BMJ Case Reports

Novel treatment (new drug/interventions; established drug/procedure in new situation)

# *Ashwagandha* root in the treatment of non-classical adrenal hyperplasia

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## Summary

Congenital adrenal hyperplasia (CAH) is a well-characterised family of disorders of the adrenal cortices, resulting in varying degrees of cortisol, aldosterone and androgen deficiency or androgen excess, depending on the enzyme(s) affected and the degree of quantitative or functional enzyme deficit. *Withania somnifera* (WS), commonly known as *Ashwagandha*, is a medicinal plant that has been employed for centuries in ayurvedic medicine. Preclinical studies have shown that WS increases circulating cortisol levels and improves insulin sensitivity. We report the case of a 57-year-old woman with non-classical adrenal hyperplasia due to both 3-β-ol dehydrogenase deficiency and aldosterone synthase deficiency who was self-treated with WS for 6 months. After 6 months of treatment her serum 18-OH-hydroxycorticoserone, 17-OH-pregnenolone, corticosterone and 11-deoxycortisol decreased by 31%, 66%, 69% and 55%, respectively. The biochemical improvement was accompanied by a noticeable reduction in scalp hair loss.

## BACKGROUND

Congenital adrenal hyperplasia (CAH) is a family of autosomal-dominant disorders with variable penetrance resulting from a quantitative and/or functional deficiency of enzymes involved in the biosynthesis of the adrenal steroid endproducts including cortisol, aldosterone, dehydroepiandrosterone (DHEA) and possibly adrenal ouabain. Deficiency may result from exonic mutations, mutations in a gene's promoter region, gene methylation abnormalities, epigenetic interference with gene transcription, mRNA translation or post-translational activity of the enzyme. The most common form of CAH is 21-hydroyxlase deficiency, reportedly accounting for >90% of cases.[1] Deficiency of this enzyme or its function results in greater or lesser degree of aldosterone and cortisol deficiency, and excess androgen. The non-classical form (non-classical adrenal hyperplasia, NCAH) is due to a functionally milder mutation or to a heterozygous expression of a functionally more severe mutation.[2 3] The incidence of non-classic 21-hydroxylase deficiency is reported to be 1:1000 live births and most patients present with signs and symptoms of androgen excess, for example, hirsutism, acne, alopecia, menstrual irregularity and infertility.[4 5] It has been reported that CAH, like polycystic ovarian syndrome (PCOS) is associated with insulin resistance.[6–11]

*Withania somnifera* (WS), also known as *Ashwagandha* or Indian ginseng, is a medicinal plant that has been used for more than 2500 years in ayurvedic medicine.[12] Its medicinal benefits such as antistress, antibacterial, anti-inflammatory, antioxidant and immuno-modulatory properties have been reported by several authors.[13–15] WS has also been reported to have efficacy in the treatment of anxiety, Parkinson's disease, insomnia and as adjunctive therapy for patients receiving chemotherapy and radiotherapy.[16] In studies conducted by Singh *et al*[17 18] WS was reported to increase circulating cortisol, improve stamina and decrease fatigue in stressed mice. Anwer *et al*[19] have reported that WS increases insulin sensitivity and improves glycemic control in non-insulin-dependent streptozotocin diabetic rats. On the basis of the literature reviewed, we believe that the biochemical and clinical improvement we observed in our patient might be attributable to a reduction of insulin resistance leading to improved cortisol and aldosterone secretion, and less accumulation of intermediates.

## CASE PRESENTATION

A 57-year-old woman presented with a chief complaint of excessive scalp hair loss and an intermittent burning sensation in the scalp, as well as excessive scalp dryness. Her reproductive history was normal. She denied hirsutism or acne. Her premenopausal menstrual history had been normal. She was not obese, body mass index=21.5 kg/m$^2$, and did not show any stigmata of Cushing's syndrome. The pubic escutcheon was normal. Examination of the internal and external genitalia was normal. Her daughter had been diagnosed with PCOS. Despite impressive scalp hair shedding, there was no apparent alopecia or thinning areas on her scalp. She did not have acanthosis or numerous skin tags, or hyperpigmentation. Her history was also notable for euthyroid Hashimoto's thyroiditis without thyromegaly, and hypercholesterolaemia. Her external genitalia and pelvic examination were normal.

## INVESTIGATIONS

These included serum thyroid-stimulating hormone by electrochemiluminescence (ECLIA), thyroid peroxidase antibody by ECLIA, thyroglobulin antibody by immunochemiluminometric assay, serum androstenedione by liquid chromatography/mass spectrometry (LC/MS), corticosterone by LC/MS, DHEA by LC/MS, DHEA-sulphate (DHEA-S) by ECLIA, 17-OH-progesterone by LC/MS, 17-OH-pregnelone by radioimmuno assay (RIA), 11-deoxycortisol by LC/MS, deoxycorticosterone by MS, 18-hydroxy-corticosterone by MS, sex hormone binding globulin by ECLIA, total testosterone by TC/tandem MS (MS-MS), free testosterone by direct analogue RIA, dihydrotestosterone by high-performance liquid chromatography (HPLC) with MS-MS, and oestrone by LC/MS-MS. The patient's baseline serum 17-OH-pregnenolone was elevated at 460 ng/dl (53–357) and her baseline serum corticosterone was elevated at 2416 ng/dl (130–820), supporting diagnoses of non-classic 3-β-ol dehydrogenase deficiency and non-classic aldosterone synthase deficiency. Cosyntropin stimulation was unnecessary as baseline values were already very elevated. Non-contrast MRI of the cervical spine revealed multilevel discopathy of the brachial plexus, likely accounting for the burning scalp paresthesias.

## DIFFERENTIAL DIAGNOSIS

The diagnosis included: postmenopausal PCOS-hyperthecosis syndrome, NCAH and hair shedding due to hyperthyroidism.

## OUTCOME AND FOLLOW-UP

Previously the patient had been treated for her NCAH with pioglitazone 15 mg orally daily with normalisation of her elevated serum adrenal metabolites and some reduction in the rate of scalp hair loss. However, she was reluctant to remain on this medication due to concerns about weight gain, bone loss and bladder cancer and, therefore, discontinued it. After watching Dr Oz's television show in which he recommended the use of *Ashwagandha* 400 mg twice daily for its antioxidant and antistress benefits, the patient began taking a standardised preparation of *Ashwagandha* root at this dosage. At her next visit, 2 months later, she observed that the amount of hair she was finding each morning on her pillow upon awakening had diminished considerably. We suggested that she repeat the levels of her previously abnormal and high normal adrenal metabolites to determine if they had fallen in response to *Ashwagandha* as a possible explanation for her apparent clinical improvement. While still on treatment it was observed that her serum 18-hydroxycorticosterone had fallen 31% from 55 to 38 ng/dl (9–58), her serum 17-OH-pregnenolone fell 66% (figure 1) from 460 to 155 ng/dl (53–357), serum corticosterone fell 69% (figure 2) from 2416 to 748 ng/dl (130–820) and serum 11-deoxycortisol fell 55% from 89 to 40 ng/dl (12–158). She has maintained normal levels of these metabolites to the present (a period of 8 months).

## DISCUSSION

NCAH is a relatively common family of disorders which, in those pedigrees in whom an exonic mutation has been identified, shows an autosomal-dominant inheritance pattern with variable penetrance. The most common form of NCAH is 21-hydroxylase deficiency with the highest prevalence among Ashkenazi Jews, Hispanics, Italians and people from the former Yugoslavia; among these groups the prevalence of the homozygous form is 2–4%, with heterozygotes and compound heterozygotes being variably affected.[1] The non-classic form of 3-β-ol dehydrogenase deficiency is no longer considered to be due to an exonic mutation.[20–22] It has been speculated that it could be due to a mutation in the promoter region of the gene, such has been reported in some patients with 21-hydroxylase deficiency[23] or due to epigenetic phenomena affecting the transcription of the gene, the translation of its mRNA, or causing a post-translational diminution in enzyme function. Until quite recently only the severe classic form of aldosterone synthase deficiency (Visser-Cost syndrome) was known and it was chiefly confined to people from the Netherlands and Prussia.[24 25] In 1999, we reported the first mild, non-classic case of this disorder and have subsequently learned that it can be ameliorated with fludrocortisone, glucocorticoids, weight loss or metformin.[8] It is likely that many patients with basal or cosyntropin-stimulated elevations of serum deoxycorticosterone were misclassified as having non-

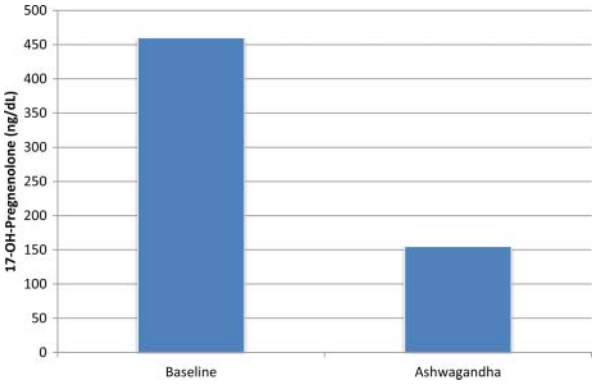


**Figure 1** Change from baseline in patient's serum 17-OH-pregnenolone level on *Ashwagandha* 400 mg twice daily.

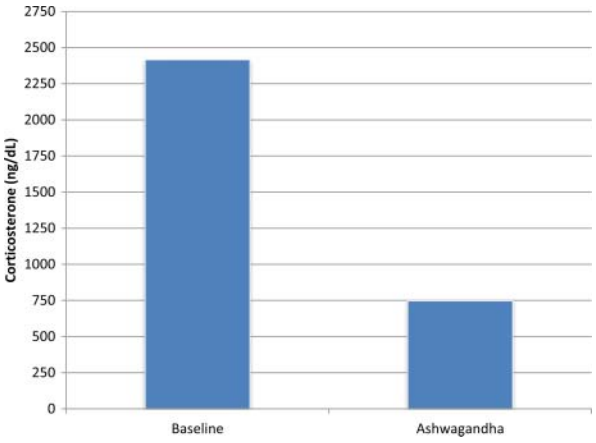


**Figure 2** Change from baseline in patient's serum corticosterone level on *Ashwagandha* 400 mg twice daily.



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classical 11-hydroxylase deficiency due to the very considerable homology between the two enzymes.

Conventional treatment varies with the age, gender and reproductive goals of the individual patient. The mainstay of conventional treatment is replacement of glucocorticoid and often mineralocorticoid. In female patients androgen receptor blockers, 5-α-reductase inhibitors and oral contraceptives have also been used to achieve more complete therapeutic/cosmetic results. Treatment principles are quite similar to those used in adrenal insufficiency, with the difference that, if prednisone is prescribed the dose is usually given at bedtime and if cortisone acetate or hydrocortisone is prescribed, the larger dose is usually given at bedtime. This dosing protocol has been shown to better suppress the early-morning increase in circulating androgens. Fludrocortisone is usually administered even if the patient does not experience salt wasting, as it will allow a lower dose of glucorticoid to be prescribed, thus curtailing certain glucocorticoid side effects. More recently, insulin sensitisers, insulin-sensitising lifestyle changes, and Roux-en-Y gastric bypass surgery (also insulin sensitising) have been reported to be effective in treating both NCAH and classical 21-hydroxylase deficiency.[8]

Although quite effective, medications and surgery may be associated with short-term and long-term side effects. In a study by Azziz *et al*[26] 1281 hyperandrogenic women, including some with NCAH, were treated with hormonal suppressive therapy. Over 80% of the patients were documented to have shown improvement in hirsutism, acne and menstrual irregularity; however, 64% of them reported medication side effects including: irregular vaginal bleeding, nausea, vomiting, migraine and depression. In addition, alopecia improved in only 30% of patients. Furthermore, hormonal suppression fails to correct the insulin resistance and associated metabolic problems accompanying these virilising disorders. These impressive, yet somewhat disappointing outcomes, might be due to the fact that conventional therapy does not address the underlying insulin-resistance in these disorders or to what Wermuth[27] has termed the single module mechanism of conventional medicine. In contrast, herbal medicines such as *Ashwagandha*, work through multitarget mechanisms and may, in some instances, elicit a better response than conventional medicines.

*Ashwagandha* is used worldwide as a nutritional supplement.[28] Its therapeutic effects have been mainly attributed to steroidal lactones, collectively known as withanolides, which have a wide range of biological actions.[29] It has been used for centuries for a variety of conditions and this case report is the first to describe a benefit in a patient with NCAH.

Our patient experienced a gratifying and apparently durable reduction in scalp hair loss and previously elevated adrenal steroid metabolites over 8 months of using a standardised preparation of *Ashwagandha*. She has not experienced any adverse effects from using this preparation. We conclude that *Ashwagandha* root may be useful as an alternative treatment for NCAH, if randomised double-blind control trials confirm our patient's experience.

## Learning points

- Insulin resistance appears to underlie non-classical adrenal hyperplasia (NCAH) as it does polycystic ovarian syndrome.
- *Ashwagandha* has been reported to have insulin sensitising and anti-inflammatory effects.
- *Ashwagandha* might have ameliorated this patient's NCAH by improving her insulin sensitivity.

**Competing interests** None.

**Patient consent** Obtained.

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