CASE REPORT

Exogenous Cushing's syndrome due to a Chinese herbalist's prescription of ointment containing dexamethasone

Viola Franke,¹ Winnie Francien Scholtens,² Ines Alexandra von Rosenstiel,³ Marie Jose Walenkamp⁴

¹Oncologic Surgery, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
²Pediatrics, OLVG West Hospital, Amsterdam, The Netherlands
³Pediatrics, Rijnstate Hospital, Arnhem, The Netherlands
⁴Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

Correspondence to

Miss Winnie Francien Scholtens,
 winnie_scholtens@hotmail.com

Accepted 2 April 2017

SUMMARY

Eczema in children is a chronic disabling condition. The impact of this condition on the lives of families is often underestimated by conventional physicians. As a consequence parents may investigate complementary treatment options. Close monitoring by a paediatrician is essential, considering that a variety of adverse effects can occur during the use of complementary treatment. We present a 5-year-old girl with eczema. She visited a Chinese herbalist who prescribed an ointment. The parents noticed that the eczema resolved fast, itching decreased and she was finally sleeping well. However, her behaviour changed and appetite increased. Undetectable levels of serum cortisol were found, which was indicative of exogenous Cushing's syndrome. Analysis of the ointment revealed the presence of dexamethasone. Hydrocortisone substitution and subsequently a reduction schedule were implemented, after which endogenous cortisol production recovered after 4 months. Physicians should be aware that unregistered herbal medicine can contain potent drugs such as glucocorticoids.

BACKGROUND

Our case report extends the literature on adrenal insufficiency due to unregistered herbal medicine with high-dose glucocorticoids. Previous studies have shown adrenal insufficiency in patients receiving corticosteroid therapy, yet few articles have been published concerning herbal medicine. As adrenal insufficiency can be a life-threatening condition, we hope to prevent future cases and raise awareness among medical professionals about the use of complementary medicine with potentially dangerous amounts of glucocorticoids.

CASE PRESENTATION

A 5-year-old girl was seen in our outpatient clinic with atopic dermatitis and recent symptoms of changed behaviour and increased appetite. She had a history of extensive dermatological treatment for atopic dermatitis and multiple allergies. Before presentation her parents had consulted a Chinese herbalist, who prescribed supplements (Calm Skin Form, Green Nature, Hong Kong), lotion (full body application, three times daily) and ointment (full body application, three times daily) for the treatment of her atopic dermatitis. Lotion and ointment were stated to be self-made. The dermatitis

recovered well during an intermittent treatment of 5 weeks. Physical examination showed an elated, hyperactive girl with moderate eczema of the scalp, face and trunk. She had a moon face. Her height was 106.5 cm (−1.33 SD score (SDS)), target height 169.9 cm (−0.11 SDS), body weight 17.6 kg (−0.7 SDS weight for height) and blood pressure 102/66 mm Hg (85th percentile for height). Analysis of her growth chart showed no height deviation or abnormal weight gain.

INVESTIGATIONS

The exceptional effect of the herbal treatment on the atopic dermatitis was suspicious of exogenous corticosteroid administration. Laboratory evaluation was performed and revealed a morning cortisol level of <10 nmol/L, which was indicative of adrenal insufficiency. A specialised laboratory (Medlon BV, Enschede, the Netherlands) performed liquid chromatography–mass spectrometry analysis of the ointment and revealed a dexamethasone concentration of at least 44 µg dexamethasone per gram of the ointment. The supplements and lotion contained corticosteroid compounds, but an exact concentration was indefinable. Betamethasone, which has the same anti-inflammatory potency as dexamethasone, is prescribed for atopic dermatitis in a concentration of 640 µg/g for short-term and local application. Our patient was exposed to a lower concentration of dexamethasone than betamethasone; however, it was applied on the whole body three times daily for several weeks.

DIFFERENTIAL DIAGNOSIS

Adrenal insufficiency is characterised by low morning cortisol levels. A repeated cortisol value below 138 nmol/L is suspicious for insufficiency. A measurement of the adrenocorticotrophic hormone (ACTH) can distinguish between primary (adrenal) and secondary (central or pituitary) insufficiency. Unfortunately ACTH concentration was not measured on the first presentation. Patients between 2 and 14 years most commonly have an autoimmune adrenalitis causing primary insufficiency with high ACTH levels, as a result of the negative feedback loop. In our case exogenous Cushing's syndrome was suspected, caused by corticosteroids in the ointment. Dexamethasone in the ointment

CrossMark

To cite: Franke V, Scholtens WF, von Rosenstiel IA, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-218721

suppresses the ACTH secretion in the pituitary, resulting in adrenal insufficiency.

TREATMENT

The application of all non-prescribed medication was discontinued and hydrocortisone substitution was implemented (4-2-2 mg daily=11.4mg/m²), according to the general paediatric guidelines recommending a substitution dose of 8-12mg/m². Parents were instructed to give extra hydrocortisone during illness. A schedule reducing the dose hydrocortisone was advised based on local guidelines.

OUTCOME AND FOLLOW-UP

In the following months two episodes of intercurrent illness with fever occurred, for which a stress schedule of hydrocortisone was prescribed. Endogenous cortisol production had recovered after 3 months, indicated by a morning cortisol level of 160 nmol/L. The substitution therapy with hydrocortisone was discontinued. A low-dose ACTH stimulation test (1µg/m²) revealed a recovered hypothalamic-pituitary-adrenal (HPA) axis after 4 months (cortisol response: 580 nmol/L). Follow-up showed mild hyperactivity. Her atopic dermatitis has been treated by our dermatologist with a combination of betamethasone, desoximetasone on her scalp and clobetasol on her face.

DISCUSSION

Topical corticosteroids are used in the treatment of a variety of dermatological disorders. Misuse of corticosteroids may cause systemic adverse effects, such as HPA axis suppression. Infants and young children are at greater risk for developing adrenal insufficiency due to a thinner skin leading to more percutaneous penetration and a higher ratio of body surface to body weight. Other risk factors may include the use of high potency corticosteroids, the amount and duration of application, skin condition, and use of occlusive treatment.

Cushing's syndrome in children due to the use of topical corticosteroids is mainly described in infants with diaper dermatitis¹; other primary diseases include psoriasis and skin dryness.¹⁻³ In rare occasions Cushing's syndrome is related to topical treatment of uveitis⁴ or intradermal treatment with triamcinolone acetonide.⁵

In a review of Tempark *et al*,¹² 22 cases of iatrogenic Cushing's syndrome due to topical corticosteroid application were described. The mean recovery time for HPA axis suppression in children was 3.49±2.92 months. In reports describing other types of corticosteroid application, recovery time varied between 9 and 15 months.^{4,5} Until now there has been no documentation of a non-reversible secondary adrenal insufficiency due to topical corticosteroids.⁶

Medical professionals should acknowledge the widespread use of complementary medicine, especially for chronic diseases.⁷ Up to 42.5% of a general paediatric outpatient population with atopic dermatitis has used alternative therapies.⁸ Positive effects of herbal medicine for the treatment of atopic dermatitis are reported in the literature.^{9,10} On the contrary, adverse effects of unconventional therapies in children have been described in case reports and case series, in which most adverse events are associated with the use of herbal medicine.¹¹ International monitoring conducted by the WHO showed 8985 case reports from 1986 to 1997 of adverse events associated with herbal medicine, including 100 cases related to children up to 10 years.¹² Some of these herbal medicines can cause serious adverse

reactions because of added undeclared synthetic drugs, as in our case. Reported adverse effects of exogenous glucocorticoids in non-prescription ointment or supplements include iatrogenic Cushing's syndrome and isolated side effects.^{13,14} A dermatological study analysed 11 Chinese herbal creams used in the treatment for eczema and revealed that 8 creams contained dexamethasone at a mean concentration of 456µg/g.¹⁵

Good quality reporting of adverse events after the use of herbal medication is essential to develop recommendations and alert drug safety monitoring boards.¹⁶ Our case contributes to the knowledge of potential serious adverse events following herb use. We have reported this case to the Health Care Inspectorate. Parents, medical professionals and governing boards will have to work together in preventing dangerous or even lethal situations as a consequence of unofficial herbal treatment.

In conclusion, we report a 5-year-old girl with eczema who developed exogenous Cushing's syndrome after using topical herbal ointment containing dexamethasone prescribed by a Chinese herbalist. Physicians who treat children with chronic conditions should be aware of the great percentage of parents investigating complementary treatment. An open dialogue with parents and a careful medical history with special attention to the use of unconventional treatment are essential to find adverse effects of alternative treatment containing potent drugs, including glucocorticoids. This case illustrates that drug safety monitoring boards and healthcare governments have a vital role in regulating and controlling complementary and alternative medicine.

Patient's perspective

We are very glad this case will be reported and shared with other paediatricians and parents. It is really important that the possibility of adverse effects with herbal use is more widespread known. Especially in cases of atopic dermatitis and allergies, or other chronic diseases, multidisciplinary and complementary treatment might help. In our case our daughter had a history of extensive dermatological and multidisciplinary treatment, but unfortunately it didn't work. After a last intensive treatment with hydrocortisone cream for 2 weeks without results, months without proper sleep and no showers because it was too painful, we were so desperate to find something that would help our daughter. A friend of ours had the same symptoms as a child and was completely recovered by a 3-week treatment of this Chinese herbal doctor, who also used acupressure and Qigong techniques next to herbal products. During this period of time, we told our paediatrician and dermatologist we started the Chinese treatment. They told us to be aware of the ingredients this Chinese doctor may be using. When we repeatedly asked the Chinese doctor about the use of hormones in the herbal ointment, the doctor even showed us laboratory results indicative of negative cortisone levels measured in the medication. When the treatment needed to be continued after 3 weeks, we first wanted to test the medication in a laboratory, something that is almost impossible to get done as a private person in Holland. We are very thankful this was made possible by the doctors we were working with at our hospital. Afterwards it turned out that there was dexamethasone present in the medication. We strongly advise all parents and doctors in similar situations to be very open about the use (or consideration of using) of unofficial herbal treatments. Only open communication, cooperation and a critical look on complementary treatments can prevent serious adverse events.

Learning points

- ▶ A great percentage (42.5%) of the paediatric population with atopic dermatitis uses complementary treatment.
- ▶ More adverse events are associated with the use of herbal medication compared with homeopathy and other unconventional treatments.
- ▶ Unregistered herbal medication may contain dangerous amounts of potent drugs, including glucocorticoids.

Contributors VF and WFS wrote the first draft of the paper. IAR and MJW contributed to the design and revised the work critically for intellectual content. The paper has been seen and approved by all authors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Tempark T, Phatarakijirund V, Chatproedprai S, *et al.* Exogenous Cushing's syndrome due to topical corticosteroid application: case report and review literature. *Endocrine* 2010;38:328–34.
- Seyedzadeh A. Infantile exogenous cushing syndrome due to misuse of topical corticosteroid. *Journal of Clinical Case Reports* 2012;02.
- Siklar Z, Bostanci I, Atli O, *et al.* An infantile cushing syndrome due to misuse of topical steroid. *Pediatr Dermatol* 2004;21:561–3.
- Kröger L, Kotaniemi K, Jääskeläinen J. Topical treatment of uveitis resulting in adrenal insufficiency. *Acta Paediatr* 2009;98:584–5.
- Finken MJ, Mul D. Cushing's syndrome and adrenal insufficiency after intradermal triamcinolone acetonide for keloid scars. *Eur J Pediatr* 2010;169:1147–9.
- Levin C, Maibach HI. Topical Corticosteroid-Induced adrenocortical insufficiency. *Am J Clin Dermatol* 2002;3:141–7.
- Cuzzolin L, Zaffani S, Murgia V, *et al.* Patterns and perceptions of complementary/alternative medicine among paediatricians and patients' mothers: a review of the literature. *Eur J Pediatr* 2003;162:820–7.
- Anderson PC, Dinulos JG. Atopic dermatitis and alternative management strategies. *Curr Opin Pediatr* 2009;21:131–8.
- Hon KL, Leung TF, Ng PC, *et al.* Efficacy and tolerability of a Chinese herbal medicine concoction for treatment of atopic dermatitis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2007;157:357–63.
- Hon KL, Lee VW, Leung TF, *et al.* Corticosteroids are not present in a traditional chinese medicine formulation for atopic dermatitis in children. *Ann Acad Med Singapore* 2006;35:759–63.
- Ernst E. Serious adverse effects of unconventional therapies for children and adolescents: a systematic review of recent evidence. *Eur J Pediatr* 2003;162:72–80.
- Farah MH, Edwards R, Lindquist M, *et al.* International monitoring of adverse health effects associated with herbal medicines. *Pharmacoevidenciol Drug Saf* 2000;9:105–12.
- Hughes JR, Higgins EM, Pembroke AC. Oral dexamethasone masquerading as a Chinese herbal remedy. *Br J Dermatol* 1994;130:261.
- de Smet PA, Wagenaar HW, Smeets OS. [Dexamethasone in a non-registered ointment from the Far East]. *Ned Tijdschr Geneesk* 1997;141:1626.
- Keane FM, Munn SE, du Vivier AW, *et al.* Analysis of Chinese herbal creams prescribed for dermatological conditions. *BMJ* 1999;318:563–4.
- Gardiner P, Adams D, Filippelli AC, *et al.* A systematic review of the reporting of adverse events associated with medical herb use among children. *Glob Adv Health Med* 2013;2:46–55.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow