

Cushing Syndrome Arising during Alternative Allergy Treatment with Homeopathic Preparations and Snake Venom

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A 6-year-old girl presented with clinical signs of Cushing syndrome. Her medical history revealed that she had been treated with an unusual alternative therapy for atopic eczema and bronchial asthma.

Case Report

WE REPORT ON a 6-year-old girl presenting with clinical signs of Cushing syndrome. She showed truncal obesity, moon face, and hypertrichosis on the back. Additionally, her parents reported frequent fits of rage and a ravenous appetite. All these symptoms had developed a few months before presentation to our clinic (Fig. 1a, b). Blood pressure was 123/62 mm Hg (95th percentile: 109/72 mm Hg). Anthropometric data were height 111 cm (10th percentile), weight 26.9 kg (97th percentile), and body-mass index 21.8 kg/m² (2.0 kg/m² > 97th percentile). Further clinical examination showed dry skin with a reddish, squamous eczema, located mainly in the face, the cubital fossae, and the hollows of the knees, with scabs after scratching. Lung auscultation revealed bronchial obstruction. Sonography of abdominal organs, including the ovaries, was normal. Pulmonary function tests showed an obstructive pattern (FEV1 55% predicted). After inhalation of 200 µg albuterol, there was a significant increase in FEV1.

Laboratory results: Cortisol was significantly reduced in serum and urine (serum cortisol at 8:00 a.m.: 2.1 µg/dL, at 4:00 p.m.: 0.6 µg/dL [normal range {n.r.} 6.0–19.0 µg/dL]; urine cortisol: 2 µg/24 h [n.r. 36–137 µg/24 h]). Adrenocorticotrophic hormone (ACTH) concentration in plasma was also significantly reduced (4.9 pg/mL at 8:00 a.m. [n.r. 7.2–63.0 pg/mL]). 11-Desoxy cortisol concentration was within low n.r. (0.9 ng/mL, n.r. 0.5–8.0 ng/mL). Serum concentrations normal for the girl's age were measured for luteinizing hormone (<0.1 mIU/mL, n.r. <1.4 mIU/mL), 17-hydroxy progesterone (<0.1 ng/mL, n.r. <1.7 ng/mL), testosterone (<0.02 ng/mL, n.r. <0.82 ng/mL), progesterone (0.3 ng/mL, n.r. <1.7 ng/mL), and dehydroepiandrosterone (<15 µg/dL, n.r. <68 µg/dL) (electrochemiluminescence immunoassays; Roche Diagnostics). Allergy tests (fluoroenzyme immunoassay) showed polyvalent allergic sensitization: for dog epithelia (specific IgE > 100.00 kU/L), horse epithelia (> 100.00 kU/L), cat epithelia (86.60 kU/L), peanut (35.4 kU/L),

L), Dermatophagoides pteronyssinus (21.90 kU/L), *Dermatophagoides farinae* (12.80 kU/L), wheat (3.99 kU/L), cow's milk protein (3.55 kU/L), soy bean (3.25 kU/L), and egg protein (0.90 kU/L). Specific IgE for tree pollen mixture was 54.9 kU/L, for grass pollen mixture 54.2 kU/L, and for mold mixture 26.7 kU/L. Total serum IgE was > 5,000 kU/L. Further laboratory blood test results were normal (hemoglobin, white blood cells, platelets, sodium, potassium, calcium, chloride, phosphate, fasting glucose, cholesterol, triglycerides, alkaline phosphatase, blood gas analysis, thyrotropin [TSH], free thyroxine, human chorionic gonadotropin, alpha-fetoprotein, follicle-stimulating hormone, and estradiol).

The girl's parents reported that their daughter had been suffering from severe atopic eczema since her first year of life. Bronchial asthma had also developed later. All conventional therapy to treat atopic eczema had been unsatisfactory. Therapy had included corticosteroids, but the parents wanted to avoid these substances because of their possible side effects. Therefore, the family had turned to an alternative practitioner. There, treatment was initiated with the homeopathic preparations Cefabene® (Cefac) and Cutis compositum N® (Heel), and additionally with an extract of the snake venom of *Crotalus durissus terrificus* (Horvi, The Netherlands). All preparations were administered intramuscularly (i.m.) once per month. This therapy had been initiated 11 months before and had been stopped 2 months before the girl's presentation at our clinic, because the parents noticed extraordinary weight gain. Symptoms of atopic eczema had disappeared during the course of the i.m. therapy and had only recently recommenced. The alternative practitioner asserted that no corticosteroid preparation had been administered to the girl. The parents excluded the possibility that their daughter could have obtained a corticosteroid preparation in any other way.

The girl's treatment has been reverted to orthodox scientific medical interventions. She is on a dietary regimen according to her proven food allergies. The family has been advised to give away their dog. Basic skin care is applied

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FIG. 1. Photographs of our patient before start of alternative therapy (a), and at the time of first presentation at our clinic (b).

regularly. The girl receives cetirizine 5 mg/day. The skin condition has noticeably improved. Bronchial asthma is treated with fluticasone per inhalation (p.i.) 200 µg/day, salmeterol p.i. 100 µg/day, and montelukast orally 0.5 mg/day.

To save the patient repeated punctures for acquiring blood samples, cortisol concentration in urine has been chosen as a control parameter of the hypothalamo-pituitary-adrenal (HPA) axis function. Without additional specific treatment, cortisol concentrations in urine have gradually

increased, and presently, 17 months after the end of alternative treatment, they are only slightly below a n.r. (27.6 µg/24 h). Cushingoid features have disappeared completely. The girl has lost weight and displays catchup growth (Fig. 2).

Discussion

We report on a girl who developed features of Cushing syndrome while being treated with an alternative therapy, including homeopathic preparations and snake venom. The two homeopathic preparations are approved for i.m. application. Adverse side effects listed for Cefabene are local edema and local burning after application. Adverse side effects listed for Cutis compositum N are salivation, and rare allergic reactions. Cefabene is not approved for children under 12 years of age. Snake venom preparations are being used by some alternative practitioners for the treatment of various diseases, such as autoimmune diseases, allergies, or chronic pain. The snake venom preparation used in our patient contains 1.0 µg venom of *C. durissus terrificus* per dose, as indicated by the manufacturer's product information. Very little information is available on this preparation. To find out whether the venom preparation contains a corticosteroid derivative, we had the preparation be tested on 18 different corticosteroid derivatives, with negative results (Institute for Biomedical and Pharmaceutical Research, Heroldsberg, Germany. Analyses by mass spectrometry [MS], MS/MS, or liquid chromatography-MS/MS).

An important component of the venom of *C. durissus terrificus* is phospholipase A2 group IIA.¹ Phospholipase A2 (PLA2) releases free fatty acids, mainly arachidonic acid, by hydrolysis of the fatty acyl ester of membrane phospholipids.² Arachidonic acid is further metabolized, and its cascade metabolites modulate the HPA axis function by controlling corticotropin-releasing hormone (CRH) and ACTH release.³⁻⁵ A study in mice has shown a dose-dependent release of CRH and a dose-dependent release of ACTH after intraperitoneal administration of *C. durissus terrificus* snake venom (25 µg/animal).¹ In *in-vitro* studies, the direct effect on ACTH release

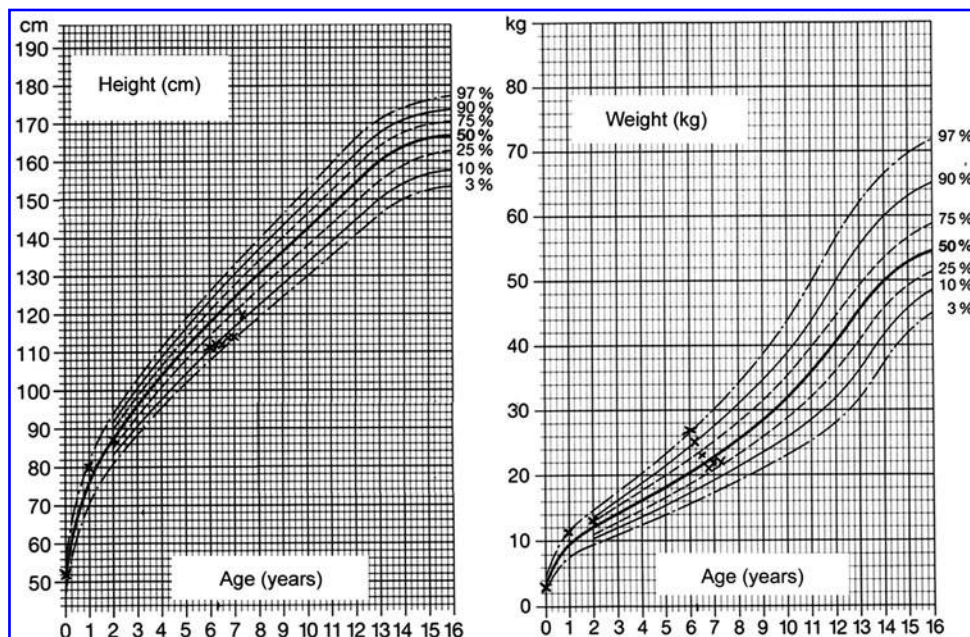


FIG. 2. Growth charts of our patient. (By courtesy of Milupa GmbH, Wachstums-kurven in Perzentilen⁹).

was shown to be additive to ACTH release due to CRH activity. Additionally, a significant rise in corticosterone release was measured. Corticosterone secretion was not directly modified by administration of snake venom, but was increased as a result of elevated ACTH release.¹

In contrast to human PLA2 group IIA, PLA2 derived from *C. durissus terrificus* does not have a cationic face. Therefore, it lacks the ability to interact, independently from the generation of arachidonic acid, with anionic sites in phospholipid bilayers, a feature that explains numerous interactions of human PLA2 with a variety of cell types in a relatively nonspecific fashion.^{6,7}

Stimulation of the HPA axis may be a coherent explanation for the development of Cushing syndrome features in our patient during treatment with *C. durissus terrificus* snake venom, and their disappearance after treatment termination. In our patient, serum and urine analyses of cortisol and ACTH have only been performed 2 months after cessation of the alternative therapy. Laboratory results showed reduced concentrations of cortisol in serum and in urine, and of ACTH in plasma. No studies on the course of corticosteroid and ACTH levels after cessation of snake venom administration can be found in the literature. It is well known that after long-term systemic administration of corticosteroid preparations, the endogenous production of the releasing hormone ACTH is downregulated after a negative feedback mechanism. Also, after long-term use of high-dose inhaled corticosteroids, suppression of the HPA axis can occur.⁸ We hypothesize that in the present case, hypercortisolism during alternative treatment leads to suppression of ACTH by a negative feedback. Regarding other hormones possibly being influenced by ACTH, we found normal TSH concentrations, normal prepubertal sex hormone concentrations, and normal serum electrolytes. However, a former suppression of hormones, followed by restoration of normal release within the 2 months before blood sampling, cannot be ruled out.

We consider the clinical course in our patient, and the laboratory results as evidence of Cushing syndrome that emerged as a serious side effect of i.m. snake venom injections by an alternative practitioner.

Certainly, other reasons for the development of a temporary Cushing syndrome in our patient cannot be ruled out completely. Cefabene is not approved for children under 12 years of age. However, the nature of the drug as a homeopathic preparation and the listed adverse effects in persons above 12 years of age make it unlikely that it might induce Cushing syndrome in a young girl. Finally, despite the affirmation of the alternative practitioner, we cannot rule out that a corticosteroid preparation was given deliberately to the girl. The clinical course in our patient argues against the existence of an undetected corticosteroid-producing tumor.

It is very unfortunate that—while on alternative treatment—the little girl suffered from exactly those side effects that the family had wanted to avoid by turning away from conventional therapy.

Seemingly, unsatisfactory orthodox therapy options in chronic diseases may lead patients to search for alternative possibilities. Alternative treatments with nature-derived substances are often naïvely classified as free from adverse side effects by the general population. In particular, atopic

eczema with its tedious and often unsatisfactory therapy regimens represents a typical candidate disease for the lay search for alternative treatment options.

More scientific data on the so-called alternative treatments are essential to allow mature evaluation of the benefits and risks of these therapies, so that patients can be counseled and guided in their understandable search for best treatment possibilities. As pediatricians, we are to advise families against irresponsible nonscientific practitioners who may treat children with biologic substances that have not been sufficiently evaluated.

Author Disclosure Statement

The authors declare that no competing financial interests exist.

References

1. Chisari A, Spinedi E, Voirol MJ, Giovambattista A, Gaillard RC. A phospholipase A2-related snake venom (from *Crotalus durissus terrificus*) stimulates neuroendocrine and immune functions: determination of different sites of action. *Endocrinology* 1998; 139:617–625.
2. Balsinde J, Winstead MV, Dennis EA. Phospholipase A(2) regulation of arachidonic acid mobilization. *FEBS Lett* 2002; 531:2–6.
3. Knebel W, Meyen G. Effect of various blockers of arachidonic acid metabolism on release of beta-endorphin- and adrenocorticotropin-like immunoreactivity induced by phospholipase A2 from rat adenohypophysis *in vitro*. *Neuroendocrinology* 1986; 43:44–48.
4. Lee AK, Smart JL, Rubinstein M, Low MJ, Tse A. Reciprocal regulation of TREK-1 channels by arachidonic acid and CRH in mouse corticotropes. *Endocrinology* 2011; 152:1901–1910.
5. Spinedi E, Salas M, Chisari A, Perone M, Carino M, Gaillard RC. Sex differences in the hypothalamo-pituitary-adrenal axis response to inflammatory and neuroendocrine stressors. Evidence for a pituitary defect in the autoimmune disease-susceptible female Lewis rat. *Neuroendocrinology* 1994; 60:609–617.
6. Moreira V, Gutiérrez JM, Soares AM, Zamunér SR, Purgatto E, Teixeira Cde F. Secretory phospholipases A(2) isolated from *Bothrops asper* and from *Crotalus durissus terrificus* snake venoms induce distinct mechanisms for biosynthesis of prostaglandins E2 and D2 and expression of cyclooxygenases. *Toxicon* 2008; 52:428–439.
7. Birts CN, Barton CH, Wilton DC. Catalytic and non-catalytic functions of human IIA phospholipase A2. *Trends Biochem Sci* 2010; 35:28–35.
8. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. *Respir Med* 2006; 100:1307–1317.
9. Wachstumskurven in Perzentilen. Friedrichsdorf, Germany: Milupa GmbH, 1997.

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