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ORIGINAL ARTICLE

Adrenal hypofunction associated with ashwagandha (*Withania somnifera*) supplementation: a case report

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Abstract

Objective The use of herbal medicinal supplements has gained huge popularity world-wide, but scientific evidence of their effectiveness and safety remains scarce. Ashwagandha (*Withania somnifera*) is one such product, claimed to alleviate pain and anxiety by lowering circulating cortisol levels. Withanolides, which are the principal bioactive compounds of ashwagandha, are naturally occurring steroids and may suppress adrenal function. Here, we describe the effect of ashwagandha on adrenal function of a 41-year-old woman with a low body mass index and who suffered chronic pain and lethargy.

Methods Adrenal function was assessed by the short Synacthen test (SST) during and after treatment with ashwagandha supplementation.

Results Whilst taking daily ashwagandha supplement (21.4 mg of Withanolides), for ten weeks, a SST showed a minimal response to 250 µg of an intramuscular injection of Synacthen (tetracosactide): cortisol levels at $T_{0min} = 287$ nmol/l, $T_{30min} = 289$ nmol/l, and $T_{60min} = 328$ nmol/l; from a morning baseline cortisol level of 480 nmol/l prior to taking the supplement. Ashwagandha was discontinued for two weeks, and a repeat SST was performed showing a completely normal adrenal response: cortisol level at $T_{0min} = 275$ nmol/l, $T_{30min} = 623$ nmol/l and $T_{60min} = 674$ nmol/l.

Conclusion Ten weeks of ashwagandha supplementation was associated with adrenal hypofunction, which was reversible after a two-week break. Individuals taking ashwagandha should be aware of this potentially detrimental effect. Future studies are suggested to assess whether long-term treatment with ashwagandha could lead to permanent suppression of adrenal function, and to elucidate the effects of ashwagandha compounds on adrenal steroidogenic pathway and hypothalamic–pituitary–adrenal axis.

Keywords Ayurveda · Dietary supplements · HPA axis · Hypocortisolism · Short Synacthen test · Steroidogenesis · Toxicity

Introduction

Over the past four decades, the use of herbal medicinal products and supplements has gained huge popularity worldwide. These products are sold on the Internet and in health shops, but many are not rigorously tested for their effectiveness and safety by clinical trials. Individuals with symptoms of generalised bodily pain and anxiety are particularly attracted to these supplements [1]. Ashwagandha (*Withania somnifera*) extract is one such herbal product marketed globally [2, 3]. Although commonly known as ashwagandha, it has been called by some ten other names. An evergreen shrub, ashwagandha is a genus of flowering plants in the *Solanaceae* (nightshade) family, and most of it is grown in South Asia, the Middle East and North Africa, but may also be found in Southern Europe and the Mediterranean [4].

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This plant has been used for thousands of years as a medicinal herb in traditional Ayurvedic medicine (Ayurveda). Withanolides, which are the principal bioactive compounds of ashwagandha, are naturally occurring steroids. About 35 steroidal withanolides, along with 12 steroidal alkaloids and several sitoindosides have been isolated from ashwagandha [5–7].

In modern days, ashwagandha is advertised widely for its apparent "multiple beneficial effects on a number of organs including the central nervous and endocrine systems, as well as the ability to alleviate pain by its anti-inflammatory property and generate calming effects by lowering adrenal steroids". However, similar to many other herbal medicinal products, adverse effects of ashwagandha on humans have not been well documented [2]. Here, we describe the effect of ashwagandha on the adrenal function of a woman.

Results

Case presentation

A 41-year-old woman was reviewed in the Endocrine clinic on 4 May 2021. She had a two-year history of generalised bodily pain sustained from a road traffic accident. To relieve pain she was treated with the tricyclic antidepressant amitriptyline at 25 mg a day (amitriptyline has no known effects on the steroidogenic pathways), and she had never taken opioid-based drugs or steroids. She had been taking an oral contraceptive pill (OCP) but stopped one year previously. She had regular periods whilst not taking OCP. She had no history of weight loss and was always slim (body mass index = 17.5 kg/m^2). She did not smoke or drink alcohol excessively. Her thyroid function and basic haematological and biochemical parameters were normal; lyme borreliosis was also excluded (Table 1). A short Synacthen test (SST) to exclude adrenal insufficiency was suggested. Whilst SST was being arranged, the patient inadvertently visited the phlebotomy department where a morning random cortisol was done, showing a level of 480 nmol/l. The formal SST was performed on 12 August 2021. To our surprise, the baseline cortisol level had dropped to 287 nmol/l, whilst the response to 250 µg of an intramuscular injection of Synacthen (tetracosactide) was minimal (T_{30min} = 289 nmol/l, and T_{60min} = 328 nmol/l).

On direct questioning, the patient's symptoms remained unchanged. However, it became apparent that shortly after the initial consultation in May 2021, the patient began to conduct Internet search on health topics relating to the adrenal glands. She discovered a number of websites selling ashwagandha root extract, which was advertised for its "anti-inflammatory property and ability to lower cortisol levels, leading to reduction of pain and stress". The patient ordered this product (*Clean Ashwagandha*, British Supplements, UK) [8] and took one capsule twice a day up to the end of August 2021 (two capsules = 858.6 mg ashwagandha extract, containing 21.4 mg Withanolides, plus 95.4 mg of the manufacturer's uptake blend). Therefore, the patient was taking ashwagandha for ten weeks by the time she had the first SST. Ashwagandha was discontinued for two weeks and a repeat SST was performed on 14 of September showing a completely normal adrenal response to Synacthen: cortisol level at T_{0min} = 275 nmol/l, T_{30min} = 623 nmol/l and T_{60min} = 674 nmol/l (Fig. 1). The adrenocorticotropic hormone (ACTH) level at baseline (T_{0min}) of this second SST was normal at 11 ng/l (reference range: < 50 ng/l).

Table 1 Physiological and biochemical characteristics of the patient prior to taking ashwagandha supplement

Patient characteristics	Parameters	Reference range
Age, years	41	–
Body mass index, kg/m^2	17.5*	20–25
Systolic/diastolic blood pressure, mmHg	120/75	< 160/90
Morning cortisol, nmol/l	480	> 550†
Thyroid stimulating hormone, mU/l	2.09	0.35–4.78
Haemoglobin, g/l	124	115–165
Creatinine, µmol/l	60	< 60
Alanine transferase, U/l	25	10–49
Calcium, mmol/l	2.26	2.2–2.6
Ferritin, µg/l	169	15–250
Borrelia burgdorferi IgG	Not detected	–

*Weight = 50 kg, height = 1.69 m; †Some centres accept a random cortisol level of > 450 nmol/l as normal

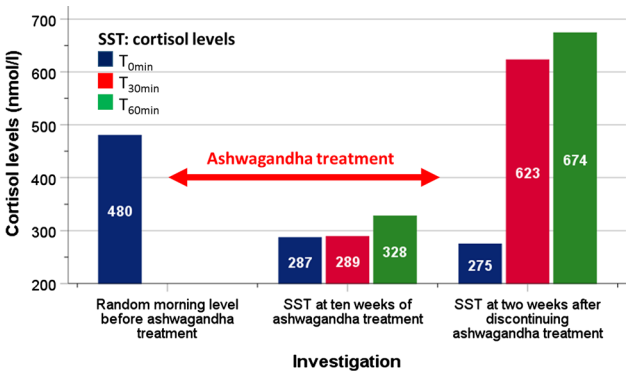

Fig. 1 Cortisol levels measured prior to, during treatment and after discontinuation of treatment with ashwagandha

Discussion

Summary

We present a case whose adrenal function was suppressed during the period when the patient was taking ashwagandha, which was reversed to normal function after discontinuation of this herbal product. As far as we are aware, this is the first observation of temporal changes in adrenal function, as assessed by SST, during and after stopping supplementation with ashwagandha. This case highlights the ability of ashwagandha to suppress adrenal function in a relatively short duration (ten weeks), but could be reversed after two weeks of discontinuation.

Clinical implications

There is a lack of scientific evidence of the effectiveness and safety of ashwagandha for treating any disease, and according to expert review from www.drugs.com website, trials supporting its clinical use in humans are limited [2]. Animal studies suggest it has effects on the immune, endocrine and central nervous systems, and inflammatory conditions. There are a handful of randomised controlled trials (RCT) from India [9, 10]. A recent RCT of sixty healthy Indian adults showed supplementation with 240 mg of ashwagandha extract once daily for 60 days led to a reduction in the Hamilton anxiety rating scale ($P=0.040$) and morning cortisol levels ($P<0.001$) compared with placebo [10]. The major flaws with such study were that there was no valid medical reason for lowering anxiety or cortisol levels of volunteers who were described as healthy adults. Cortisol reduction should indeed be interpreted as an adverse effect of ashwagandha rather than benefit. The subnormal adrenal response to tetracosactide (assessed by SST) observed in our patient could potentially lead to serious health consequences due to the inability of the patient to mount a response to an acute stress, such as a major illness or infection. As far as we are aware, there is no existing literature on dynamic endocrine tests of adrenal function (such as SST) during and after taking this supplement.

Adverse effects

A number of potential toxic actions associated with ashwagandha have been comprehensively reviewed and described by experts, including clinicians and pharmacists, on the www.drugs.com website [2]. Studies with Wistar rats showed that repeated injections of ashwagandha extract, at a dose of 100 mg/kg body weight for 30 days, led to reduction in the weights of adrenals, thymus and spleen [11], whilst hepatotoxicity effects of ashwagandha have recently been reported in humans [12, 13]. Dosing in humans is variable, ranging from 120 mg to 2 g a day. Contraindications and interactions and its use in pregnancy and lactation have not been well documented, but adverse effects are scarcely or inappropriately reported in human studies. For example, in two recent RCTs, one reported "no adverse events" [9] whilst the other inadequately monitored treatment safety by full blood counts and lipids [10]. Since there is no existing published literature on adrenal function amongst people taking ashwagandha, it is not possible to determine if this herbal product affects the adrenal function differently in people of different age, sex, body composition or ethnic background.

Mechanisms

Plants have evolved to produce a number of toxic substances as defence mechanisms against predation from microorganisms (bacteria and fungi), insects and animals [14–17]. A large number of plants, including ashwagandha, used in herbal medicines possess this toxic property. The withanolides from ashwagandha contain a highly oxygenated C28 ergostane-type steroidal nucleus with C22-hydroxy-C26-oic acid δ-lactone in a nine-carbon side chain, and oxidised to form a six-membered lactone ring [18–20]. It is possible that the steroidal compounds from ashwagandha, such as withanolides and alkaloids, may have a direct effect on adrenal function. Adrenal steroidogenesis is complex, involving a pathway of precursor hormones that require specific enzymatic steps [21], the genes that encode the enzymes involved in the control of steroid biosynthesis may be interrupted by withanolides and alkaloids, giving rise to adrenal hypofunction. A recent study has shown that withanone, a bioactive constituent of withanolides found in ashwagandha extract, may cause deoxyribonucleic acid (DNA) damage by forming adducts to DNA. Withanone also forms adducts with amines, which are reversibly detoxified by glutathione (GSH) but may cause DNA damage when the GSH system is overwhelmed by excessive levels of withanone [22]. Studies have also found that alkaloids from a number of herbal medicines react with DNA, causing cellular toxicity or genotoxicity (damage to the genome), leading to structural alterations of the genetic material through induction of DNA binding and cross-linking, as well as chromosomal abnormalities [23].

The effects of steroidal compounds from ashwagandha may extend to higher neuroendocrine centres controlled by the hypothalamus and pituitary. The hypothalamic-pituitary axis is known to be vulnerable to stress from restricted dietary practice and excessive exercise [24] and a number of drugs including exogenous steroids and opioids [25]. It is plausible that the steroidal withanolides and alkaloids

from ashwagandha could suppress the hypothalamic–pituitary–adrenal (HPA) axis, in a similar way that exogenous corticosteroids (used to treat chronic inflammatory conditions) do to the HPA axis, leading to hypoadrenalism [25, 26].

Patient perspective

The patient expressed that she would take greater caution before considering taking any dietary supplements in the future. She would do thorough research on independent sources and consult with healthcare professionals.

Materials and methods

Information for demographic factors and medications and physiological measurements were obtained from clinical history and examination. Blood was taken for biochemistry and haematology investigations. Adrenal function was assessed by SST: the levels of cortisol were obtained at baseline (prior to Synacthen injection), and at 30 min and 60 min after an intramuscular injection of 250 µg of Synacthen into the deltoid muscle. An incremental rise of cortisol level by at least 200 nmol/l or a peak cortisol of > 550 nmol/l was considered as a normal adrenal response. The SST was performed whilst the patient was taking ashwagandha and two weeks after coming off this supplement. Analyses were performed using SPSS Statistics for Windows, v.25.0 (IBM Corp., Armonk, NY, USA).

Conclusion

This study shows that a relatively short course of ashwagandha is associated with adrenal hypofunction, which was reversible after two weeks of discontinuation of supplementation. Individuals taking ashwagandha should be aware of its detrimental effects. Future studies are suggested to assess whether long-term treatment with ashwagandha could lead to permanent suppression of adrenal function. Further in vitro and in vivo studies are necessary to elucidate the effects of ashwagandha compounds on adrenal steroidogenic pathway and HPA axis.

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Declarations

Conflict of interest Christopher H. Fry, David Fluck and Thang S. Han declare that they have no conflicts of interest.

Ethical approval This study does not require NHS Research Ethics Committee approval since it involves secondary analysis of anonymised data. This study was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement of human and animal rights This article does not contain any studies with animals performed by any of the authors.

Statement of authorship TSH reviewed the topic related literature and wrote the first draft, interpreted the data and revised the manuscript. CHF and DF checked, interpreted results and commented on the manuscript. All authors critically revised the manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work and read and approved the final manuscript.

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