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Research article

Different Potent Glucocorticoids, Different Routes of Exposure but The Same Result: Iatrogenic Cushing's syndrome and Adrenal Insufficiency

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What is already known on this topic?
The most common cause of Cushing's syndrome in the childhood is the administration of high doses of synthetic glucocorticoids for treatment purposes or misuse of these steroids.

What this study adds?
This is the largest series presenting iatrogenic Cushing's syndrome (ICS) and adrenal insufficiency caused by potent steroids in childhood. Adrenal insufficiency is a rare cause of hypercalcemia in infancy and childhood, and hypercalcemia was detected in two infants in this study. In addition, an infant with ICS had exposure to a cream that the manufacturer claimed not containing glucocorticoids whereas the patient's urine and blood steroid analyses revealed the exposure to high-dose steroids.

Abstract
Objectives: Potent glucocorticoids (GC) cause iatrogenic Cushing Syndrome (ICS) due to suppression of hypothalamo-hypophyseal-adrenal (HPA) axis and later even adrenal insufficiency (AI). The aim of this study is to review the clinical and laboratory findings of patients with ICS and to demonstrate other serious side effects.
Methods: The possibility of AI was investigated by low-dose ACTH test. Hydrocortisone was started in patients with adrenal failure.
Results: Fourteen patients (5 boys) with ages ranging from 0.19 to 11.89 years were included. The duration of GC exposure ranged from 1 to 72 months. Ten patients had been given topical GC, rest of them had oral exposure. One infant used a cream for diaper dermatitis that was claimed to contain panthenol. The infant's blood and urine steroid analyses revealed that all endogenous steroids were suppressed. Moon face and abdominal obesity were detected in all patients. At presentation, 12 of 14 patients had AI and two infants had hypercalcemia and nephrocalcinosis. Of 11 patients, ultrasonography revealed hepatosteatosis in five patients. The HPA axis returned to normal at a median of 60(160) days.
Conclusion: In this series, 85 % of the patients had life-threatening AI and two patients had hypercalcemia. These results pointed out that potent GCs cause serious side effects especially in infants, and the recovery of the HPA axis in children might take as long as 780 days. The parents should be informed regarding the possibility of containing synthetic glucocorticoids in cosmetic products and their side effects.
Keywords: Cushing's syndrome, adrenal insufficiency, glucocorticoids, adverse effect, hypercalcemia, non-alcoholic fatty liver disease

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Introduction

Cushing's syndrome (CS) is very rare in childhood and the most common cause is the administration of high doses of synthetic glucocorticoids for treatment purposes or misuse of these steroids (1). Glucocorticoids are one of the most widely used drugs in the treatment of numerous diseases including hematological diseases, oncological malignancies, respiratory system diseases, rheumatologic diseases, neurological diseases, kidney diseases, organ transplantations and adrenal insufficiencies. As the potency and duration of administration of glucocorticoids increase, the risk of serious side effects increases as well. These side effects include hypercortisolism, hypothalamo-pituitary adrenal axis (HPA) suppression, non-alcoholic fatty liver disease (NAFLD), osteoporosis, or even adrenal atrophy. Hypercortisolism due to exogenous steroids is called "Iatrogenic CS (ICS)" (2).

Synthetic glucocorticoids exogenously applied via oral, intravenous, intramuscular, intra-articular, topical, inhaled, intra-ocular or intra-nasal routes can cause ICS. It is known that glucocorticoids, which are frequently administered orally and topically in childhood, cause ICS (3,4). In particular, application of topical steroids to the diaper region of the infant may lead to Cushing's syndrome and subsequent adrenal insufficiency (5). It even facilitates the spread of infectious diseases that might be fatal (6). In addition to potent steroids, long-term and high-dose administration of low-potent glucocorticoids such as hydrocortisone, prednisolone and methyl-prednisolone, which are frequently used in the treatment of several diseases, may cause similar side effects (7,8).

In this article, the clinical and laboratory findings of 14 patients who had ICS due to the oral glucocorticoid treatments given by the physicians for treatment purposes and topical steroids applied by their parents were presented. The aim of this study is to review the clinical and laboratory findings of patients with ICS and to demonstrate other rare but important side effects.

Material and Methods:

Patients:

In this retrospective study, all of data is obtained from patients' medical records. Only those exposed to high-dose potent glucocorticoids were included in this study. Anthropometric measurements were recorded. Body mass index (BMI) of the patients was calculated. Height, weight and BMI-standard deviation score (SDS) of the patients were calculated using "Child metrics" (9). Fourteen patients (9 girls, 5 boys) aged between 0.19 and 11.89 years, were enrolled in the study. All patients had been given a high dose of moderate to high potent glucocorticoids per oral or topical. Those who were exposed to topical potent glucocorticoids for more than a week and using oral potent steroids for more than 15 days were included in the study.

Ten patients had been given topical GC such as clobetasol-propionate, diflucortolone-valerate, metilprednisolon-aceponate and betamethasone exposure, to the rest of them metilprednisolon (MPZ) and prednisolone (PZ) had been administered orally.

The mother of case 12 was using an ointment to prevent diaper dermatitis since birth, thinking that it contains panthenol. The manufacturer stated that there was no glucocorticoid in the cream.

In addition to the side effects of steroids in these patients, adrenal insufficiency due to suppression of the HPA axis, which is frequently seen in patients with iatrogenic Cushing syndrome, was investigated. Low-dose adrenocorticotrophic hormone (LD-ACTH) test was performed to investigate adrenal insufficiency in all patients except two. (The family did not consent in one patient and the other patient with severe thrombocytopenia could not be tested since iv Synacthen was not available at the time.)

The equivalent daily dose (EDD) of the exposed GCs was calculated in five patients according to hydrocortisone. However, the EDD could not be predicted for those who exposed to topical steroids. The potency of glucocorticoids according to hydrocortisone was determined (2).

Ophthalmologic examination was performed in seven patients. Abdominal ultrasonography was performed in 12 patients.

Detailed clinical information about all patients is given in supplemental file.

Laboratory Investigations:

After an overnight fast (children were fasted for at least eight hours and infants for at least six hours) blood samples were taken. Serum levels of glucose, calcium, phosphorus, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP), total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C) and triglyceride (TG) were measured. Fasting levels of serum TC, TG and LDL-C were considered as high when levels were above 200 mg/dl, 100 mg/dl and 130 mg/dl, respectively. The desirable level of HDL-C was above 40 mg/dl, so the cut-off point for HDL-C was accepted as 40 mg/dl. Serum parathyroid hormone (PTH), magnesium, $25OHD_3$ and $1,25\ (OH)_2D_3$ levels were measured in two patients with hypercalcemia. Spot urine calcium and creatinin ratio also was calculated.

A 24-hour urine sample and a morning fasting blood sample of the Case 12 were obtained before treatment was initiated. Blood steroid analysis was performed at Marmara University Medical Faculty Hospital Biochemistry laboratory. High-performance liquid chromatography was used to analyze. Also, urine steroid metabolites of this infant were measured using quantitative gas chromatography-mass spectrometry in selected ion monitoring at University of Birmingham College of Medical and Dental Sciences, Steroid Metabolome Analysis Core (SMAC), Institute of Metabolism and System Research (IMSR).

A low-dose (1 g) ACTH test was performed in 12 patients (Synacthen 250 g, intravenous, Novartis, Basel, Switzerland) for adrenal investigation. The stimulated peak cortisol level in the low-dose ACTH test more than 500 nmol / L (equivalent 18 gr / dL) is considered as adequate (10). Lower levels of cortisol demonstrate adrenal insufficiency. In patients who received hydrocortisone, MPZ or PR with a drug reduction scheme, the LD-ACTH test was performed 4-7 days after the discontinuation of the drug,

Therapy and Follow-up:

Nine of the patients had been treated with hydrocortisone (HC) (15-20 mg/m^2/day), and one patient with prednisolone (PR) (4-5 mg/m^2/day) for 2-3 weeks for prevention of the glucocorticoid withdrawal syndrome. The case 1 the had been treated with (MPZ) (15mg/m^2/d), since a total of 5000 mg MPZ po was given during five days for severe immun thrombocytopenic purpura (ITP) before the admission. Hydrocortisone, MPZ or PR doses were gradually decreased over the 2-3 weeks. According to the age of the patients, LD-ACTH test was re-performed with an interval of one to two months. The HPA axis was considered to be recovered when stimulated cortisol increased above 18 μgr / dL.

Ethics:

Written informed consent was obtained from the parents.

The hospital ethics committee approved this study (Zeynep Kamil Women and Children Education and Research Hospital Clinical Research Ethics Committee, 116/18.12.2019).

Statistical Analysis

All the analysis was done by using Statistical Package for the Social Sciences 21(SPSS)

(IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). In order to determine whether the data normally distributed Shapiro-Wilk method is used. Descriptive statistics of the data, which are normally distributed, are summarized with mean ± standard deviation; the data that does not exhibit normal distribution are summarized with Median (Interquartile range: IQR). For all tests, a p-value of less than 0.05 was accepted as statistically significant.

Results:

A clinical summary of the patients is given in Table 1. The age of them was median 1.76 (11.05) years (0.19-11.89). Mean BMI of the patients was 24.3±7.8 kg/m^2, median height was 79.7 (80.23) cm and median weight was 12 (58.5) kg. Height-SDS of the patients was -0.46±1.32, weight -SDS was 1.32±2.1, and BMI-SDS was 1.82±2.0. There was no patient with short stature expect the girl who received a high dose of MPZ orally for two years. At the admission, six patients (four girls) were obese and three were overweight. However, BMI-SDS of the two infants was found as -1.44 and -1.63. Systolic and diastolic blood pressure was normal in patients whose blood pressure could be measured (systolic: 108±15 mmHg and diastolic: 69±4.9mmHg, respectively).

Five patients were exposed to potent glucocorticoids orally, and nine patients via transdermal route. High dose glucocorticoid exposure duration was median 4 (22.1) months (range1-72 months). The equivalent daily dose of the exposed GCs according to hydrocortisone was calculated in five patients (93±78 mg/m^2/d) who were exposed orally. However, the EDD could not be estimated in nine patients, since the amount applied to skin and its absorption could not be calculated.

Basal ACTH and cortisol levels of the patients were 16.9 (22.91) pg/mL and 3.73 (6.37) μgr/ dL, respectively. Mean stimulated cortisol was detected as 8.55±6.5μgr /dL. At presentation, 100% of the infants were found to have adrenal insufficiency, while 85% of all patients had adrenal insufficiency.

Persistent adrenal insufficiency was detected in-Case 2 due to adrenal atrophy. At the admission HPA axis was normal in two patients. However, HPA axis normalization time was not predicted in three patients because their parents did not bring them to follow-up after discharge.

The normalization of the suppressed HPA axis occurred in a median of 60 (160) days in nine patients. Patients were followed for 240 (825) days.

Although the majority of the patients' transaminases were within normal range (AST 31.1±14 IU and ALT 35.3±23 IU, respectively), they were found to be elevated in two patients. Mean fasting serum triglyceride level was 131±63 mg/dL. Hypertriglyceridemia was detected in six of nine patients whose fasting triglyceride levels were measured. The youngest patient with hypertriglyceridemia was 2 months old. Hypercholesterolemia and increased LDL-C was found in the same two patients. Low HDL-C was detected in other two patients (Table 2). Adrenal insufficiency was detected in 12 patients with serum basal and /or stimulated cortisol (Table 2). Bilateral posterior segment cataract was detected in the Case 1 in ophthalmologic examination. Abdominal ultrasonographic examination was performed in 11 patients. Five patients had hepatosteatosis. Two patients with hypercalcemia had nephrocalcinosis. In case 12, all adrenal steroids including androgen precursors and glucocorticoids and their precursors were found to be decreased in the blood steroid profile. The urine results also showed low androgen precursors, glucocorticoids and their precursors. TH-aldosterone was all slightly increased above normal, but others were normal or low. This profile was not consistent with endogenous Cushing's syndrome, but compatible with exogenous administration of glucocorticoids and subsequent suppression of endogenous glucocorticoid production.

Discussion:

In this study, clinical and laboratory results of children who were prescribed high-dose and potent glucocorticoids by a doctor or given by their parents were investigated. In the present study, six of the 14 patients were younger than two years of age, five of which were exposed to high-dose glucocorticoids via transdermal route. Topical steroids were administered to these patients by their parents to prevent or treat diaper dermatitis. A LD-ACTH test was applied to all of them except for case 5, and revealed adrenal insufficiency. In infants diagnosed with adrenal insufficiency, low potency glucocorticoids such as prednisolone and MPZ as well as high potency GK such as diflucortolone valerate 0.3% and clobetasol propionate 0.05% were used.

It has been accepted that glucocorticoids, when used traditionally in doses less than 20 mg/day for less than three weeks, will not cause adrenal insufficiency. However, it was reported that adrenal insufficiency might be seen in adult patients who are exposed to prednisone or equivalent dose of glucocorticoids at doses greater than 20-30 mg/day for more than five days (11). Also, studies in adults have shown that high-dose glucocorticoid therapy can cause HPA axis suppression even with a five day-treatment (12). Different results have been published regarding the recovery times of HPA axis suppression in children. In children with asthma who received prednisolone for five days, the full improvement in HPA axis was observed in 10 days, whereas in infants who received 12-25 weeks of high dose prednisolone, this period was 6-12 weeks (13-14). Moreover, it has been demonstrated that the HPA axis returns to normal within 1-2 weeks

following discontinuation of prednisolone treatment for more than six months (15). In this study, it was found that the HPA axis returned to normal between 30 and 780 days.
Adrenal insufficiency might also occur in patients exposed to topical, inhaled, or intra-nasal glucocorticoids depending on dose and potency (3,4). Patients in this series had been exposed to potent glucocorticoids for at least 7 months. Adrenal insufficiency was inevitable due to the fact that the patients were children, especially half of them were infants, and the vast majority of them were exposed to topical potent-glucocorticoids with unpredictable amounts.
Topical glucocorticoids with mild and moderate potency used in children to treat atopic dermatitis have been shown to rarely suppress the HPA axis, even if used for a long time (16,17). However, potent or high-potent topical glucocorticoids or combinations of other glucocorticoids are well known to suppress the HPA axis and cause adrenal insufficiency (3,4). In addition, it has been disclosed that the severity of HPA suppression was negatively correlated with cortisol response in the LD-ACTH test (17). The suppression of HPA axis is dose dependent after systemic glucocorticoid treatment (18). In older children, potent glucocorticoids usually cause mild to moderate adrenal insufficiency, more than hydrocortisone, but rarely cause severe AI (16).
Although obesity is an expected finding in patients with Cushing's syndrome, the three infants and one child in this study were not obese. Two of these infants were underweighted for their age. The reasons for not gaining weight such as malabsorption, food intolerance, and gastroesophageal reflux in these patients could not be investigated. The reason for weight loss may be central adrenal insufficiency caused due to suppression of the HPA axis by potent glucocorticoids. Anorexia, nausea, and weight loss are well-known signs of adrenal insufficiency (19,20) and may be the reason of poor weight gain in these infants. In addition, the girl infant was born prematurely and was followed up in the neonatal intensive care unit, had a history of cardiac arrest on the 4th day of her life. She was being followed up with a diagnosis of ichthyosis since birth. On admission, she was still being treated with different potent glucocorticoids simultaneously by the dermatologist. She also could not catch up growth yet. Taken together, there is no definite comment about the reasons for not gaining weight in infants in this study.
In this study, adrenal insufficiency was not found on admission in two patients who were exposed to potent steroids. Clobetazol-containing pomade has not been applied to the 13th case for the last two months. Although she was obese, the cause of the absence of adrenal insufficiency in the LD-ACTH test was the improvement in the HPA axis within two months. Oral MPZ was given to Case 14 for treatment of asthma for a month. A month before his admission, he abruptly stopped MPZ treatment due to weight gain. In this patient, adrenal insufficiency was not detected at the admission since the duration of MPZ usage was short and probably the HPA axis improved within one month. Depending on the dosage of glucocorticoids, the route of administration, and the duration of drug administration, complete recovery on the HPA axis after discontinuation may vary from one week to several weeks (12-15). The reason we could not detect adrenal insufficiency following ICS in these patients was considered to be the complete recovery of HPA in the period between discontinuation of glucocorticoids and their admission to the clinic.
Metyrapone test is not recommended in the diagnosis of adrenal insufficiency in children and especially infants since it could trigger adrenal crisis. Furthermore, insulin tolerance test (ITT) is inconvenient in younger children, and in patients with a history of seizure or cardiac insufficiency (21). Since both the ITT and the metyrapone test carry major risks such as precipating acute adrenal insufficiency, corticotrophin analog stimulation test has been introduced. The low-dose (1 µg of corticotrophin) ACTH stimulation test is easier to perform than the ITT and carries a very low risk of side effects (10,22). In a recent study in adults, the stimulated cortisol values of the 1 mcg ACTH test were compared and it was emphasized that the number of false positive patients would be significantly reduced by accepting the stimulated cortisol value as 401.5 nmol / L (14.55 mcg/dL) instead of 500 nmol / L (18.12 mcg/dL) (23). However, in studies conducted in children, it was stated that values above 500 nmol /L (8) or 550 nmol /L (24) of stimulated cortisol in the 1 mcg ACTH test may exclude adrenal insufficiency. In this study, in 10 of the 12 patients tested, the stimulated cortisol response was inadequate, whereas in only two patients, stimulated cortisol was greater than 18 mcg / dL.
It has been shown that glucocorticoids increase lipid production in rats and they increase circulating triglycerides, as well as hepatosteatosis (25). Glucocorticoids increase the conversion of carbohydrates to fatty acids in hepatocytes, and decrease fatty acid oxidation. They also cause an increase in the synthesis of triglycerides in hepatocytes using increased fatty acids (26). In the liver of a baby with adrenal insufficiency caused by topical clobetasol propionate, we demonstrated for the first time that macrovesicular fat was present in the liver (6). After our original report, a subsequent study regarding non-alcoholic hepatosteatosis (NAFLD) detected by ultrasonography in infants with ICS had been published (5). In this series, NAFLD was detected in six of 11 patients that had ultrasonographic examination. The youngest patient with NAFLD was 2.2 months old, the others older than nine years. The mother of the baby with NAFLD was applying a cream to prevent diaper dermatitis. Blood and urine samples taken before treatment revealed that the synthesis of this patient's endogenous steroids was suppressed. Since this patient had not been given glucocorticoid treatment orally or otherwise, it was suggested that the cream used for diaper dermatitis contained potent glucocorticoid. Misuse of a potent corticosteroid was responsible for hepatosteatosis in our patients. Hypertriglyceridemia as well as an increase in transaminases belong to expected findings in patients with NAFLD (26,27). In the present study, increased transaminase associated with hypertriglyceridemia level was detected in an infant without NAFLD. Interestingly, serum lipids and transaminases were normal in another infant with NAFLD. Among the patients presented here, hypertriglyceridemia was detected in 2/3 of the measured patients. The abnormal lipid profile of our patients might be due to the exposure of the potent glucocorticoid.
Hypercalcemia has been reported in patients with primary or secondary adrenal insufficiency (28-30). In addition, the reduction of glomerular filtration due to fluid loss in adrenal crisis, acute kidney injury and hypercalcemia were also found in adult patients (31-33). Decreased glomerular filtration results in a reduced filtered load of calcium, and increased calcium renal reabsorption occurs due to volume depletion in adrenal insufficiency. Enhanced calcium mobilization from bone in the case of adrenal insufficiency also contributes to the development of hypercalcemia.

The postulated mechanism of adrenal insufficiency causing hypercalcemia is through a combination of increased calcium flux into the extracellular space and reduced calcium renal excretion (34). Stanniocalcin secreted from the adrenal gland reduces circulating calcium (35). The level of calcium is also reduced due to a decreased production in stanniocalcin in the state of adrenal insufficiency. Endogenous glucocorticoids decrease the absorption of calcium from the intestines and increase the excretion of calcium in the urine (36). It is postulated that increased calcium absorption is caused by glucocorticoid insufficiency (37). Glucocorticoid replacement therapy has been shown to improve hypercalcemia.

In the presented patient series, hypercalcemia was detected in two infants. Both patients were less than three months old and had been exposed to glucocorticoids since the first days of their lives. Vitamin D hypervitaminosis and subcutaneous fat necrosis were not detected in these patients. Nephrocalcinosis was found in both babies. Nephrocalcinosis persisted in one patient until the age of 2.5 years but he was not brought to follow-up afterwards. CYP24A1 mutation was investigated in this patient. The other baby's father also had nephrolithiasis. Nephrocalcinosis disappeared at 30 months of age. Adrenal insufficiency caused by potent glucocorticoids may be the cause of nephrolithiasis in these infants.

Study Limitations

This study had some limitations. First limitation of the study was that not all patients were examined for possible side effects of glucocorticoids such as intracranial benign hypertension, osteoporosis, myopathy, glaucoma and neuropsychiatric symptoms (depression, mood changes). Second limitation was that not all cases could be followed up for a long time.

Conclusion:

As a result of this study, the high frequency of adrenal insufficiency in children exposed high-dose oral and topical potent glucocorticoids, has been emphasized once again. In this study it has been demonstrated that the recovery of the HPA axis might last as long as 780 days in children. It should be noted that NAFLD could be seen even in very young infants exposed to potent glucocorticoids. It should be also kept in mind that hypercalcemia and nephrocalcinosis may be detected in exposure to potent glucocorticoids. Clinicians should warn parents about side effects, when prescribing glucocorticoids.

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Table 1. Clinical Findings of The Patients with Iatrogenic Cushing's Syndrome at the Admission

Patient's number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age (years)	12	0.21	9	0.56	0.41	2.45	1.08	11.56	11.89	10.88	0.46	0.19	11.4	6
Gender	F	M	F	F	F	M	M	F	M	F	F	F	M	F
Complaint	CS suspicion during treatment of ITP	Puffiness on the face and abdomen	Maculopapular rash	Pubic hair	Rapid weight gain	Hair on the face	Widespread hypertrichosis	Weight gain	Weight gain, psoriasis	Weight gain	Pubic hair, ichthyosis	Weight gain	Weight gain	Weight gain
Causes of exposure and Corticosteroid (CS) type	91250 mgr pulse MPZ was given 2-3 times a month by the pediatrician in one year for ITP treatment.	Prednisolone was given by the pediatrician before congenital cataract surgery	MPZ was given by the pediatrician for the treatment skin rashes	Diflucortolone Valerate 0.3% and isoconazole nitrate containing cream was used by her mother for the treatment of diaper dermatitis	Diflucortolone Valerate 0.3% and isoconazole nitrate containing cream was used by her mother for the treatment of diaper dermatitis	Clobetasol Propionate 0.05% containing cream was used by his mother for the treatment of diaper dermatitis	Clobetasol Propionate 0.05% containing cream was used by his mother for the treatment of diaper dermatitis	Clobetasol Propionate 0.05% containing cream was used intermittently by physician for the treatment of atopic dermatitis	MPZ contained tablets and clobetasol propionate 0.05% containing cream was used by physician for the treatment of psoriasis	MPZ was given by pediatric neurologist for the treatment of Rasmussen encephalitis	MPZ, dexamethasone, betamethasone valerate were used by the dermatologist for five-day periods, respectively, to treat psoriasis. She was also given dexamethasone nasal drops	A cream for diaper dermatitis, which is thought to contain only panthenol was used by his mother	MPZ was given by the pediatrician for the treatment of allergic asthma	Clobetasol Propionate 0.05% containing cream was used by his mother for treatment diaper dermatitis until two months before admission
Duration of exposure	24 months	1.6 months	1 months	Since birth	Since birth	7 months	2 months	3 years	6 years	2 years	1 month	2 months	1 month	3 months
CS potency/ HC equivalent dose, mg/m^2/d	5 times/ 180	4 times/148	5 times/165	100-150 times/ Unpredictable	100-150 times/ Unpredictable	Up to 600times/ Unpredictable	Up to 600times/ Unpredictable	Up to 600times/ Unpredictable	Up to 600times/ Unpredictable	5 times	5 times/30 times/25 times	Unknown	5 times	Up to 600times/ Unpredictable
CS application route	Oral	Oral	Oral	Topical	Topical	Topical	Topical	Topical	Topical and oral	Oral	Topical	Topical	Oral	Topical
Weight	0.04	0.08	2.75	0.74	5.23	-1.25	-1.93	2.43	2.27	4.06	-2.1	2.26	2.12	1.79

SDS														
Height SDS	-3.35	-1.33	0.6	0.03	-0.22	-1.47	-1.21	-1.24	1.37	0.58	-1.7	1.45	-0.03	-0.01
BMI SDS	1.98	1.57	2.9	0.91	6.21	-0.3	-1.63	3.12	2.08	3.74	1.44	1.58	2.47	2.22
Physical Examination Findings	Buffalo hump, moon face, central obesity, purple striae	Moon face, central obesity, facial acne, oral and diaper candidiasis	Moon face, central obesity, widespread maculopapular rash in the whole body	Diffuse fine hair in the genital and sacral region	Moon face, central obesity, prominent skin folds	Moon face, central obesity, widespread hypertrichosis	Moon face	Moon face, buffalo hump, central obesity, purple striae	Moon face, central obesity, widespread white-yellow plaques in the whole body	Moon face, central obesity, purple striae	Moon face, hepatomegaly fine hair on mons pubis	Moon face, central obesity, prominent skin folds	Moon face, Buffalo hump, central obesity, purple striae	Moon face, central obesity
Ophthalmologic examination	Normal	Right Congenital cataract-left operated	Normal	Not performed	Not performed	Not performed	Not performed	Normal	Normal	Normal	Not performed	Not performed	Normal	Not performed
Blood Pressure (mmHg)	120/75		110/60					90/70	130/70	92/70			110/70	

Table 2. Laboratory Findings of The Patients

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Fasting glucose, md/dL	348	91	168	99	NA		99		85	87	80		73	
Insulin, µIU/mL	17.07	-	-	3.5	NA			24	29.9	40.5				
Ca, mg/dL	9.1	10.2	8.7	10.3	NA	9.9	10.1	9.8				11.2	10.1	10.9
P, mg/dL	4.8	5.9	3.5	5.5	NA	5.4	5.5					4.9	5.1	
25-OH D3, ng/mL	18,93	37.10			NA							24		
1,25-OH D3, pg/mL, 15-90		2.30			NA							21		
PTH		<3			NA			148				3		

ALT,U/L	13	67	331	28	NA	41	11	23	46	14	50	22	80	15
AST,U/L	11	44	254	52	NA	17	28	22	31	17	29	28	55	42
ALP,U/L	99		180		NA	325	308				294		228	372
Total Cholesterol, mg/dL	186	361	142	149	NA			140	230	138			137	
Triglyceride, mg/dL	186	143	270	75	NA	NA	69	140	102	124	NA	NA	75	
LDL, mg/dL	87	263	66	98	NA			70	153	52			74	
HDL,mg/dL	62	69	22	36	NA			42	62	61			48	
Basal Cortisol, µgr/dL	3.73	2.1	0.6	4.52	<1	<1	7.85	3.76	6.87	<1.0	<1.0	<1.0	11.7	12.4
Basal ACTH, pg/mL	<5	7.48	15.3	19	<5	19.5	37	19	16.9	9.1	<5	<5	35.2	56
Stimulated Cortisol, µgr/dL	ND	5.4	6.21	16.3	ND	3	9.44	4.57	12.6	6	<1.0	1.1	18.1	21.2
Abdominal USG	Splenomegaly	Bilateral nephrocalcinosis	Hepatosteatosis grade 2	Normal	NA	Normal	NA	Hepatosteatosis, hepatosplenomegaly	Hepatosteatosis	Hepatosteatosis	Normal	Hepatosteatosis grade 1, nephrocalcinosis at right kidney	Hepatosteatosis grade 2, hepatomegaly	NA
Other	BMD-SD L1-L4: -0.2								Hyperinsulinism at the OGTT			Spot Urine Ca/Creatinin ratio: 1.12	BMD-SD L1-L4:-0.6	
Normalization time of the HPA axis, day	40	None	150	51	Unknown	60	Unknown	Unknown	780	1110	30	66	HPA axis was normal	HPA axis was normal
Therapy	MPZ started as 15mg/m2/d. Splenectomy for ITP;	HC started as 20mg/m2/d and FC 0.1 mg/d for adrenal	HC started as 20mg/m2/d	None	Parents refused to all investigations and therapy	HC started as 20mg/m2/d	HC started as 20mg/m2/d	HC started as 20mg/m2/d	PR equivalent to 20mg/m2/d hydrocortisone	HC started as 20mg/m2/d	HC started as 20mg/m2/d	HC started as 20mg/m2/d	None	None

	metformin for hyperglycemia	atrophy; furosemide and pamidronate for hypercalcemia												

HC: hydrocortisone, FC: fludrocortisone, PR: prednisolone, MPZ: metilprednisolon