

Case Report

Iatrogenic Cushing Syndrome and Secondary Adrenal Insufficiency in a Child due to Topical Ocular Corticosteroids: A Case Report

Joana Santos-Oliveira^a Luís Torrão^{a,b} Sónia Torres-Costa^{a,b} Marta Silva^a
Ana Catarina Pedrosa^{a,b} Joana Araújo^{a,b} Luís Figueira^{a,b,c}
Cláudia Oliveira-Ferreira^{a,b}

^aOphthalmology Department, Centro Hospitalar Universitário de São João, Porto, Portugal;

^bSurgery and Physiology Department, Faculty of Medicine of the University of Porto, Porto, Portugal; ^cPharmacology and Therapeutics Unit, Department of Biomedicine, Faculty of Medicine of University of Porto, Porto, Portugal

Keywords

Cushing syndrome · Steroids · Uveitis · Anterior · Child · Case reports

Abstract

Introduction: Iatrogenic Cushing syndrome (ICS) can be caused by synthetic glucocorticoids administered through various routes. ICS caused by corticosteroid eye drops is an exceptional event, being more frequent in pediatric age. Herein, we describe a case of ICS associated with secondary adrenal insufficiency (SAI) caused by ocular topical corticosteroid treatment. **Case Presentation:** An 11-year-old girl was referred to our ocular inflammation department due to idiopathic, chronic, non-hypertensive, non-granulomatous bilateral anterior uveitis, treated with topical dexamethasone (eye drops, 1 mg/mL) for 1 year. During the past year, the child and her mother observed a gradual change in her physical appearance, particularly noting the development of a cushingoid facial appearance. Laboratory data revealed morning serum adrenocorticotrophic hormone (ACTH) of 3.6 ng/L (7.2–63.3) and morning serum cortisol of 0.20 µg/dL (6.2–19.4). She was treated with methotrexate (15 mg/week, orally), and the topical corticosteroid regimen was progressively tapered and discontinued after 3 months. Nine months after the patient discontinued corticosteroid eye drops, her cushingoid face disappeared, and her laboratory data improved. Regarding the ophthalmological examination, the uveitis remained in remission with methotrexate, with no new episodes of intraocular inflammation. **Conclusion:** Although rare, ophthalmologists must be aware of ICS and SAI and prioritize using the least potent

corticosteroid for the shortest duration necessary. Additionally, clinicians should avoid abrupt cessation of long-term corticosteroid therapy as this can precipitate an adrenal crisis in the presence of adrenal insufficiency.

© 2025 The Author(s).

Published by S. Karger AG, Basel

Introduction

Glucocorticoids (GCs) are widely used in clinical practice as the treatment of choice for many common pathologies due to their potent anti-inflammatory and immunosuppressive actions. It is well established that prolonged use of GC can cause iatrogenic Cushing syndrome (ICS) [1, 2]. ICS can be caused by synthetic GC administered through various routes, including oral, intravenous, intramuscular, intra-articular, cutaneous, inhalation, ocular, or nasal methods [1].

Few case reports of ICS induced by topical steroids have been documented in the literature. It is most often linked to cutaneous and inhaled GC, with most cases occurring in younger children. ICS caused by corticosteroid eye drops is an exceptional event, being more frequent in pediatric age [3–8].

Moon facies, an enlarged dorso-cervical fat pad, easy bruising, and truncal obesity are the prominent physical characteristics of ICS. Nevertheless, patients are also susceptible to several systemic disorders, such as hypertension, glucose intolerance, lipid abnormalities, decreased bone density, and irregular menstruation [2].

GC-induced adrenal insufficiency is a well-recognized complication of GC therapy, particularly when systemic GCs are administered at doses equivalent to 7.5 mg of prednisolone. However, GC administered via other routes can also lead to adrenal suppression [9]. The clinical case that will be described below stands out as being a case of ICS associated with secondary adrenal insufficiency (SAI) induced by dexamethasone eye drops, in a female child, with idiopathic, chronic, bilateral anterior uveitis.

Written informed consent for publication of this clinical case report was obtained from the patient's mother. Formal ethics approval was not required to complete this case report. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000543908>).

Case Presentation

An 11-year-old female was referred to our ocular inflammation department for evaluation and management of chronic bilateral anterior uveitis, which had been progressing over the past year. Before being referred to our ophthalmology unit, the patient was followed in a private ophthalmology consultation. According to the private ophthalmologist, at presentation, the patient was diagnosed with bilateral non-hypertensive and non-granulomatous anterior uveitis that was treated with topical dexamethasone (1 mg/mL, eye drops) on a tapering schedule. The patient recovered completely and discontinued the medication 6 weeks later. Nonetheless, 5 days later, she returned with complaints of bilateral eye pain, redness, and photophobia and was diagnosed again with bilateral anterior uveitis. She was treated with topical dexamethasone (1 mg/mL, eye drops). However, in the 5th week, as the medication was tapered once daily, the patient reported red eye and photophobia, indicating a

new exacerbation of the condition. Subsequently, 5 new exacerbations occurred, despite the continuous application of topical dexamethasone over 1 year (minimum of 2 times per day and a maximum of every hour).

Her past medical and ophthalmological histories were irrelevant, and her parents denied any recent or previous use of corticosteroids by any other route of administration (oral, intra-articular, cutaneous, inhaled, or nasal), as well as any other type of chronic medication. Her family medical history was notable for skin melanoma in her mom and an adrenocortical carcinoma in her maternal grandmother.

In our department, the patient underwent a comprehensive ophthalmic evaluation, revealing a best-corrected visual acuity of 8/10 in the right eye and 10/10 in the left eye. The intraocular pressure, measured by Goldmann applanation tonometry, was 12 mm Hg in both eyes (OU). Anterior segment examination revealed OU circumciliary congestion and anterior chamber activity, characterized by 1+ cells and 1+ flare (the Standardization of Uveitis Nomenclature – SUN criteria) [10]. Posterior synechiae, iris nodules, or keratic precipitates were absent OU and the lens was clear as was the vitreous OU (without cells/flare). Dilated fundus evaluation OU did not show any relevant findings at the optic disc, foveal reflex, retina, and vessels. At this time, she has been medicated with dexamethasone eye drops (1 mg/mL) twice a day, so it was decided to intensify the therapeutic regime, tapered till the next evaluation (1 eye drop each 1 h for 3 days, every 2 h for 3 days, 5 times/day for 1 week, 4 times/day for 1 week, and 3 times/day until the next appointment).

The patient was referred for a pediatric rheumatology consultation, where systemic symptoms, including history of joint pain and swelling, oral or genital ulcers, and erythema nodosum, were ruled out. A comprehensive systemic evaluation was conducted to exclude infectious and autoimmune diseases (shown in Table 1).

At the initial appointment in our unit, the child and her mother expressed concerns about the child's physical appearance, which had been gradually changing, over the previous year, specifically noting the development of a cushingoid facial appearance (shown in Fig. 1). For that reason, she was referred for a pediatric endocrinology appointment. She weighed 37.8 kg (percentile 50–75) in her first physical examination and her height was 139 cm (percentile 50–85). There were no buffalo hump or stretch marks. Her sitting blood pressure was 132/90 mm Hg (>percentile 95).

Laboratory data revealed the following: fasting blood glucose 88 mg/dL, glycated hemoglobin 6.0%, (<5.7), total cholesterol 280 mg/dL (<170), HDL cholesterol 59 mg/dL (>60), and LDL cholesterol 199 mg/dL (<110). The hypothalamic-pituitary-adrenal (HPA) axis investigation revealed a significantly low serum cortisol level of 0.20 µg/dL (6.2–19.4) with a concomitantly low serum level of ACTH 3.6 ng/L (7.2–63.3) and low level of 24 h urine cortisol excretion <6.8 µg (0.0–36.0).

A pituitary evaluation was subsequently completed: insulin-like growth factor-1 (IGF-1) 228 ng/mL (147–549), growth hormone (GH) 0.7 ng/mL (0–0.8), free thyroxine (T4) 1.03 ng/dL (0.88–1.58), thyroid stimulating hormone (TSH) 2.42 mU/mL (0.35–5.0), prolactin 12 ng/mL (2.0–17.0), follicle-stimulating hormone (FSH) 2.48 mU/mL (1.7–7.70), and luteinizing hormone (LH) 1.0 mU/mL (1–11.40). Brain magnetic resonance imaging was performed to exclude a pituitary tumor, pituitary apoplexy, and infiltrative diseases and was unremarkable. Therefore, the most probable diagnosis was ICS with SAI associated with exogenous steroid treatment.

Parents were informed about the potential risk of adrenal crisis and were provided with an emergency supply of hydrocortisone to use if needed. She started methotrexate (15 mg/week, orally) associated with folic acid (5 mg/week, orally), 10 days after the first medical visit in our department. Topical corticosteroid treatment was gradually reduced and ended 3 months later.

Table 1. Laboratory workup

Laboratory workup	Result
Full blood count (with leukocytes and platelets)	Normal
Electrolytes, AST, ALT, GGT, urea, creatinine	Normal
Sedimentation velocity and C-reactive protein	Normal
Serology: herpes simplex virus type 1	IgM–, IgG+
Serology: herpes simplex virus type 2, cytomegalovirus, Epstein-Barr virus, <i>Toxoplasma gondii</i> , <i>Borrelia burgdorferi</i>	IgM–, IgG–
Serology: human immunodeficiency virus, hepatitis C	Negative
Serology: hepatitis B	Immunity through vaccination
TPPA	Nonreactive
VDRL	Negative
Serum beta-2 microglobulin	Normal
HLA-B27	Negative
ACE	Normal
RF	Normal
ANA	Negative
ANCA	Negative
Anti-TG	Negative
TPOAb	Negative
IGRA	Negative
Mantoux test (TST)	0 mm
Chest X-ray	Normal
Urinalysis	
Hematuria or proteinuria	Negative
Beta-2 microglobulin	Normal

AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma glutamyl transferase; TPPA, treponema pallidum particle agglutination assay; VDRL, venereal disease research laboratory; HLA-B27, human leukocyte antigen B27; ACE, angiotensin-converting enzyme; RF, rheumatoid factor; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; anti-TG, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies; IGRA, interferon gamma release assay; TST, tuberculin skin test.

In the most recent appointment, 9 months after the patient discontinued the use of the GC eye drops, her weight was 35.2 kg (percentile 25), her height was 141 cm (percentile 50–85), her blood pressure was 100/60 mm Hg (percentile 50), and her cushingoid face disappeared (shown in Fig. 2). The laboratory data improved with morning serum ACTH 29.6 ng/L (7.2–63.3), morning serum cortisol 12.0 µg/dL (6.2–19.4), glycated hemoglobin 5.4%, (<5.7), total cholesterol 190 mg/dL (<170), HDL cholesterol 60 mg/dL (>60), and LDL cholesterol 110 mg/dL (<110).

Regarding the ophthalmological examination, the uveitis remained in remission with methotrexate, with no new episodes of intraocular inflammation. The patient maintains follow-up appointments in ophthalmology, pediatric endocrinology, and pediatric rheumatology.



Fig. 1. Patient in the first appointment in our hospital. The “moon face” is notorious.

Discussion

In this work, we present a clinical case of an ICS associated with SAI induced by chronic exposure to dexamethasone eye drops in a female child with idiopathic, chronic, bilateral anterior uveitis. It is well established that long-term use of exogenous systemic/cutaneous GC can lead to ICS and suppression of the HPA axis. However, it is extremely rare to develop ICS and SAI with corticosteroid eye drop use [9].

Topical ocular corticosteroids can enter the systemic circulation through 2 main routes. The conjunctiva, being thin and highly vascular, facilitates the rapid diffusion of oxygen and metabolites to and from adjacent structures, including the tear film. Furthermore, the lacrimal pathway transports the tear film and its solutes to the highly vascularized and efficiently absorbent nasal mucosa [11]. For this reason, patients and their families should be instructed on proper drop instillation techniques, including punctal occlusion, to minimize systemic corticosteroid absorption. Moreover, corticosteroids absorbed via the ocular or nasal mucous membranes bypass the portal circulation and are not metabolized by the liver, meaning that intensive ocular therapy may produce systemic effects greater than an equivalent oral dose [12]. In our case, a potent corticosteroid (dexamethasone) at a high concentration (1%) was used over an extended period (1 year) with varying application frequencies, ranging from every hour to twice daily.

In the literature, there are a few cases of ICS associated with topical ocular steroids, for example, a 6-week-old child submitted to bilateral goniotomy due to glaucoma [13], a 5-month-old child operated on due to bilateral congenital cataract [14], a 2-year-old girl with congenital glaucoma who underwent several eye surgeries [15], and a 9-year-old child with bilateral iridocyclitis [16]. There is also 1 case of ICS in an 11-year-old child with bilateral non-granulomatous iridocyclitis and anterior vitritis who was treated with the association of topical and periocular steroid [11].

However, the underlying reasons for the rare occurrence of this condition remain unclear. Individual variations in GC sensitivity have been observed in both healthy and diseased



Fig. 2. Patient 9 months after having suspended the ocular corticosteroids.

individuals and may be influenced by genetic and acquired factors. The NR3C1 gene, which encodes the GC receptor, is known to harbor polymorphisms that can influence GC sensitivity [16]. In a study by Fukuhara et al. [16], a single heterozygous nucleotide substitution was identified in the 3' untranslated region of this gene in a 9-year-old patient who developed ICS. Given these findings, genetic analysis of the NR3C1 gene may be valuable for patients who develop ICS [16].

Regarding SAI, it can result from inadequate stimulation of the adrenal glands due to either insufficiency or inadequate secretion of ACTH. This may occur due to a variety of reasons including hypothalamic defects, hypopituitarism, defects in synthesis and processing ACTH, and chronic GC use. The underlying etiology determines the mortality and morbidity linked to SAI [17].

Persistent use of exogenous GC is the most common cause of adrenal insufficiency. The HPA axis is responsible for GC regulation and has a sensitive negative feedback loop, decreasing ACTH production in response to circulating GC. The effect of maintaining artificially high concentrations of circulating GC is widespread and includes the inhibition of endogenous cortisol production in the adrenal gland [12].

SAI is a potentially life-threatening condition. Therefore, it is crucial that patients and their families are thoroughly informed about the risks and management strategies. Steroid tapering should be performed gradually, and in cases of acute illness, hydrocortisone administration is recommended. In our case, the full suppression of the pituitary-adrenal axis in our patient was confirmed by the hormonal status that showed undetectable levels of serum cortisol, ACTH, and cortisol urinary excretion. Our case closely mirrors a previously published report of a 7-year-old boy with similar findings [18].

In this clinical case, interdisciplinary collaboration between ophthalmology, pediatric endocrinology, and pediatric rheumatology departments was essential for an accurate diagnosis and management. The patient was initiated on methotrexate for systemic immunosuppression under close monitoring by these specialized teams. Methotrexate effectively controlled the chronic anterior uveitis, facilitating a gradual tapering of topical ocular corticosteroids.

Although it is a rare diagnosis, ophthalmologists should remain vigilant and prioritize using the least potent corticosteroid for the shortest necessary duration. Additionally, clinicians should avoid abrupt cessation of long-term corticosteroid therapy as this can precipitate an adrenal crisis in the presence of adrenal insufficiency.

Statement of Ethics

Ethical approval is not required for this study following local guidelines. Written informed consent for publication of this clinical case report was obtained from the patient's mother.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

J.S.-O. did data collection analysis and interpretation and the drafting of the manuscript. C.O.-F. was the doctor responsible for the case in our department and contributed to the data collection analysis and interpretation and the drafting of the manuscript. L.T., S.T.-C., M.S., A.C.P., J.A., and L.F. advised on the evolution of the case and were involved in the critical revision of the manuscript. All authors approved the final version of the manuscript and take responsibility for the accuracy or integrity of all parts of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

References

- 1 Paragliola RM, Papi G, Pontecorvi A, Corsello SM. Treatment with synthetic glucocorticoids and the hypothalamus-pituitary-adrenal axis. *Int J Mol Sci.* 2017;18(10):2201. <https://doi.org/10.3390/ijms18102201>
- 2 Stratakis CA. An update on Cushing syndrome in pediatrics. *Ann Endocrinol (Paris).* 2018;79(3):125–31. <https://doi.org/10.1016/j.ando.2018.03.010>
- 3 Taylor O, Mejia-Otero JD, Tannin GM, Gordon K. Topical triamcinolone induced Cushing syndrome: a case report. *Pediatr Dermatol.* 2020;37(3):582–4. <https://doi.org/10.1111/pde.14140>
- 4 Ahmed SM, Ahmed SF, Othman S, Abdulla BA, Mohammed SH, Salih AM, et al. Topical corticosteroid-induced iatrogenic cushing syndrome in an infant; a case report with literature review. *Ann Med Surg.* 2021;71:102978. <https://doi.org/10.1016/j.amsu.2021.102978>
- 5 Sachdeva S, Arora P, Kulhari A, Sardana K. Iatrogenic Cushing's syndrome due to topical steroid abuse in a child with Psoriasis presenting as septicaemia. *Dermatol Ther.* 2020;33(4):e13514. <https://doi.org/10.1111/dth.13514>
- 6 Notay M, Fazel N, Awasthi S. Cushing syndrome induced by topical corticosteroids for the treatment of lichen sclerosus. *J Pediatr Adolesc Gynecol.* 2019;32(1):83–5. <https://doi.org/10.1016/j.jpag.2018.09.004>
- 7 Hansen S J, Lacourt R P. Iatrogenic cushing's syndrome in a infant due to prolonged use of topical corticosteroids. Case report. *Rev Chil Pediatr.* 2018;89(3):368–72. <https://doi.org/10.4067/S0370-41062018005000302>
- 8 Güven A. Different potent glucocorticoids, different routes of exposure but the same result: iatrogenic cushing's syndrome and adrenal insufficiency. *J Clin Res Pediatr Endocrinol.* 2020;12(4):383–92. <https://doi.org/10.4274/jcrpe.galenos.2020.2019.0220>
- 9 Pazderska AA, Pearce BSH. Adrenal insufficiency – recognition and management. *Clin Med.* 2017;17(5):480. <https://doi.org/10.7861/clinmedicine.17-5-480a>
- 10 Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature SUN Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol.* 2005;140(3):509–16. <https://doi.org/10.1016/j.ajo.2005.03.057>
- 11 Ozerdem U, Levi L, Cheng L, Song MK, Scher C, Freeman WR. Systemic toxicity of topical and periocular corticosteroid therapy in an 11-year-old male with posterior uveitis. *Am J Ophthalmol.* 2000;130(2):240–1. [https://doi.org/10.1016/s0002-9394\(00\)00501-8](https://doi.org/10.1016/s0002-9394(00)00501-8)
- 12 Mcghee CNJ, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids benefits and risks. *Drug Saf.* 2002;25(1):33–55. <https://doi.org/10.2165/00002018-200225010-00004>
- 13 Choudhary S, Singh AK, Gupta K, Pandav SS, Kaushik S. Topical steroid-induced cushing's syndrome in a newborn following goniotomy for glaucoma. *J Glaucoma.* 2023;32(1):65–7. <https://doi.org/10.1097/IJG.0000000000002116>
- 14 Scherrer KS, Weitz M, Eisenack J, Truffer B, Konrad D. Cushing syndrome after bilateral lensectomy. *Eur J Pediatr.* 2015;174(3):399–401. <https://doi.org/10.1007/s00431-014-2477-1>
- 15 Matejek N, Hoos J, Holterhus PM, Bettendorf M, Choukair D. Topical glucocorticoid application causing iatrogenic Cushing's syndrome followed by secondary adrenal insufficiency in infants: two case reports. *J Med Case Rep.* 2022;16(1):455. <https://doi.org/10.1186/s13256-022-03659-2>
- 16 Fukuhara D, Takiura T, Keino H, Okada AA, Yan K. Iatrogenic cushing's syndrome due to topical ocular glucocorticoid treatment. *Pediatrics.* 2017;139(2):e20161233. <https://doi.org/10.1542/peds.2016-1233>
- 17 Nachawi N, Li D, Lansang MC. Glucocorticoid-induced adrenal insufficiency and glucocorticoid withdrawal syndrome: two sides of the same coin. *Cleve Clin J Med.* 2024;91(4):245–55. <https://doi.org/10.3949/ccjm.91a.23039>
- 18 Messina MF, Valenzise M, Aversa S, Arrigo T, De Luca F. Iatrogenic Cushing syndrome caused by ocular glucocorticoids in a child. *BMJ Case Rep.* 2009;2009:bcr11.2008.1224. <https://doi.org/10.1136/bcr.11.2008.1224>