Iatrogenic Cushing's Syndrome Due to Topical Ocular Glucocorticoid Treatment

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abstract

Iatrogenic Cushing's syndrome (CS) is a severe adverse effect of systemic glucocorticoid (GC) therapy in children, but is extremely rare in the setting of topical ocular GC therapy. In this article, we report the case of a 9-year-old girl suffering from idiopathic uveitis who developed CS due to topical ocular GC treatment. She was referred to the ophthalmology department with a complaint of painful eyes, at which time she was diagnosed with bilateral iridocyclitis and started on a treatment of betamethasone sodium phosphate eye drops. Six months after the initiation of topical ocular GC treatment, she was referred to our pediatric department with stunted growth, truncal obesity, purple skin striate, buffalo hump, and moon face. Because her serum cortisol and plasma adrenocorticotropic hormone levels were undetectable, she was diagnosed with iatrogenic CS. After the doses of topical ocular GC were reduced, the clinical symptoms of CS were improved. The fact that the amount of topical ocular GC with our patient was apparently less than that of similar previous cases tempted us to perform genetic analysis of her NR3C1 gene. We found that our patient had a single heterozygous nucleotide substitution in the 3′ untranslated region of the NR3C1 gene, which may explain why she developed CS. However, additional investigations are required to determine if our findings can be extrapolated to other patients. In conclusion, clinicians should be aware that even extremely low doses of topical ocular steroid therapy can cause iatrogenic CS.

Iatrogenic Cushing's syndrome (CS) is a severe adverse effect of glucocorticoid (GC) therapy in both children and adults, and is mostly caused by long-term and abundant systemic GC administration. Topical GC treatment with nasal drops or ointment rarely induces iatrogenic CS.[1,2] GC treatment via eye drops is commonly used to treat ocular inflammatory diseases, including juvenile idiopathic uveitis. This treatment causes local adverse effects, such as glaucoma or cataracts. However, iatrogenic CS is extremely rare.

The sensitivity to endogenous and synthetic GCs is individually different and depends on genetic and acquired factors.[3] The actions of GCs are mediated by the GC receptor (GR), which acts as a ligand-activated transcription factor regulating the transcription of thousands of GC-responsive genes in a positive or negative fashion.[4] It is currently known that 4 functionally characterized single-nucleotide polymorphisms (SNPs) of GR (9β, ER22/23EK, BclI and N363S) modulate GC sensitivity.[3,5] On the other hand, 1 patient exhibiting manifestations of GC hypersensitivity caused by a novel NR3C1 gene mutation has been described previously.[6] In this article,

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Dr Fukuhara conceptualized and designed the study and drafted the initial manuscript; Dr Takiura carried out the initial analyses and reviewed and revised the manuscript; Drs Keino and Okada reviewed and revised the manuscript; Dr Yan oversaw the data and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: 10.1542/peds.2016-1233

Accepted for publication Oct 10, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Fukuhara D, Takiura T, Keino H, et al. Iatrogenic Cushing's Syndrome Due to Topical Ocular Glucocorticoid Treatment. *Pediatrics.* 2017; 139(2):e20161233

we report the case of a 9-year-old girl suffering from idiopathic uveitis who developed CS due to topical ocular GC treatment but had only a single nucleotide variation rather than such SNPs or mutation.

CASE REPORT

A 9-year-old girl was referred to the ophthalmology department with a complaint of painful eyes. Her medical history was unremarkable, without any ocular injury or surgery. In addition, she did not complain of any joint pain or bowel symptoms. She was diagnosed with bilateral iridocyclitis and started on a treatment of betamethasone sodium phosphate eye drops (0.1% solution). The frequency of eye drops was increased to up to 6 times per day due to uncontrollable ocular inflammation. She was referred to our pediatric department after 6 months of treatment, at which time she presented with purple skin striae. She was not taking any oral or parenteral GCs, nor was she taking any other medication.

Physical examination at our outpatient clinic revealed that she was afebrile with a heart rate of 80 beats per minute and blood pressure of 104/60 mm Hg. Her body weight and height were 49.6 kg (+1.7 SD) and 140.8 cm (–0.3 SD), respectively. Her physical signs included truncal obesity, buffalo hump, moon face, and femoral skin striae, which are representative clinical findings of CS (Fig 1B). These findings were not observed the previous year (Fig 1A). She was at a prepubertal stage, defined to be grade 1 on the Tanner scale. At this time, she was diagnosed with stunted growth (Fig 1D).

Laboratory findings revealed no abnormal data with the peripheral blood, biochemistry, or urinalysis. Her serum cortisol and plasma adrenocorticotropic hormone (ACTH) levels at 8.00 AM were <1.0 μg/dL and <2 pg/mL, respectively. Based on her physical findings and low endogenous cortisol and ACTH levels, we diagnosed her with CS, which was most likely due to excess absorption of ocular GC. Therefore, we started oral methotrexate treatment to reduce the amount of eye drops of betamethasone sodium phosphate. Consequently, her weight gain decreased while her height increased to a typical SD (Fig 1D). Six months after the initiation of methotrexate treatment, she exhibited morning serum cortisol and plasma ACTH levels of 10.1 μg/dL and 42.6 pg/mL, respectively, as well as no clinical symptoms of CS (Fig 1C).

Amplification and Sequencing of the NR3C1 Gene

Written informed consent was obtained from the parents of the patient. We performed genotyping of the coding sequence, which comprised exons 2 through 9, and the intron–exon junctions of the NR3C1 gene, including the 4 functional GR SNPs (9β, rs6198; ER22/23EK, rs6189, and rs6190; BclI, rs41423247; and N363S, rs6195) using Sanger sequencing as described below. Genomic DNA was isolated from peripheral blood by using the DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany, catalog number 69504). These sequences were validated via polymerase chain reaction amplification by using TaKaRa Ex Taq (TaKaRa Bio, Inc, Otsu, Shiga, Japan, catalog number RR001A) according to the manufacturer's protocol. Primers were designed to amplify each locus (Table 1). The PCR products were analyzed via Sanger sequencing by using the 3500 Dx Genetic Analyzer (Applied Biosystems, Foster City, CA) according to the manufacturer's protocol.

RESULTS

We identified a single heterozygous A to G nucleotide substitution at position 3584 in exon 9 of the NR3C1 gene, rs13306585, which is located in the 3′ untranslated region (3′-UTR). No other mutations or polymorphisms were identified.

DISCUSSION

In this article, we report an extremely rare case of iatrogenic CS due to topical ocular GC treatment. Synthetic GCs are one of the most important and widely used drugs in both adults and children. They are used to treat a variety of disorders, such as allergies and dermatological, inflammatory, and autoimmune diseases, because they have a striking antiinflammatory and immunosuppressive effect. All clinicians are aware that prolonged use of systemic GCs at high doses results in severe adverse effects. However, topical GC therapy uncommonly results in those adverse effects, and ocular GC therapy is an extremely rare cause compared with nasal and dermatological therapies.[1,2]

There are 2 major potential routes to absorb topical ocular GCs into circulation. One is the conjunctiva, which is thin and vascular, and facilitates rapid diffusion, and the other is the nasal mucosa via the lacrimal drainage system. In addition, the topically applied GC, which penetrates the eye via the cornea, can also be absorbed into circulation. In this process, the lipid-rich corneal epithelium works as a barrier to intraocular penetration for hydrophilic derivatives, such as betamethasone sodium phosphate. However, the presence of intraocular inflammation is suggested to accelerate the penetration of GCs.[7] Therefore, there is a possibility that the concentrations of GCs were relatively high in the blood in our patient.

Although the potential systemic effects of topical GCs are less clearly defined, a 50% decrease in endogenous GC production was observed in male volunteers given 0.1% dexamethasone drops

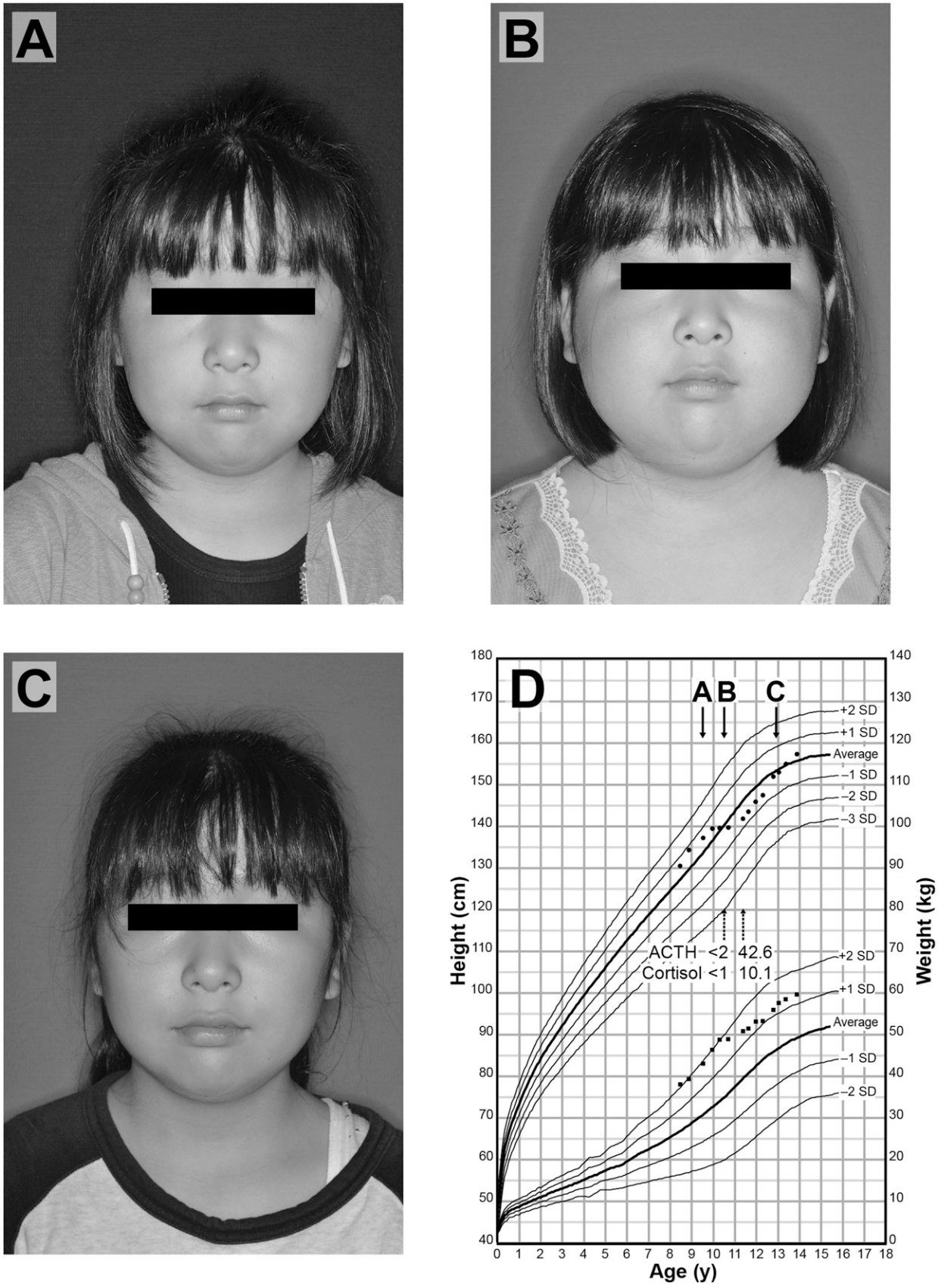

FIGURE 1

(4.5 mg/day: estimated as prednisolone) for 6 days.[8] McGhee et al[7] suggest that intensive topical ocular GCs, such as 1.0% prednisolone acetate and 0.1% dexamethasone, seem to be absorbed into circulation at a level that can produce adrenal suppression. For example, intensive dosing, such as hourly application per day, although totaling an empirical dose of only 6 to 8 mg of prednisolone, may produce an inherently greater GC effect than the equivalent orally administered dose because ocular GC does not undergo first-pass metabolism by the portal system.[7]

There have only been 4 pediatric cases previously reported in the literature with iatrogenic CS caused by topical ocular GC therapy (Table 2).[9–12]

Case 1 was an 11-year-old boy who developed CS after 6 months of intensive topical ocular GC therapy. Although this patient was similar in age to our patient, the dose of GC was slightly higher than ours. Furthermore, this patient was also treated with posterior sub-Tenon's injections of 80-mg methylprednisolone acetate suspension every 6 weeks for 6 months. After 6 months of these injections, CS in this patient was aggravated. Case 2 was a 6-year-old girl with diminished growth from the age of 2 years. This patient had been taking higher dose of topical ocular GC compared to our patient. Case 3 was a 7.5-year-old boy who had an accidental penetrating orbital injury. He had been treated with an extremely high dose of topical ocular GC, estimated as a dose of 75 mg/day of prednisolone. Finally, case 4 was a 5-month-old boy who developed CS after 3 months of topical ocular GC therapy. Because this patient was much younger than the others, the dose of GC was relatively high. The patients in these cases received topical GCs every 1 or 2 hours, whereas our patient received doses every 4 hours. Moreover, our patient was treated with the lowest dose of topical ocular GC compared with the previous cases.

Not all individuals equally respond to GC therapy, depending on both functionality and expression of the intracellular GR. Four functional GR SNPs and some mutations have been identified, and the minor alleles of the BclI and N363S SNPs and the D401H mutation are closely associated with increased GC sensitivity.[6,13,14] Therefore, we performed genetic analysis of all the coding sequences of the NR3C1 gene to determine whether our patient had any defects. We found that our patient had a single heterozygous A to G nucleotide substitution in the 3′-UTR, rs13306585. This variation has been reported in 5 of 5008 alleles, 4 of which are from Japanese populations (http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/). It is well known that the 3′-UTR plays a critical role in translation and posttranscriptional gene modification.[15,16] Indeed, one of the SNPs in the 3′-UTR of the NR3C1 gene, 9β, is known to cause relative GC resistance.[4,14] Based on

TABLE 1 Primer Pairs for Genetic Analysis of the NR3C1 Gene

Locus[a]	Forward	Reverse
Exon 2	GTTCGATACACTTTTGCCCT	ACAAATAAGGCAGCACAACT
	AGAGAACCCCAAGAGTTCAGCA	GTTCGACCAGGGAAGTTCAGAGT
Exon 3	TAGGAGGCATCTTTTTGGGA	TGCCCAAACTTAACACCATC
Exon 4	TTTTGACCTCTCGACCTCAT	AACCCATCCAGTTCTTCCTT
Exon 5	AATGTTTTTAGTCCCACGCA	AACATTGACCTCTGCCATTC
Exon 6	CATTTTCTGTTAGGGGTGCC	GAGTGAGGAAACAACTGCAA
Exon 7	TAGGATGGACTGCTGTGAAA	TCTCTGTTTCTGCCATACCT
Exon 8	ATCCTGCATTTTCTCTTGGC	AAGCACTTCCGTACAAAACA
Exon 9	AGTTTGTGGATGTTGGTGATAG	TGCAAAAATAGGGCGTTAGG
	AATTCCCCGAGATGTTAGCTGA	GACAGATGGGAATGTGAAAATGGG
	GTGGATGATGGTTGCAAAAGAC	GGCAACCTATGAGATTCTGCAC
	GCATTCATACAGGCAGCGATG	TGAATTCTGAAGGGAGCGTGG
	GGTGCCTAAGAAAACTGCTT	TACCCTTTGCAGTAATTGGC
BclI SNP	AGCAGAAGTACTAACAAAGAGC	ATCTGAATTGGGGATGAGGT

[a] All exons include their intron–exon junctions.

TABLE 2 Reports in the Literature of Iatrogenic Cushing's Syndrome Caused by Topical Ocular Glucocorticoid

Report	Sex	Age, y	Disease	Ocular Steroid	Dose,[a] mg/d	Duration, min
Case 1[9]	Boy	11	Idiopathic uveitis	1% predonisolone acetate	12	6
Case 2[10]	Boy	2	Congenital corneal clouding	1% predonisolone acetate	6–24	24
Case 3[1]	Boy	7.6	Orbital injury	2% dexamethasone	75	6
Case 4[12]	Girl	0.5	Congenital cataract	0.1% dexamethasone	7.5	2
Our case	Girl	9	Idiopathic uveitis	0.1% betamethasone	3.75	6

[a] The dose is estimated to prednisolone.

FIGURE 1 Continued

Appearance of the patient before (A), at the onset of (B), and after (C) revealing clinical manifestations of Cushing's syndrome. D, Longitudinal growth and weight curves of the patient. The arrows indicate the time points for her photographs in A–C. The dashed arrows indicate time points for the laboratory findings of ACTH and cortisol.

the results of the gene analysis, we speculated that rs13306585 may influence NR3C1 posttranscriptional modifications, leading to increased GC sensitivity, as was noted in the present case. Additional experiments, including studies regarding epigenetic NR3C1 gene regulation, may enable us to understand why this patient developed CS.

ABBREVIATIONS

ACTH: adrenocorticotropic hormone
CS: Cushing's syndrome
GC: glucocorticoid
GR: glucocorticoid receptor
SNP: single-nucleotide polymorphism
3′ UTR: 3′ untranslated region

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