Chapter 10

HAIR-AN syndrome: a rare subphenotype of PCOS (polycystic ovary syndrome) / PMOS (polyendocrine metabolic ovarian syndrome)

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Abstract

Polycystic ovary syndrome (PCOS), recently renamed as polyendocrine metabolic ovarian syndrome (PMOS), is a common endocrine condition with reproductive, metabolic, dermatological and psychological features, affecting around 10–13% of women worldwide. HAIR-AN syndrome, an unusual multisystem disorder defined as a coexistence of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN), is a rare and severe subtype of PCOS/PMOS. Patients with HAIR-AN syndrome tend to experience more severe form of insulin resistance compared to women with typical PCOS, and obesity is also more prevalent and severe in this group of patients. As one of the most under-diagnosed clinical entities in endocrinology, more research on the molecular mechanisms and cellular events contributing to the pathogenesis of HAIR-AN is required to be able to develop novel treatment strategies for women with this rare subtype of PCOS/PMOS.

1.1. PCOS

Polycystic ovary syndrome (PCOS), recently renamed as polyendocrine metabolic ovarian syndrome (PMOS), is the most common reproductive endocrinopathy in women (observed in around 11–13% of pre-menopausal women (women of reproductive age)), with impacts across the lifespan (e.g. in fertility and metabolic health) [1-6]. In other words, it affects approximately 1 in 7 to 1 in 10 women globally. These differences in prevalence are mostly

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due to the diagnostic criteria used and the specific population studied [7, 8]. This syndrome is classified into several phenotypes whose incidence can also vary by race and ethnicity. PCOS/PMOS is characterized by irregular menstrual cycles, irregular ovulation (oligo-ovulation or anovulation), polycystic ovaries (PCOM; polycystic ovarian morphology), hyperandrogenism (high androgen levels), and metabolic disturbance; and it is also the primary cause of female infertility [9-12]. Patients with PCOS were found to have around 15-fold increased risk of infertility compared to non-PCOS women [13]. Women with PCOS/PMOS are also three times more likely to have obesity compared to their healthy (non-PCOS) counterparts [14]. Besides, these women have a higher prevalence of insulin resistance (26.7%) with a four-fold increased risk of type 2 diabetes (T2DM) before the age of 40 [15, 16]. Furthermore, this condition is associated with a higher risk of cardiovascular disease (CVD), hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD), psychological disorders, baldness and some other comorbidities, contributing significantly to the global health burden [15, 17]. In addition to imposing high burden on their long-term health in affected women, PCOS also causes a significant increase in health-care-related costs for these women [18].

Patients with PCOS/PMOS exhibit a heterogeneous clinical presentation characterized by a broad range of symptoms, resulting in different potential consequences for the affected women [19]. This variation in clinical phenotypic presentation contributes to challenges faced in the diagnosis, treatment and prevention of the disease [20]. Current therapies for PCOS are suboptimal: they only provide partial relief of certain symptoms associated with PCOS. For instance, in women with PCOS and severe obesity, bariatric surgery is an effective treatment option; however, it fails to provide the complete resolution of PCOS [21, 22]. Therefore, there is an urgent need for preventive and targeted treatments in PCOS [12].

PCOS/PMOS was found to have a high heritability—estimated at up to 0.70 in twin studies, suggesting that genetic factors are a major contributor to the pathogenesis of PCOS [23, 24]. A recent genome-wide association study (GWAS) identified 29 risk-increasing genetic loci associated with PCOS, expanding the number of genetic loci by 13. Together with the newly identified genes, these PCOS-associated genes are HHAT, THADA, MSH6, FSHR, INHBB, TEX41, ERBB4, TOPAZ1, MYO10, IRF / RAD50, ID4, CYP3 complex, NEIL2 / GATA4, FANCC, DENND1A, FSHB, PRSS23, YAP1, ZBTB16, ERBB3, HELB / HMGA2, KRR1, TOX3, FTO, MAF, SHBG, AMH, MAPRE1 and CHEK2 [4, 25]. Most of the risk-increasing loci at these genes were found to be associated with later age at natural menopause

(ANM), underscoring the reproductive longevity related to an increased oocyte number and/or availability throughout the lifespan [4].

The diagnosis of PCOS are based on the presence of certain reproductive features [26]. More specifically, the diagnostic criteria for PCOS require the presence of two of three features—hyperandrogenism (HA; high androgen levels), oligo-anovulation and/or polycystic ovarian morphology (PCOM). PCOS is the most frequent cause of anovulatory infertility, and is associated with insulin resistance, conferring an increased risk of metabolic outcomes including type 2 diabetes (T2D) as detailed above [27, 28]. This complexity in associated symptoms, high heterogeneity of the disease and the presence of different clinical phenotypic presentations also complicate the diagnosis of PCOS.

Previous large-scale genetic studies demonstrated that PCOS/PMOS is a complex polygenic disorder encompassing interactions between brain, metabolic and gonadal function, and it is now recognized as a multi-organ disorder having impacts extending beyond the ovaries [4, 25, 29]. Thus, it is not possible to diagnose PCOS based on, for instance, the presence of particular mutations in certain genes. Moreover, current expert opinion-based diagnostic criteria for PCOS do not include associated metabolic disturbances such as insulin resistance, dysglycaemia, obesity, dyslipidaemia, metabolic syndrome and MASLD [26].

1.2 HAIR-AN syndrome

HAIR-AN syndrome, an unusual multisystem disorder defined as a coexistence of hyperandrogenism (HA), insulin resistance (IR), and acanthosis nigricans (AN), is a rare and severe subtype of PCOS/PMOS [30-32]. This syndrome is observed in around 5% of all women with hyperandrogenism [33, 34]. These patients have severe insulin resistance [35]. In other words, women with HAIR-AN syndrome tend to experience more severe form of insulin resistance compared to women with typical PCOS [36-38]. This disease is also accompanied by obesity, metabolic abnormalities, acne, hirsutism, chronic anovulation, irregular menstruation, and other androgen excess symptoms [31, 32, 39]. Besides, obesity is also more prevalent and severe in patients with HAIR-AN syndrome [36-38]. The physiopathology of HAIR-AN syndrome is mostly based on insulin resistance, creating a vicious circle: the resulting hyperinsulinism (hyperinsulinemia) leads to an increased production of androgens (hyperandrogenism / overproduction of androgens in the ovaries), which then increases abdominal fat deposition, worsening the insulin resistance and hyperinsulinemia [37]. In other words, insulin and

androgens potentiate each other's actions, and therefore, a vicious circle of chronic anovulation and hyperandrogenic signs followed by a male pattern fat deposition is expected in patients with HAIR-AN syndrome. Hyperinsulinism is also responsible for the acanthosis nigricans via the stimulation of the IGF-1 receptors present on keratinocytes and fibroblasts [30, 32]. In other words, acanthosis nigricans is considered to be an epiphenomenon resulting from hyperinsulinemia [30].

This rare syndrome begins soon after puberty (usually manifests in early adolescence; a period of significant hormonal changes) and is currently under-diagnosed. The management of this syndrome is challenging, since standard therapeutic modalities usually prescribed to patients with typical PCOS/PMOS including metformin or oral contraceptives seem ineffective to adequately control the associated symptoms [39]. The treatment is often based on an improvement in insulin-resistance by weight loss and the use of insulin sensitizers. Furthermore, anti-androgenic drugs help improving high androgen-associated hirsutism. Moreover, bariatric surgery has shown a significant efficacy in this syndrome by inducing weight loss, normalizing insulin-sensitivity, enabling improvements in hyperandrogenism and acanthosis nigricans [32]. In addition, treatment is aimed at regulating ovulation, and decreasing acne and acanthosis nigricans [35]. In other words, multifaceted and aggressive treatment seem to be required in reducing the severity of symptoms and preventing further consequences in these patients [40]. Moreover, the diagnosis of HAIR-AN syndrome (and its diagnostic differentiation from PCOS) remains to be improved to be able to offer appropriate treatment timely for those affected at the clinic. Besides, treatment modalities specifically designed for patients with HAIR-AN syndrome, considering the presence of more severe conditions (increased insulin resistance, etc.) in this group, need to be developed in the future.

The characteristic acanthosis nigricans (the dark, velvety, hyperpigmented patches of skin observed generally in the axilla or the neck of patients) is attributed to the long-term exposure of the keratinocytes to insulin, as a result of high insulin levels. Receptors for both insulin and insulin-like growth factors have been found on the surface of human keratinocytes [39]. Acanthosis nigricans serves as a key clinical feature of HAIR-AN but is less common in other forms of PCOS.

The HAIR-AN syndrome is one of the most underdiagnosed clinical entities in endocrinology. This syndrome is classified to type A and B, with regard to whether the severe insulin resistance is either inherited (A) or acquired (B) [35-39]. Previous research showed that certain mutations in the insulin

receptor gene (INSR) can be found in patients with HAIR-AN syndrome [41] The use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) (e.g. liraglutide) have been linked to the improvement of preexisting HAIR-AN syndrome, pointing to the involvement of this receptor in disease pathology [41, 42]. As performed for PCOS, genome-wide association studies (GWAS) for HAIR-AN syndrome should be performed in the future, in order to determine risk-increasing loci in this rare syndrome. These identified HAIR-AN syndrome risk variants will help us understand the specific molecular processes contributing to pathogenesis of HAIR-AN syndrome. It will be also interesting to see whether there are certain risk variants associated with HAIR-AN syndrome but absent in other (typical) PCOS patients.

A study showed that among around a thousand young women (between ages 10-21), 5% were diagnosed with HAIR-AN syndrome. Mean age of these patients was calculated as 15.5, initial mean weight at diagnosis was determined as 94.5 kg, and the mean BMI was 33.33 kg/m^2. In this study, these patients were treated with programs aiming weight-stabilization and -reduction, with oral contraceptive pills, and in most cases, with metformin (an insulin sensitizer). 80% of these HAIR-AN patients were compliant with the follow-up and treatment regimen, 60% of them maintained or reduced their weight, 95% had regular menstrual cycles, and in most patients, the acne and/or hirsutism were the same or better than at the start of treatment [40]. The authors of this study reported that, in this syndrome, treatment noncompliance might lead to increased severity of the disease (advanced disease), such as weight gain [43]. This points to the importance of treatment in reducing the severity of the disease in affected patients although current treatment options are still not optimum.

The occurrence of HAIR-AN syndrome is significantly higher in particular ethnicities, such as women from African American, Hispanic, and South Asian populations, who are also at a high risk for metabolic disorders including IR and type 2 diabetes. Furthermore, a family history of PCOS, type 2 diabetes, IR, or HA increases the likelihood (risk) of developing HAIR-AN syndrome, pointing to the presence of a genetic predisposition for this syndrome [34, 43-45]. However, as stated above, risk variants for HAIR-AN syndrome and the prevalance/frequency of these potential variants in different populations remain to be studied.

1.3. Hyperandrogenism in PCOS

Hyperandrogenism is a critical component of PCOS/PMOS pathophysiology and able to drive different phenotypic features, such as follicular dysplasia,

impaired ovulation, endometrial disorders (endometrial dysfunction), and metabolic dysfunction [15, 46, 47]. A very recent study identified four reproducible subtypes of PCOS, one of which is PCOS with hyperandrogen. The authors found that hyperandrogenic PCOS (hyperandrogenic subtype; HA-PCOS; 25%) is characterized by high testosterone–dehydroepiandrosterone sulfate (DHEA-S) levels, together with mild metabolic disorders, and it also has the highest risk of second trimester pregnancy loss and dyslipidemia incidence [48]. Recent findings also highlighted the importance of androgen-driven metabolic reprogramming in PCOS [12]. For instance, a study published recently showed that hyperandrogenic-PCOS patients exhibit significantly increased glutamine uptake in their ovarian granulosa cells which is mediated by the androgen-induced upregulation of SLC1A5, a specific glutamine transporter, showing that androgens are able to influence diverse metabolic events in ovarian cells [1]. Whether HAIR-AN syndrome is closer/more similar to any of these newly identified reproducible subtypes of PCOS (such as HA-PCOS) remains to be determined.

In HAIR-AN syndrome, severe hyperinsulinemia observed (resulting from severe insulin resistance) might be largely responsible from hyperandrogenism, due to insulin-mediated overproduction of androgens in the ovaries. High androgen levels further exacerbate insulin resistance, creating a positive feedback loop, resulting in the intensification of the severity of the syndrome with time. Therefore, molecular mechanisms (high insulin-dependent or -independent) contributing to increased androgen production in HAIR-AN syndrome should be better identified mechanistically. Besides, in addition to increased production of androgens, pathological events potentially increasing the bioavailability of androgens remain to be further studied in the context of HAIR-AN syndrome.

1.4. Insulin resistance in PCOS

Insulin resistance is an intrinsic characteristic of PCOS/PMOS. It is commonly present (predominant) in this syndrome (40% of women with PCOS develop type 2 diabetes mellitus by 40 years of age). In other words, women have a higher prevalence of insulin resistance (26.7%) and a 4-fold higher risk of type 2 diabetes (T2DM) before the age of 40 [16]. The associated increase in insulin levels drives excess production of androgens by the ovaries [46, 48, 49]. In other words, insulin stimulates ovarian androgen production, and increases the bioavailability of testosterone via lowering the hepatic release of sex hormone-binding globulin (SHBG) [50-52]. In parallel, hyperandrogenism promotes insulin resistance [52]. Based on this androgen-dependent changes in insulin sensitivity, patients with PCOS commonly have compensatory

hyperinsulinemia. Such bidirectional crosstalk between high androgen levels and insulin resistance/hyperinsulinemia potentially have a very critical role in the PCOS pathogenesis [53]. For instance, both hyperandrogenism and insulin resistance are known to contribute to endometrial dysfunction, anovulation, infertility and metabolic alterations in PCOS [46, 54].

The presence of typical clinical manifestations of PCOS/PMOS including hyperandrogenism, menstrual irregularities and polycystic ovarian morphology (PCOM)) is associated with severe insulin resistance in patients with PCOS [26]. Besides, treatment with metformin, an insulin-sensitizing (insulin-sensitizer) drug (used as the second-line treatment when lifestyle changes are insufficient), has been found to improve peripheral insulin sensitivity, lower testosterone levels in circulation (i.e. decrease insulin-mediated stimulation of ovarian androgen secretion), ameliorate menstrual cyclicity, restore ovulation and increase pregnancy rates in patients with PCOS, pointing to the role of insulin resistance as a pathogenic factor in this disorder [10, 11, 55-58].

Hyperinsulinaemia also influence granulosa cells: it upregulates the expression of LH receptors on granulosa cells of small antral follicles in the early phase of the folliculogenesis, resulting in the premature differentiation of these cells. This premature differentiation then leads to follicular growth arrest and subsequently accumulation of immature follicles and anovulation [26, 59]. Whether granulosa cells in patients with HAIR-syndrome have higher LH receptor expression compared to those from other PCOS patients needs to be studied. Considering the presence of a more severe form of hyperinsulinaemia in patients with HAIR-AN syndrome, their granulosa cells might potentially have increased expression of LH receptors (which is mediated by insulin), compared to granulosa cells from other PCOS patients. This might then lead to the increased number of follicular growth arrest events and increased accumulation of immature follicles and more frequent anovulation in patients with HAIR-AN syndrome, compared to those with PCOS. However, these hypotheses should be experimentally validated. In short, the majority of insulin-mediated molecular pathologic processes in PCOS patients might be more pronounced in patients with HAIR-AN syndrome based on their relatively higher insulin levels.

Besides, high fasting insulin levels were identified as causal risk factors for PCOS/PMOS [4, 60]. Whether high fasting insulin levels similarly (or even to a greater extent) increase the risk for HAIR-AN syndrome remains to be further investigated. Weight loss of as low as 5% was shown to be able to decrease androgen levels and insulin resistance, improve menstrual function and likely enhance fertility outcomes in patients with PCOS [61]. In the

case of HAIR-AN syndrome, the benefits of weight loss might be even more significant compared to PCOS, considering that obesity is more common and severe in patients with HAIR-AN syndrome [36-38]. Comparative studies are needed to determine if certain interventions provide greater benefit to the women with HAIR-AN syndrome compare to those with PCOS.

In the context of HAIR-AN syndrome, molecular mechanisms contributing to insulin resistance should be particularly studied since patients with this rare syndrome experience more severe insulin resistance compared to other patients with PCOS. In other words, molecular differences separating HAIR-AN syndrome from PCOS in terms of insulin resistance should be better understood and experimentally defined. Furthermore, considering the fact that hyperinsulinism is responsible for the acanthosis nigricans, a better mechanistic understanding of hyperinsulinism in patients with HAIR-AN syndrome will benefit the development of more effective targeted therapies in the treatment of this rare syndrome.

Future prospects

Currently, studies on HAIR-AN syndrome is highly limited. Although recent research increasingly focused on the better understanding of molecular mechanisms associated with hyperandrogenism and hyperinsulinemia in the context of PCOS, whether there are specific cellular events and molecular processes contributing to HAIR-AN syndrome, different than PCOS/PMOS, is largely unknown.

Novel strategies in addition to metformin treatment and lifestyle intervention remain to be developed in order to improve insulin sensitivity and reduce androgen excess in patients with HAIR-AN syndrome. Future mechanistic research is needed to better understand the molecular pathogenesis of HAIR-AN syndrome.

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