ZEBRAS OF MEDICINE

HIRSUTISM VERSUS SYNDROME OF AMBRAS: A COMPACT COMPARISON

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Abstract

Review

Excessive hair growth has a broad variety in clinical presentations. Its evaluation is subject to personal, social and cultural perceptions. Hirsutism is a frequent form of excessive hair growth in females, with an incidence in 10 percent of the female population [1]. Hirsutism presents itself as limited patterns of excessive terminal hair growth on androgen-dependent areas of the body, such as the upper lip and chest. The syndrome of Ambras shows an extreme form of specific hair growth from birth and is not only present in women. Furthermore, the syndrome of Ambras can show werewolf-like dysmorphic facial features. Treatment of either of these conditions have only one overlapping mechanism, which is removal of excessive hair. This can be done by laser therapy, topical treatment or shaving. Due to the aetiology of hirsutism, some medication can be utilised to reduce the hair growth.

KEYWORDS: Hair growth, androgens, vellus hair, lanugo hair, werewolf syndrome

Introduction

Excessive hair growth has a broad variety in clinical presentation. Its evaluation is subject to personal, social and cultural perceptions. Unwanted hair growth can be a source of embarrassment with negative effects on the quality of life [1]. Hirsutism is a frequent form of excessive hair growth in females, with an incidence of ten percent of the female population [1]. The excessive pattern of hair growth is usually related to androgen-dependent (androgens are steroid hormones that maintain and regulates the development of male characteristics) areas of the body, such as the upper lip and lower abdomen [1]. Hair growth is considered excessive if an individual experiences the pattern of hair growth as 'abnormal' and is thus influenced by cultural and individual perspectives. Although hirsutism is bothersome, other conditions show a more extreme extent of abnormal hair growth. The syndrome of Ambras is an extremely rare condition that shows excessive hair growth from birth, alongside specific werewolf-like dysmorphic facial features [2]. In contrast to hirsutism, that presents itself only in women (mostly of reproductive age), the syndrome of Ambras is not subject to a specific gender or age and has only been described in the literature in ten cases until now [2, 3]. This review sets out to compare hirsutism with the syndrome of Ambras in terms of clinical presentation, diagnosis and treatment.

Clinical presentation

Hirsutism is a condition that mostly appear in women in their reproductive age [1]. It is defined as excessive female terminal hair growth on androgen-dependent areas of the body (figure 1). These areas include the face, chest, upper-lip and thighs [1]. In contrast, the syndrome of Ambras is present from birth and is a condition where the whole body is covered with fine, long vellus hair (figure 1) except for places where hair usually does not grow, such as the palms and soles [2]. Werewolf syndrome is a synonym for the syndrome of Ambras and has arisen due to the werewolf-like features that come with this disorder, such as a broad triangular face with a round nasal top and long spinal hair growth [4]. Furthermore, dental abnormalities are seen in the first and second teeth [4]. The hair growth increases in density and distribution as patients grow older and the hair can get several centimetres long if not shaved [3, 5].

Diagnosis

There are three aetiologies that give rise to hirsutism and are divided in hyperandrogenic, non-hyperandrogenic and idiopathic origins [1]. Hyperandrogenic and non-hyperandrogenic origins mean that it originates from a disturbed androgen balance or not. Androgens are steroids that are involved in the regulation of male characteristics, such hair growth [1]. A well-known androgen is testosterone, a steroid that exhibits functions such as development of muscle strength and male specific hair growth [1]. Hyperandrogenic and non-hyperandrogenic origins have a known aetiology, whereas idiopathic means that the exact cause of the disease remains unknown [1]. Hyperandrogenic origins can be subdivided in polycystic ovary syndrome, androgen-secreting tumours and non-classic adrenal hyperplasia [1]. Medication or Cushing's syndrome can give rise to non-hyperandrogenic hirsutism. Examples of medication that can cause hirsutism include performance-enhancing anabolic steroids, such as danazol and the anti-hypertensive drug minoxidil [1]. Idiopathic hirsutism might be hereditary [1]. The syndrome of Ambras, however, does not originate from any of the pre-mentioned aetiologies, but is caused due to genetic mutations.

Hirsutism can be diagnosed using female history (e.g. onset of hirsutism, symptoms of virilisation, menstrual history, family history and drug history), physical examination (e.g. Ferriman-Gallwey-score, signs of hyperandrogenism, signs of virilisation, signs of Cushing's syndrome and thyroid examination) [1]. The Ferriman-Gallwey-score is the preferred method to evaluate the severity of hirsutism and is based on a four-scaled evaluation of hair growth on nine different body areas (e.g. upper lip, chest and lower abdomen) [1]. Laboratory examinations might be used to determine the origin of hirsutism and is based on concentrations such as total testosterone, sex hormone binding globulin and thyroid stimulating hormone, alongside six other not mentioned tests [1].

Due to the extremely rare frequency of the syndrome of Ambras, no specific diagnostic tools are developed. However, genetic analysis has revealed pericentric- and paracentric inversions or an insertion in chromosome 8 in 80% of the cases [2]. As the patient ages, the fine light coloured primary hair (lanugo hair) that is usually only seen in embryonic development, differentiates to secondary hair (vellus hair) [1]. In a number of body regions, vellus hair further differentiates to fine terminal hair [4]. However, lanugo, vellus and fine terminal hair cannot be distinguished without the

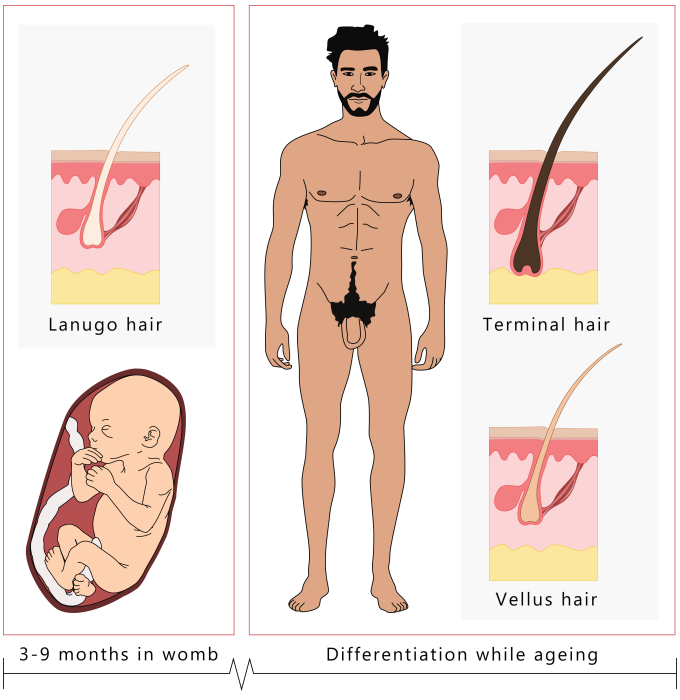

Figure 1: Hair differentiation while ageing.
The unborn develops very thin, often light pigmented hair (lanugo) in the womb. This hair is the first type of hair a person develops, and is therefore called primary hair. Lanugo hair is often shed in the womb or just after being born. The lanugo hair differentiates to vellus hair (secondary hair). In some parts of the body, vellus hair differentiates to terminal hair later in life. Terminal hair is often thicker, and is frequently pigmented. Hirsutism shows a hair growth pattern as seen in males, the typical areas where male hair grows are often androgen dependent. A disturbance in the hair growth cycle in the Ambras syndrome makes vellus hair to remain in the growth phase. This results in vellus hair that can reach considerable length.

use of a microscope [4]. What differentiates the syndrome of Ambras from hirsutism and healthy persons in terms of hair growth, is the characteristic disturbance of hair growth cycles. In healthy persons, hair grows in cycles that consist of a growth (anagen) phase and a resting (telogen) phase [2]. Hair of patients with the syndrome of Ambras remain in the anagen phase [2]. The hair that have differentiated to secondary hair also remain in anagen phase, which results to excessive growth of fine, sometimes pigmented hair, that can reach considerable length if not shaven [4]. Aside from extensive genetic analysis such as DNA-sequencing to find mutations, the syndrome of Ambras is diagnosed using its characteristic clinical presentation, mainly on the growth of consistently growing hair (anagen phase) which remain on the body (either vellus- or terminal hair) [4].

Treatment

The treatments of hirsutism and the syndrome of Ambras overlap. However, due to the underlying aetiology of hirsutism, this condition has several more treatment options. Treatment of hirsutism can be divided into two subgroups, namely medical therapy and physical hair removal [1]. Medical therapy might consist of topical therapy (e.g. eflornithine), contraceptives or anti-androgens (e.g. spironolactone) [1]. Topical therapy, such as eflornithine, is applied locally to the affected skin region and results in slower hair growth and utilises ornithine decarboxylase inhibition in the hair follicle [1]. Ornithine decarboxylase plays a crucial role in hair follicle development and hair growth [1]. Contraceptives reduce the free testosterone levels to slow down hair growth [1]. Furthermore, anti-androgens prevent the activity of androgens at their specific target site, but drug-specific side effects should be monitored [1]. In case of spironolactone, electrolyte imbalance must be checked on a regular interval (every three months), since it can cause diuretic-related side effects [1]. Contraceptives and anti-androgens can be used simultaneously and can have synergistic effects [1].
In contrast to hirsutism, the syndrome of Ambras is not androgen-based [4]. Therefore, only physical hair removal and eflornithine cream are current treatment options [2]. There are several ways to remove excessive hair, such as shaving, bleaching, and chemical depilation [1]. However, each of the available methods has a downside to be considered, especially in children due to their more vulnerable skin [5]. For example, repeated chemical depilatories can lead to skin irritation and might eventually cause contact dermatitis [5]. Waxing is an effective, but painful, treatment option. However, removal of fine vellus hair can result in the transformation to terminal hair, which subsequently leads to the impression of increased hairiness [5]. In the past few years, 5-α-reductase inhibitors are more frequently used off-label for the treatment of hirsutism. However, this is only partially effective in best case, and is negatively advised as off-label prescription [6]. One final discussed therapy is the consideration of laser therapy. This therapy risks scarring after destruction of the deeper parts of the skin, but also other adverse events have been noted such as pigmentary changes [5, 7]. Especially for children, repeated shaving remains the best treatment option, to reduce the risk of permanent damage [5].

Although excessive hair growth does not increase mortality or morbidity, lack of psychosocial acceptance can have an immense impact on individuals [1, 5]. For the syndrome of Ambras, excessive hair removal might be crucial to prevent social isolation [5].

Conclusion

The diagnosis of Ambras syndrome is mainly clinical, whereas hirsutism utilises several measurement tools to evaluate the clinical symptoms [1, 2]. The Ambras syndrome is characterised by excessive hair growth from birth, a familial inheritance pattern and facial dysmorphism, whereas hirsutism has an onset in a later phase in life, has several aetiologies and is only present in women [2]. Treatment of hirsutism and the Ambras syndrome focuses mainly on hair removal, although hirsutism is less limited in treatment options due to the difference in aetiology that gives rise to the condition. Ambras syndrome is limited to therapies that remove hair, such as chemical hair removal, shaving and laser therapy. Hirsutism can optionally be treated with oral medication such as anti-androgens and contraceptives.

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