due to contraceptives therapy occurs in 8.8% of patients. The telogen effluvium occurs usually 3 month after the cessation of treatment and is similar to postpartum effluvium. It is due to the fact that estrogens prolong anagen duration and synchronize the hair cycle. Therefore, the hair loss results from simultaneous entry of enlarged number of the follicles into the telogen phase. Contraceptives contain also androgenic progestagens that may induce or worsen androgenic alopecia in susceptible subjects.

Other hormonal drugs that are reported to induce typical androgenic alopecia include: androgens, anabolic steroids (testosterone and nandrolone), antiestrogens, aromatase inhibitors (tamoxifen, letrozole) and gonadoliberrine agonists. In affected women, despite proper serum androgens levels followed by valid endocrine system function, cytochrome P-450 levels are decreased, 5α reductase levels and density of androgen receptors are increased (20).

The drug induced hair loss described above usually results from toxic effect of the drug on the hair follicle, which depends on the dosage, type of drug and patient susceptibility. Therefore, it may occur as: telogen effluvium, anagen effluvium or both.

Telogen effluvium usually begins after a few months of treatment, affects the scalp and often is subclinical because patients lose less than 50% of the scalp hair. Moreover, sometimes other body hair are also involved. What's important, the relation between drug intake and alopecia is not always clear. Past and present general medical conditions and other crucial factors also have influence on telogen effluvium.

In contrast, anagen effluvium results from impaired metabolic or mitotic activity of the hair follicle. The hair loss is more severe and obvious because of the destruction of the 85% of hair follicles that are in the anagen phase. The causative agents are: chemotherapeutics and heavy metals.

When both mechanisms coexist, we observe mixed effluvium.

Unfortunately there is no specific treatment of drug induced alopecia, so discontinuation of the drug, along with vitamin, biotin and iron supplementation are the only therapeutic strategies. Broniarczyk-Dyła suggests also a positive effect of scalp mesotherapy based on dexpanthenol, minoksidil, multivitamin cocktails, biotin

and koloid silica in contraceptives or diet induced hair loss. Regrowth of hair usually starts after 3 sessions (21).

Not only endogenous factors are crucial for hair shaft abnormalities. Chemical and physical conditions, including cosmetic hair care products and hair styling may also induce changes in hair shaft structure. Commonly observed abnormalities include: ringed hair, woolly hair, bamboo hair, twisting of hair, knotted hair, bubble hair, trichorrhexis nodosa, trichoptilosis, trichoschisis and trichothiodystrophy. Affected hair is usually thin, susceptible to fracture with minimal trauma, brittle, lusterless and dry. The following state is usually observed in young, blond-haired individuals and results from impaired and excessive hair brushing, permanent waving, bleaching, hair dyeing, strengthening the hair with cosmetic preparations, hair drying and curling. Dull scissors, tight braiding of hair, exposure to excessive sunlight, salt water, scratching or chafing the scalp due to other diseases are other crucial factors that affect the scalp hair. Resulting alopecia sometimes is difficult to treat. Therapeutic and cosmetic management strategies are usually based on vitamin supplementation (22, 23). Sometimes hair regrowth is also possible after cessation of traumatic behavior. Moreover spontaneously remissions during pregnancy or after adolescence have also been reported.

When therapeutic results are not satisfactory, short cut and mild care of hair may be useful.

Cicatricial alopecia is another hair disorder which is difficult to treat and results from permanent hair follicle destruction. Cicatricial alopecia may be congenital or acquired.

Acquired alopecia results from a number of different pathological, external or internal processes that promote scarring and include mechanical trauma, as well as physical, chemical and biological injuries.

Congenital alopecia is related to hereditary disorders, including aplasia cutis, sebaceous naevi, epidermal naevi, some types of hamartoma, especially decay ones, and scarring follicular keratosis.

Sometimes cicatricial alopecia occurs also due to systemic disorders including sarcoidosis, lymphoidal disorders, skin cancers or metastatic tumors to the scalp.

The term pseudopelade is used to describe primary, atrophy alopecia that affects the scalp (pseudopelade Brocq). The clinical syndrome results from underlying scalp diseases, especially lichen planus, Graham-Little syndrome, chronic lupus erythematosus, cicatricial pemphigoid, folliculitis decalvans and scleroderma morphea (sclerodermie en coup de sabre). The initial patch is small, located on the vertex, parietal or occipital regions and extends very slowly. The bald patches become confluent with remaining bundles of hair at the periphery. The scalp is abnormal and sometimes follicular keratosis may occur.

The condition usually affects dark-haired women and begins between 30-40 years of age.

If the baldness is irreversible, surgical procedures may be indicated. In adult patients, autografting from

unaffected to scarred scalp, and in children surgical 'expansion' techniques may be considered.

Pharmacological treatment is appropriate only in early stages in cases of known origin (1, 24).

Alopecia areata is another hair disorder of autoimmune or non-scarring inflammatory origin. The etiology of this condition includes: genetic factors (family history or Down's syndrome), atopy, psychological factors (adaptation disorders, anxiety disorders, social phobia, mood disorders), hormonal factors (hypothyroidism), endogenous infections (bacterial superantigens), emotional stress (vascular or nerve system disorders), autoimmune disorders like vitiligo, thyroid autoimmune diseases or others eg. diabetes type 1 or discoid lupus erythematosus.

The hair loss usually begins before the age of 30 years old and primarily affects the scalp. In some cases, entire body hair may also be involved.

Coincidence of nail dystrophy has also been reported and the commonest observed abnormality is fine pitting of the nail plate (25).

There are several clinical types of alopecia areata:

- patchy alopecia areata – circumscribed, totally bald patches located at the scalp or elsewhere on the body e.g. face, trunk, limbs,
- alopecia totalis – a total loss of scalp hair, eyelashes and eyebrows,
- alopecia universalis – a loss of all or almost all body hair,
- alopecia malignant – difficult to treat, long-lasting alopecia,
- 'serpent like' alopecia,
- ophiasis pattern alopecia – alopecia extends along the scalp margin, and affects the frontal, temporal and occipital region,
- ophiasis pattern alopecia – inverted type – the hair loss begins from the vertex and extends to the margin,
- diffuse or reticulate pattern alopecia – the patches become confluent by the diffuse loss of remaining hair (26).

Because the etiology of alopecia areata is still not entirely known, treatment is of symptomatic feature and does not prevent relapse. The effectiveness of many therapeutic treatments is questioned by the scientific authorities due to lack of reliable clinical trials.

New therapy trends can be divided into three main categories:

- a) to block the natural resistance conditioned by natural killer cells,
- b) to stop the activated T cells,
- c) to modify the network of inflammatory cytokines (27).

The treatment includes using glucocorticosteroids which are applied topically and in general (continuous and pulse therapy), contact immunotherapy (strong contact allergens are used), minoxidil, dithranol, cyclosporin A, PUVA.

The decision of a system treatment depends on the extent of the changes, the overall state of health, the age of the patient, and his motivation.

System corticosteroids have been used in alopecia areata for many years in different schemas. As a rule, the results are better in the multifocal alopecia areata than in its other variants.

Some authors consider the usage of methotrexate (MTX) alone or in combination with low doses of glucocorticosteroids or azathioprine in monotherapy (28, 29) as an effective treatment in severe and chronic alopecia areata. Cho and colleagues (30) state that intradermal injections of botulinum toxin of A type cannot be used as an alternative treatment for refractory cases of alopecia areata.

Hypnosis, however, can be effective to achieve a significant improvement and maintenance of mental well-being and quality of living in a patient with refractory alopecia areata (31). Psychological and educational support, in addition to the treatment of alopecia areata may increase the long-term improvement. Biological medicaments have been tested in alopecia areata but without effectiveness. There are reports of intensification of the disease during the treatment. Further research is necessary to clarify whether biological medicaments are of any utility in the treatment of alopecia areata.

It is worth mentioning that for a majority of patients the best alternative is to leave a single outbreak of alopecia areata without treatment. Single foci which have been present for less than one year undergo, spontaneous remission in 80% of patients (32).

Androgenetic alopecia is one of the most common causes of hair loss. It is classified in the group of non-scarring alopecia. Hair loss of various intensification is observed in approximately 1/3 of men between 20 and 40 years of age. This type of hair loss in women is significantly rarer and occurs in older age.

The decisive factor in the etiology of androgenetic alopecia are genetic and hormonal factors. A tissue metabolite of testosterone, i.e. dihydrotestosterone, plays the most important role here.

A clinical form of alopecia androgenetica is called "trangular alopecia". It begins with hair loss around the corners on the forehead and leads to the so-called "tonsure" at the top of the head. This form may also occur in women. Female hair loss pattern affects solely women. The hair border area on the forehead is well preserved and the thinning starts around 2-3 cm towards the parietal lobe area and the top of the head.

In a diffuse (female) form of hair shedding, the concentration of androgen in serum is placed within the top limit of the norm or is slightly increased.

The presence of androgenetic alopecia in women before menopause, with proper concentration of androgen, is genetically determined.

However, in post-menopausal women there is a hair loss caused by a decrease of estrogen's concentration. Androgenetic alopecia in women may also be a symptom of an increased concentration of the androgens level, caused by systemic diseases (i.e. pitu-

itary disorders, polycystic ovary syndrome, androgen-producing ovarian tumors, adrenal tumors, obesity, or idiopathic hyperandrogenism). **In the local treatment, there are used solutions containing estrogen (only in women) or minoxidil (solution of 2 and 5%) which is recommended for both sexes.**

In the general treatment of men, we recommend finasteride 1 mg/day for at least 2 years. Together with it, the minoxidil may be topically used, and in case of seborrhoea – antiseborrhoeic and antimicrobial treatment. In women, any anti-androgen, such as cyproterone acetate, chloromadinone acetate, dienogest or drospirenone, can be used. They are used in combination with estrogens, especially if there are other signs of androgen excess (33).

Indications for hair transplantation exist only in men. Because of the diffuse hair loss, this method is usually inefficient in women. Finally, a habitual self-hair pulling should be mentioned, which is a part of reversible partial hair loss caused by traumatized factors.

This alopecia is caused by intended, although sometimes unaware acting of a patient who is under stress or has a mental disorder. Children and among adults – women (twice as likely) most often suffer from this condition.

In the temple-forehead area, there appear foci of various intensive hair thinning, mainly of irregular shape (which differentiates them from the natural process of hair loss). The foci are covered partially with long or broken hair.

Occasionally, it coexists with some other psychopathic urges, such as nail biting or eating the pulled-out hair.

There exist some effective therapies, particularly involving cognitive-behavioral procedures under the joint name of habit changing trainings (35). Hair loss caused by its constant rubbing is called trichotillomania. Trichotemnomania is a habitual cutting-off hair or shaving hair scalp, and trichophagia is eating it (1, 34, 35).

In the literature, more are more often there are two syndromes described: short and loose anagen (1, 36-38).

Loose anagen syndrome is characterized by poor, short hair which can easily and painlessly be removed from the head.

This syndrome occurs sporadically, mainly in women. It often remains undiagnosed in boys due to the difference in hair styles between boys and girls. It occurs more often in fair-haired girls and begins between 2-5 years of age.

Children or parents notice that light hair pulling causes the hair being torn out without pain or resistance. The hair is short, dry and lusterless. Hair in the other parts of the body is proper. The disease can last for years but often recedes spontaneously.

On the other hand, the short anagen syndrome (39, 40) is characterized by the inability to grow long hair and to increase its density.

It also occurs more often in people with dark blond hair. Patients complain about very short hair and maintain that they have never been to the hairdresser to cut it.

The disease is mild and in most cases is not related to systemic diseases. A spontaneous improvement may occur after the adolescence period. In the case of men-

tal lability, each exacerbation of symptoms of hair loss can lead to a depressive phase.

In patients with psychoneurotic states, increased hair loss is just a psychopathic background concentration. Some disturbances may occur in contacts between people in the workplace and private life.

There are, however, some patients complaining about hair loss which can neither be diagnosed by

multiple clinical trials nor by trichological research.

It is believed that in such cases it is better to suggest a visit at a psychotherapist than to start a long and ineffective specialist treatment.

In conclusion, it should be emphasized that nutritional factors have a significant effect on the state of hair. Following the rules of proper nutrition and appropriate hair care determine proper hair condition (3, 23).

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received/otrzymano: 22.08.2012

accepted/zaakceptowano: 28.09.2012

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