ZEBRAS OF MEDICINE:
NON-CLASSICAL CONGENITAL ADRENAL HYPERPLASIA AND POLYCYSTIC OVARIAN SYNDROME

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Abstract

Polycystic ovarian syndrome (PCOS) and non-classical congenital adrenal hyperplasia (NC-CAH) are the most common endocrine disorders affecting females. Although the genetic predisposition and mechanism may be different, there is an overlap in the clinical presentations of symptoms, often leading to misdiagnosis. This review aims to summarise the current knowledge about the aforementioned diseases and discusses the various parameters involved in their diagnosis and treatments. PCOS and NC-CAH display similar symptoms of hyperandrogenism such as hirsutism, acne, and menstrual dysfunction. These diseases are also the leading cause of many chronic conditions in women, besides infertility, such as diabetes, cardiovascular disease, obesity, and non-alcoholic fatty liver disease. Patients diagnosed with either of these disorders are also at a higher risk for endometrial cancer and multiple pregnancy complications like miscarriages, preeclampsia, anxiety, and depression. Diagnosis usually involves testing serum levels of the altered hormone concentrations such as androgens and insulin. The existing treatments are only for managing symptoms. Endocrine disorders affect the life-long health of women and have the potential to cause multiple chronic conditions affecting the quality of life. No uniform diagnosing criteria exist, leading to the underdiagnosis or misdiagnosis of such disorders. In addition, the current tests and treatments are not curative.

Introduction

Polycystic Ovarian Syndrome (PCOS) is the most common endocrine disorder that affects 4-20% of women of reproductive age (18-44 years of age) worldwide [1, 2]. It is a multifaceted disorder with various clinical manifestations, complex pathophysiology, and unknown genetic mechanisms [3]. PCOS thereby hinders scientists and endocrinologists in understanding its aetiology and the different mechanisms involved, which are important for accurate diagnoses and treatment [4].

PCOS is also associated with multiple comorbidities such as obesity, type 2 diabetes, infertility, cardiovascular diseases, endometrial cancer, metabolic syndrome, and depression [5]. Additionally, multiple diseases exist which mimic the symptoms of PCOS, such as non-classic congenital adrenal hyperplasia (NC-CAH) and menstrual irregularities in the case of hyperprolactinemia [1]. Hence, a correct and early diagnosis is vital since the usual treatments are lifelong and involve lifestyle modifications such as exercise and diet [1].

Congenital Adrenal Hyperplasia (CAH) is a family of autosomal recessive disorders in which there is a deficiency in one of the enzymes essential for cortisol synthesis in the adrenal glands causing mild to severely impaired cortisol production [6]. The residual enzyme activity decides the severity of the disorder wherein the higher the enzyme activity, the milder the disorder [7]. Congenital Adrenal Hyperplasia consists of two types: classical - which is diagnosed in infants or neonates and non-classical or late-onset, which is usually detected in adolescence or later in life [6]. No clear distinction between the two types has been defined as the symptoms presented lie on a range of phenotypes [6]. Classical CAH is severe and can be lethal if not detected early. It usually presents itself as a salt-wasting form in the neonatal stage or genital virilisation, which only occurs in females [7]. NC-CAH is a milder form of the disorder. It is not life-threatening and usually manifests later in life or can even be asymptomatic [6]. NC-CAH is one of the most common endocrine disorders, with 0.6-9% of women being affected depending on the ethnicity [6]. It occurs more frequently in Hispanics (1:53) than in non-Hispanic people [6].

The prevalence of PCOS and NC-CAH are increasing, which, due to similar clinical manifestations (figure 1), leads to misdiagnosis and, therefore, a lack of curative treatment, making their clinical management challenging. This review aims to describe the differences between PCOS and NC-CAH in light of their cause, clinical symptoms, diagnosis, and treatment.

Cause

PCOS was first characterised by Stein and Leventhal in 1935 [1]. It is a multigenic, heterogenous disorder with no known genetic cause, even though a predisposition to it due to family history is common [4]. Recently, genome-wide association studies have identified potential genes *LHR, FSHR, INSR, ERB, THADA,* and *HMGA2* that are involved in the development of PCOS [8]. These genes are vital in pathways responsible for the production of steroids, insulin production and secretion, homeostasis, lipid metabolism, inflammation, and the hypothalamic-pituitary axis [8]. However, the genetic variants that cause PCOS are strongly influenced by epigenetic and environmental factors such as diet and lifestyle [9]. Since lifestyle varies with ethnicity, race, and population, it is difficult to make any correlations with the various genetic variants and mutations with women who have a family history of PCOS. The disruption of the hypothalamic-pituitary-ovary axis is a phenomenon that occurs during PCOS [3]. Animal studies have shown that excess prenatal androgen exposure leads to the female progeny having a PCOS-like phenotype [9]. This excess of androgen during the prenatal years results in the

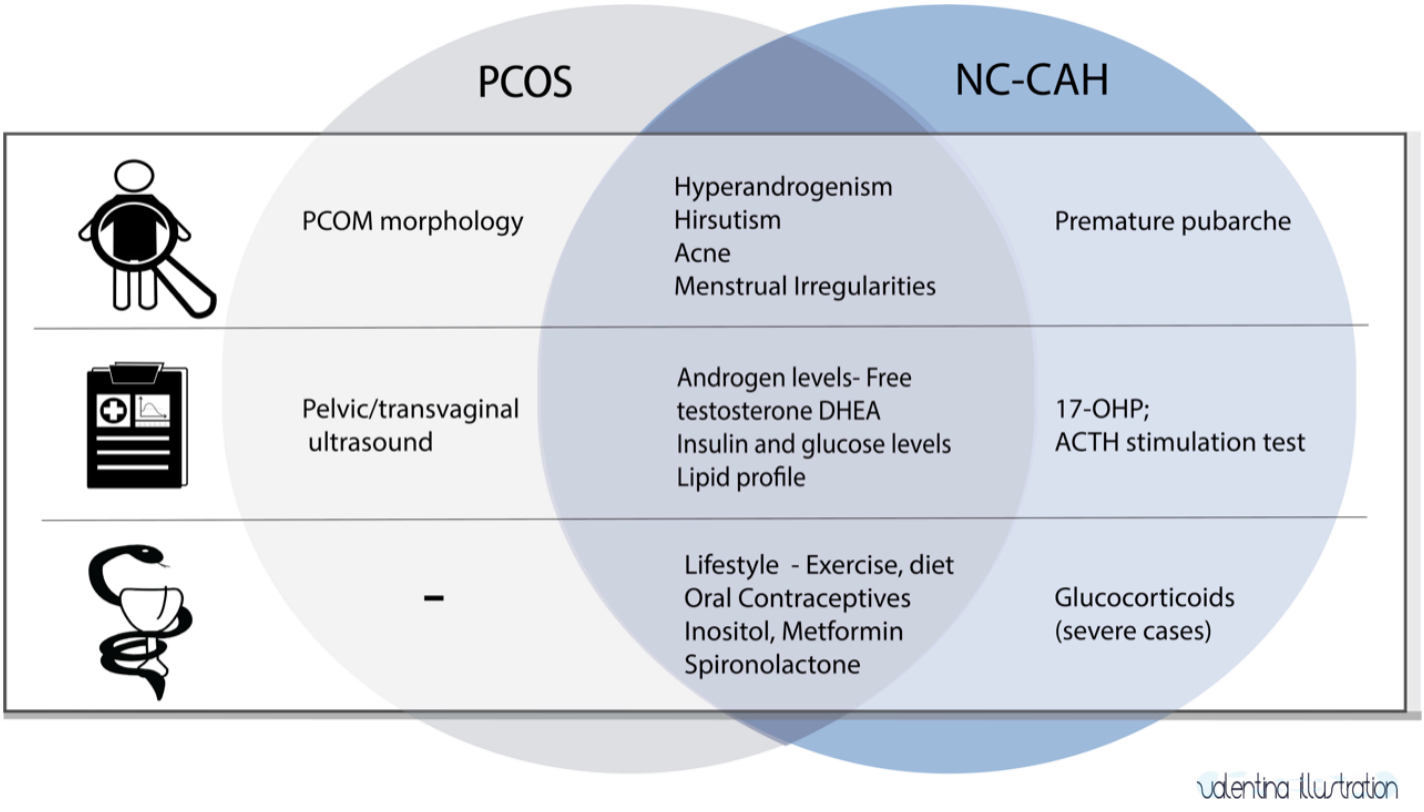

Figure 1: *Illustration depicting the similarities between PCOS and NC-CAH. These diseases have several common aspects, such as similar symptoms, diagnostic tests, and treatments. Some specific aspects in each category do exist such as testing 17-OHP levels for NC-CAH and a pelvic ultrasound for PCOS.*

hypersecretion of the luteinising hormone (LH) which eventually results in the poly-cystic morphology of the ovaries [9].

CAH is most often caused by a mutation in the *CYP21A2* gene at chromosome 6p21 [10]. *CYP21A2* encodes for the enzyme 21-hydroxylase, which is found in the adrenal glands. This enzyme converts 17-hydroxyprogesterone into 11-deoxycortisol and progesterone into 11-deoxycorticosterone and is thereby involved in the production of aldosterone and cortisol, which are responsible for sodium regulation and mental stress management, respectively [8, 11]. The *CYP21A2* gene is located next to the genes *C4* (which encodes complement 4), *RP* (serine-threonine nuclear protein kinase) and *TNX* (tenascin), forming the RCCX module [12]. However, missense mutations and non-allelic homologous recombinations in the *CYP21A2* gene result in gene conversions. In addition, during meiosis, duplications or deletions of the RCCX modules arise due to misalignment and unequal crossover [12]. These mutations on either or both of the two alleles result in the deficiency of 21-hydroxylase, which inhibits or completely blocks the conversion of 17- hydroxyprogesterone (17-OHP) to deoxycortisol and progesterone to deoxycorticosterone (steroid precursors) [6]. This leads to increased levels of 17-OHP which increases the levels of androgens giving rise to hyperandrogenism [6]. The low levels of cortisol synthesised also increase the amount of adrenocorticotropic hormone (ACTH) produced from the pituitary [12].

Clinical Presentation

There are three major features of PCOS, and most women present at least two out of three major symptoms: amenorrhea (no menstruation) or oligomenorrhea (menstruation less than six to eight times a year), increased androgen levels (hyperandrogenism), and cystic ovaries [3]. Cysts in ovaries are present in more than 70% of women affected by PCOS, along with any of the two other symptoms [2]. It has also been linked to obesity and insulin resistance leading to cardiovascular disease, infertility, type 2 diabetes mellitus metabolic syndrome, and non-alcoholic fatty liver disease [4]. These symptoms usually present themselves in adulthood, although PCOS can also affect adolescents [3].

The clinical symptoms of NC-CAH mimic PCOS. One of the main features of NC-CAH is the occurrence of premature pubarche (the first appearance of pubic hair). In a study performed on 25 females, 95% reported premature pubarche before the age of 8 [12]. However, depending on the severity of the disease, many adolescents are asymptomatic and display symptoms in late adolescence or adulthood. In post-pubarche women, the symptoms correlate to the effects of hyperandrogenism, including hirsutism, acne, androgenic alopecia (male-pattern hair loss), menstrual and ovulatory dysfunction, and infertility [13].

Diagnosis

Three guidelines with specific criteria have been outlined for the diagnosis of PCOS (figure 2) [2]. From these guidelines, the Rotterdam Criteria are commonly used to diagnose adults [2]. Complying with the Rotterdam Criteria entails diagnosing PCOS based on four phenotypes (figure 3). To investigate the ovarian morphology for the presence of PCOM (polycystic ovarian morphology), a transvaginal or pelvic ultrasound is performed to detect the string-of-pearl structure [14]. If more than 12 ovarian follicles of 2-9mm in size or an increase in the ovarian tissue are observed, the patient is diagnosed with PCOM [14].

Another major symptom of PCOS is hyperandrogenism which is categorised as either clinical or biochemical [14]. Clinical hyperandrogenism is characterised by hirsutism, while biochemical hyperandrogenism is distinguished by elevated androgen serum

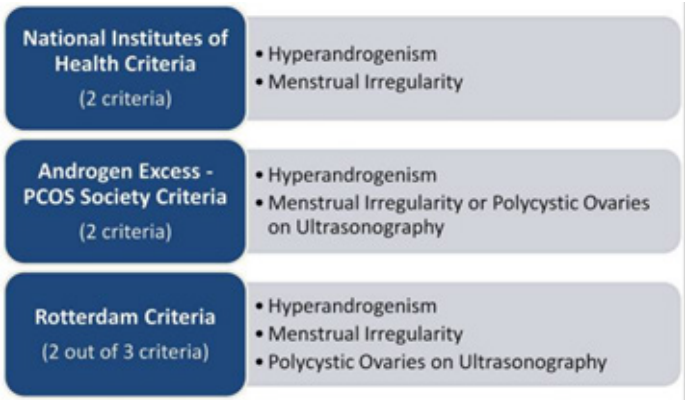

Figure 2: *Guidelines for diagnosing PCOS. Three guidelines are used worldwide for diagnosing PCOS. Each guideline has certain criteria; depending on the number of criteria the patient fulfills, it determines the diagnosis. For instance, for a patient to be diagnosed with PCOS, the patient has to meet two out of the three Rotterdam criteria [2].*

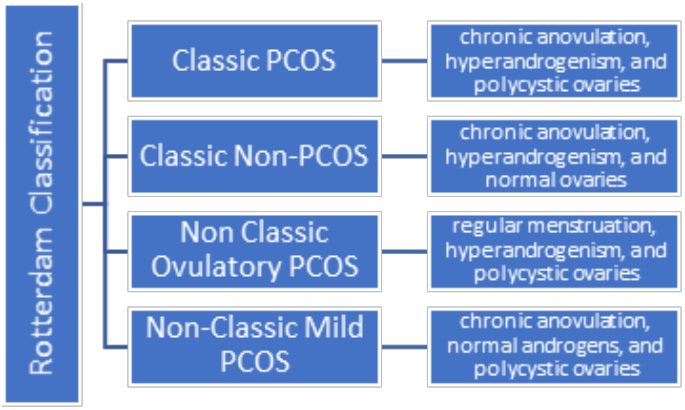

Figure 3: *Types of PCOS. Illustration displaying the different phenotypes of PCOS and the symptoms relating to each phenotype.*

levels [15]. Women who display hirsutism, acne, and androgenic alopecia are diagnosed with clinical hyperandrogenism [14]. Hirsutism is the presence of excessive coarse dark hair in women in a male-like distribution pattern such as in the inner thighs, near the navel, chest, and back. The Ferriman-Gallway score is used to define the extent of hirsutism. It is a semi-subjective system, and a score of more than 8 indicates hirsutism depending on the ethnicity of the patient [16]. For Mediterranean, Hispanic, and Middle Eastern women, a score of 9 or higher is considered hirsutism while a cut off value of 6 is used for South American women [17]. Biochemical hyperandrogenism is diagnosed when the serum levels of one or more androgens (i.e. total testosterone, free testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione) are elevated [15]. Blood levels of lipids, glucose, and other hormones like thyroid hormones, prolactin, anti-Mullerian hormone (AMH), and cortisol are also measured to rule out other hormone disorders that also cause menstrual irregularities such as hyperprolactinemia and thyroid disease [2].

One of the other main features of PCOS is the presence of menstrual irregularities – amenorrhea, oligomenorrhea, or inconsistent menstruation [4]. These irregularities are influenced and caused by multiple factors such as elevated androgen levels and irregular LH, follicle stimulating hormone, and oestrogen, which levels lead to ovulation issues such as anovulation (no ovulation) or oligo-ovulation (ovulating less than eight times a year) and therefore causing irregular menstruation in patients [4]. Patients are diagnosed with PCOS if they meet at least two out of the three criteria.

For NC-CAH, since the symptoms are clinically similar to PCOS, the diagnosis for hyperandrogenism is the same as PCOS, i.e. testing androgen levels and dermatological features such as acne, hirsutism, and alopecia [6]. In addition, the levels of 17-OHP and progesterone are measured, checking for their probable elevation during the pre-ovulatory phase of the menstrual cycle [12]. Furthermore, an ACTH stimulation test is performed, which stimulates the adrenal gland to produce cortisol and other steroid hormones to evaluate the concentrations of the hormones produced [18]. If the biochemical levels of these tests are borderline or give uncertain results, then genetic testing can be done to determine the genetic mutations involved, resulting in a firm diagnosis [19]. However, in developed countries, genetic testing is commonly performed, mostly in the neonatal stage, to determine the type of enzyme deficiency and its potential to be inherited by future offspring [20].

In some cases of NC-CAH, the patients may also have dysfunctional ovarian morphology, i.e. PCOM. However, diagnosing PCOS and NC-CAH is a clinical challenge, especially when the patient has non-classical PCOS with no polycystic ovaries. For such cases, measuring the 17-OHP levels and other steroid hormones after the ACTH stimulation test can aid in the differentiation of diagnoses between the two diseases [19].

Treatment

Currently, no cure exists for PCOS and NC-CAH, and present treatments are used for symptom management [19]. These treatments aim to reduce insulin resistance, decrease androgen levels, and correct anovulation [3]. One of the first-line treatments for PCOS and NC-CAH is oral contraceptive pills to lower androgen levels and regularise menstruation, thereby providing endometrial protection. Combined preparations of oestrogen and progestin have been found to decrease luteinising hormone secretions leading to a reduction in PCOM and decreasing elevated androgen levels [2].

Anti-androgenic therapy such as spironolactone is also considered for treatment. However, due to its teratogenic effect, it is not recommended [19]. The common drug administered for managing insulin resistance is metformin [21]. Recently, however, inositol, which works as a second messenger of insulin, is also recommended to manage insulin resistance [2]. Furthermore, lifestyle modifications such as regular exercise, weight loss, reduction in sugar intake, and a healthy diet with adequate protein intake is recommended for tackling obesity and has also been shown to enhance moods [4]. Specifically for NC-CAH, glucocorticoid therapy is sometimes recommended for females who are non-responsive to oral contraceptives and anti-androgen therapies [19]. Glucocorticoids suppress ACTH, thereby reducing androgen production from adrenal glands [19]. However, glucocorticoid therapy has potential side effects, is risky and, hence, is recommended only in certain cases [6].

Conclusion

Polycystic ovarian syndrome and non-classical congenital adrenal hyperplasia are common endocrine disorders that affect females. The clinical presentation of the symptoms overlaps, making their diagnosis hard, which increases the chance of misdiagnosis. Patients affected by these diseases are susceptible to additional chronic lifestyle diseases such as obesity, cardiovascular disease, non-alcoholic fatty liver disease, type 2 diabetes, and infertility. In addition,

there is an increased risk for pregnancy complications, anxiety, and depression. No cure exists for PCOS and NC-CAH, and, hence, the current treatments primarily focus on symptom management and normalisation of dysregulated hormone levels.

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