Case Report

Frequent and prolonged administration of glucocorticoid for acute adrenal insufficiency treatment can cause diabetes mellitus: A case of holoprosencephaly

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Abstract. Glucocorticoid (GC)-induced diabetes mellitus (DM) is theoretically unlikely to occur in patients with adrenal insufficiency if adequate physiological replacement doses of GC are given. Herein we report a patient with holoprosencephaly who developed GC-induced DM due to frequent and prolonged administration of high-dose GC for suspected adrenal crisis (AC). GC treatment should be started whenever AC cannot be ruled out. However, the initial and subsequent doses should be adjusted to the severity of AC and to the pace of clinical recovery with treatment, respectively.

Key words: glucocorticoid-induced diabetes, adrenal crisis, hydrocortisone

Introduction

Glucocorticoids (GC) are widely prescribed for the treatment of autoimmune and malignant diseases and can cause a dose-dependent increase in blood glucose levels in patients without adrenal insufficiency (AI) or pre-existing diabetes mellitus (DM) (1). The odds ratio for new-onset DM in patients treated with GC reportedly ranges from approximately 1.5 to 2.5 (1). GC-induced DM is theoretically less likely to occur in AI patients if adequate physiological replacement doses are given.

Herein we report the occurrence of GC-induced DM in a patient with holoprosencephaly (HPE). DM developed at least partly due to frequent and prolonged administration of high-dose GC for adrenal crisis (AC), referred to as acute AI in this manuscript. In this report, we highlight the importance of adjusting the initial and subsequent doses in order to avoid GC-induced DM.

Case Presentation

The patient was a 10-yr-old male child with intrauterine growth retardation born at 36 wk of gestation after a C-section due to fetal asphyxia (birth weight 1324 g). HPE was diagnosed according to the characteristic physical findings, including a cleft lip palate, microphthalmia, and diagnostic MRI findings. At the age of 2 yr, IGF-1, LH, FSH, TSH, and free T4 were 25.5 ng/mL, < 0.07 mIU/mL, 1.14 mIU/mL, 3.94 μIU/mL, and
1.10 ng/dL, respectively. The patient did not have any symptoms of hypothalamic dysfunction, such as an instability of body temperature. The patient’s obesity, shown in Table 1, was probably due to excess calories. There was no replacement of hormonal agents other than hydrocortisone (HDC) up to the age of 10 yr and 9 mo.

AI was suspected based on a low basal cortisol level early in the morning (3.5 μg/dL) and a low cortisol level at the time of the AC (11.2 μg/dL) at 6 yr and 3 mo of age. A CRH loading test showed an equivocal peak cortisol level of 17.8 μg/dL (reference value, > 18.0 μg/dL) at the time. Thus, administration of HDC (100 mg/m²/d) was started at 6 yr and 5 mo of age only in clinical situations in which AC was suspected. AI was not definitively diagnosed at this point. The patient was always bedridden, and his nutrition was provided entirely via tube feeding. He was unable to express his intentions or speak. Only objective findings, such as fever, tachycardia, and vomiting were clues to the possibility of AC.

There was no family history of DM. Risk factors for DM in this patient were obesity and lack of exercise. Prior to HDC therapy, which was initially done only when AC was suspected, random samplings of blood glucose yielded findings of 100 to 130 mg/dL. Transient postprandial hyperglycemia (368 mg/dL) was first recognized during a respiratory infection at 6 yr and 7 mo of age. The total amount of HDC was 1278.7 mg/m² until then, and the total duration of HDC administration exceeding 8 mg/m²/d was 18 d (Table 1). The highest dose (100 mg/m²/d) was administered for 16 of the 18 d. The episodes associated with suspected AC at that time were vomiting and respiratory infection, and the continuous administration of the highest dose during these episodes was 5 and 11 d, respectively. In retrospect, these durations were relatively long. Hyperglycemia in these periods resolved after discontinuation of HDC.

The total amount of HDC administered from 6 yr and 7 mo to 8 yr and 7 mo of age was 12036.3 mg/m², and the total duration of administration exceeding 8 mg/m²/d was 224 d. The highest dose (100 mg/m²/d) was administered for 67 of the 224 d. The episodes associated with suspected AC were vomiting (7 episodes), respiratory infection (5 episodes), and tachycardia (1 episode), and the continuous duration of administration of the highest dose for these episodes was 2–8 d, 3–10 d, and 4 d, respectively. Postprandial hyperglycemia remained above 200 mg/dL after the age of 8 yr and 7 mo. The anti-GAD and -IA2 antibodies were negative at the time. GC-induced DM was diagnosed based on the HbA1c value (7.5%). As blood glucose occasionally declined naturally to around 140 to 160 mg/dL before tube feeding, the endogenous secretion of insulin apparently still continued although at low levels. Indeed, the IRI level was 12.4 mIU/mL when the blood glucose level was 180 mg/dL. Since the patient was obese, metformin (125 mg/d) was first introduced to improve insulin resistance but had no effect. Thus, insulin injections with insulin aspart and glargine were started at 8 yr and 9 mo old. The HbA1c at this time was 8.0%.

At 8 yr and 6 mo of age, the basal cortisol level early in the morning was undetectable (< 1.0 μg/dL). The test was done before 9 o’clock before oral HDC administration when he visited us in a poor condition, or stressful situation. This cortisol level was consistent with the complete suppression of endogenous GC, and daily oral replacement of HDC (8 mg/m²/d) was started. ACTH deficiency at 6 yr and 3 mo was not unequivocally documented as explained above. Thus, the low peak value of cortisol (< 1.0 μg/dL) at 8 yr and 6 mo might simply have reflected the subsequent excess of exogenous GC.

All 15 episodes that were treated with HDC for suspected AC and/or prevention of AC are shown in Table 2. Hyponatremia (122 mEq/L, 128 mEq/L) was recognized in two of the 15 episodes, which were apparently the only episodes of severe AC in retrospect. The duration of treatment with 100 mg/m²/d of HDC ranged from two to 11 d for these 15 episodes. Because vomiting, one of the most frequent symptoms
Table 1. Case presentation

| Age   | BMI (%ile) | Hyperglycemia and HbA1c (%) | Treatment                                                                 | Total amount of HDC for each period | Total duration of administration exceeding the physiological dose * (continuous days at the highest dose **/ total duration of the highest dose) | Events / duration of highest dose |
|-------|------------|----------------------------|---------------------------------------------------------------------------|-------------------------------------|---------------------------------------------------------------------------------|---------------------------------|
| 6y5m  | 21.1 (98.8)| Administration of HDC (100 mg/m²/d) was started only in times of stress. | Administration of HDC (100 mg/m²/d) was started only in times of stress. | 1278.7 mg/m² (6y5m–6y7m) | 18 d (11 d / 16 d) | Vomiting / 5 d, Respiratory infection / 11 d |
| 6y7m  | 21.9 (99.1)| Postprandial hyperglycemia (368 mg/dl) was recognized for the first time. | Postprandial hyperglycemia (368 mg/dl) was recognized for the first time. | 12036.3 mg/m² (6y7m–8y7m) | 224 d (10 d / 67 d) | Vomiting 7 times / 2–8 d, Respiratory infection 5 times / 3–10 d, Tachycardia 1 time / 4 d |
| 8y6m  | 19.4 (89.4)| Daily oral replacement of HDC (8 mg/m²/d) was started. | Daily oral replacement of HDC (8 mg/m²/d) was started. | | | |
| 8y7m  | 20.1 (91.9)| Postprandial hyperglycemia (above 200 mg/dl) persisted with HbA1c at 7.5%. GC-induced diabetes was diagnosed. | Postprandial hyperglycemia (above 200 mg/dl) persisted with HbA1c at 7.5%. GC-induced diabetes was diagnosed. | Metformin was started. | | |
| 8y9m  | 19.4 (88.4)| Insulin was started. | Insulin was started. | 8397 mg/m² (8y9m–10y9m) | 168 d (12 d / 65 d) | Vomiting 3 times / 2–5 d, Tachycardia 4 times / 2–12 d, Urinary tract infection 1 time / 2 d, Tachypnea 1 time / 4 d, Respiratory infection 2 times / 3–5 days |
| 10y9m | 15.5 (18.2)| HbA1c 6.1% | The total amount of insulin required per day was 1.2–1.4 U/kg/d. | | | |

y, year; m, month. HDC: hydrocortisone. * Physiological dose: 8 mg/m²/d. ** Highest dose: >100 mg/m²/d.

In two separate periods spanning the patient’s age from 6y7m to 8y7m and from 8y9m to 10y9m, the highest dose of HDC was administered for 67 and 65 d, respectively, with continuous administration at the highest dose for 10 and 12 d, respectively. The numbers of days were similar between the two periods. Because this patient was bedridden and could not express his intention, it was difficult to reduce or stop HDC therapy earlier in stressful situations. On the other hand, the HDC administration period exceeding the physiological level decreased from 224 d in P1 to 168 d in P2, and the total HDC dose also similarly diminished from 12,036 to 8397 mg/m². This indicates that the physicians were trying to reduce the HDC dose earlier in P2 than P1. Owing to the patient’s obesity at the time of hospitalization at 8y9m, the calories given to the patient were reduced, leading to a decline in body mass index (BMI). Although the dose of insulin did not change greatly from 8y9m to 10y9m, it seemed that the BMI reduction was also involved in the improvement of his HbA1c level.
in this patient, improved with treatment, we concluded that the vomiting episodes were related to AC. Other diseases causing vomiting such as ileus or gastroenteritis were denied.

At 10 yr and 9 mo old, the total amount of insulin was 1.2–1.4 U/kg/d, and HbA1c (NGSP) was 6.1%. The dose and frequency of HDC therapy for AC were not reduced after 8 yr 9 mo, and the patient needed over 1 U/kg/d insulin for two years until the time of this writing, suggesting that the steroid diabetes had become irreversible. Mild fatty liver detected by an echograph was the only symptom or finding relevant to the excess exogenous GC besides obesity and hyperglycemia (data not shown).

Table 2. Clinical manifestations of each adrenal crisis episode on admission

| Age       | Symptoms          | Vital signs | Weight (kg) | Height (cm) | Electrolytes (Na / K) | Glucose level (mg/dL) | Duration of symptoms (d) | Days of treatment with HDC 100 mg/m²/d |
|-----------|-------------------|-------------|-------------|-------------|-----------------------|-----------------------|--------------------------|----------------------------------------|
| 6y5m      | Vomiting          | 36.2 94     | 22 ND 99    | 14.0 / 80.0 | 139 / 4.6             | 166                   | 1 5                      |                                        |
| 6y7m      | Respiratory distress | 35.0 87     | 44 85/58 94 O₂ 1.5 L | 14.3 / 80.0 | 134 / 4.4             | 90                    | 1 11                     |                                        |
| 6y9m      | Vomiting          | 35.4 89     | 25 128/77 96 O₂ 0.5L | 14.3 / 82.0 | 141 / 4.2             | 135                   | 1 4                      |                                        |
| 6y10m     | Vomiting          | 35.8 71     | 22 100/53 99 O₂ 0.5L | 13.9 / 82.0 | ND                    | ND                    | 1 2                      |                                        |
| 6y11m     | Vomiting          | 35.6 82     | 26 138/98 98 O₂ 0.5L | 14.1 / 82.0 | 137 / 4.3             | 135                   | 1 3                      |                                        |
| 6y11m     | Tachycardia       | 33.8 89–90  | 22 86/50 99–100 | 13.7 / 82.0 | 137 / 4.3             | 176                   | 3 4                      |                                        |
| 7y0m      | Respiratory distress | 35.0 96     | 22 82/58 92–97 | 13.3 / 82.0 | 138 / 4.5             | 212                   | 1 6                      |                                        |
| 7y2m      | Respiratory distress | 35.5 92     | 30 ND 100   | 14.6 / 82.0 | 137 / 4.5             | 219                   | 1 4                      |                                        |
| 7y4m      | Vomiting          | 34.6 85     | 50 120/82 100 | 14.8 / 80 | 140 / 4.6             | 118                   | 1 6                      |                                        |
| 7y8m      | Vomiting          | 35.6 84     | 26 102/72 99 | 14.0 / 80 | 122 / 4.5             | 156                   | 1 8                      |                                        |
| 8y0m      | Respiratory distress | 35.8 107    | 44 139/70 95 | 13.5 / 79.5 | 128 / 5.5             | 287                   | 1 3                      |                                        |
| 8y0m      | Vomiting          | 35.3 70–80  | 22 ND 100   | 13.5 / 79.5 | 136 / 4.2             | 183                   | 2 4                      |                                        |
| 8y1m      | Respiratory distress | 35.8 113    | 22 136/71 93 O₂ 2L | 14.5 / 79.5 | 137 / 5.4             | 165                   | 1 3                      |                                        |
| 8y2m      | Respiratory distress | 35.9 81     | 22 90/43 97 O₂ 0.5L | 14.7 / 85 | 135 / 4.2             | 136                   | 1 4                      |                                        |
| 8y4m      | Vomiting          | 35.1 92     | 22 78/46 98–100 | 14.2 / 85 | 136 / 3.4             | 162                   | 2 6                      |                                        |

y, year; m, month. HDC: hydrocortisone, BT: body temperature, HR: heart rate, RR: respiratory rate, BP: blood pressure.

Discussion

We described a case of GC-induced DM in a patient with HPE. DM developed after frequent and prolonged administration of high-dose GC for suspected AC.

The maximum dose of HDC used for AC in this report (100 mg/m²/d) was not excessive for major stress or severe AC when compared to previous recommendations. A previous report mentioned that 100–400 mg/d of HDC should be administered to adults in cases of major stress, including open abdominal surgery, severe trauma, childbirth, and frequent diarrhea/vomiting (2). The clinical practice guidelines of the Japan Endocrine Society (JES) (3) recommend a continuous infusion of 150 mg of HDC for 24
h and the administration of 100 mg of HDC on the next day for cases of major physical stress in adults. The Endocrine Society (ES) recommends that suspected AC in children should be treated with an immediate parental injection of 50 mg/m² HDC followed by 50–100 mg/m²/d of HDC (4).

One reason for the development of diabetes mellitus in this patient was the unusually high frequency of treatment with 100 mg/m²/d of HDC. If we follow the definition of major stress or severe AC by Grossman et al. (2), only two of 15 episodes treated with 100 mg/m²/d of HDC in our study apparently qualify as severe AC. The dose for treating AC theoretically varies according to the stress level; therefore, a lower dose could have been selected (2).

Another cause of GC-induced DM in our case was prolonged administration of high dose GC. While the acute symptoms persisted for one to three days, the duration of treatment with 100 mg/m²/d of HDC ranged from two to 11 d in our case (Table 2). The prolonged administration was due to the patient’s condition as described. In retrospect, the physicians had just finished administering HDC treatment when AC was completely recovered in the patient. The cortisol levels in critically ill children reportedly rise only during the first 24 h (5). The plasma CRH, ACTH, cortisol, norepinephrine, and renin activities in patients undergoing neck surgery returned to the basal levels by the first postoperative day (6). Serum cortisol levels in individuals with normal adrenal function reach a peak at the time of tracheal extubation immediately after the end of surgery and normalize within 48 h. Two of the most recent studies (1–3) do not mention the duration of GC administration during stress, whereas the Japanese guidelines recommended tapering to a maintenance dose over a period of 1–4 wk after symptom improvement in children (3). We believe that a tapering period of 1–4 wk is too long based on the findings of the present and previous reports (5, 6).

Several studies have reported on diabetes mellitus in patients with ACTH deficiency. A previous report mentioned that 2% of adults having hypopituitarism with ACTH deficiency developed DM after daily treatment with 20 mg HDC (7). In another report, GC therapy in hypopituitarism adults with 26 mg HDC was shown to cause mild elevations in the circulating glucose and insulin level without inducing overt DM even in the presence of an acceptable plasma cortisol level (8). However, these doses of 20 and 26 mg HDC are pharmacological, compared to physiological secretion of cortisol, or 6–8 mg/m².

These data suggest that the incidence of DM may not be high if the dose is physiological.

In conclusion, the possible causes of GC-induced DM in our case were frequent and prolonged administration of high-dose GC. As AC is a life-threatening complication in patients with chronic AI, treatment should be started whenever AC cannot be ruled out. However, the initial and subsequent doses should be adjusted depending on the severity of AC and on the pace of clinical recovery with treatment, respectively.

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References

1. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract 2009;15: 469–74. [Medline] [CrossRef]
2. Grossman A, Johannsson G, Quinkler M, Zelissen P. Therapy of endocrine disease: Perspectives on the management of adrenal insufficiency: clinical insights from across Europe. Eur J Endocrinol 2013;169: R165–75. [Medline] [CrossRef]
3. Yanase T, Tajima T, Katabami T, Iwasaki Y, Tanahashi Y, Sugawara A, et al. Diagnosis and treatment of adrenal insufficiency including adrenal crisis: a Japan Endocrine Society clinical practice guideline [Opinion]. Endocr J 2016;63: 765–84. [Medline] [CrossRef]
4. Bornstein SR, Alloio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and
treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016;101: 364–89. [Medline] [CrossRef]

5. Charmandari E, Lichtarowicz-Krynska EJ, Hindmarsh PC, Johnston A, Aynsley-Green A, Brook CG. Congenital adrenal hyperplasia: management during critical illness. Arch Dis Child 2001;85: 26–8. [Medline] [CrossRef]

6. Udelsman R, Norton JA, Jelenich SE, Goldstein DS, Linehan WM, Loriaux DL, et al. Responses of the hypothalamic-pituitary-adrenal and renin-angiotensin axes and the sympathetic system during controlled surgical and anesthetic stress. J Clin Endocrinol Metab 1987;64: 986–94. [Medline] [CrossRef]

7. McConnell EM, Bell PM, Hadden DR, McCance DR, Sheridan B, Atkinson AB. Prevalence of diabetes and impaired glucose tolerance in adult hypopituitarism on low dose oral hydrocortisone replacement therapy. Clin Endocrinol (Oxf) 2001;54: 593–9. [Medline] [CrossRef]

8. Al-Shoumer KA, Beshyah SA, Niththyananthan R, Johnston DG. Effect of glucocorticoid replacement therapy on glucose tolerance and intermediary metabolites in hypopituitary adults. Clin Endocrinol (Oxf) 1995;42: 85–90. [Medline] [CrossRef]