CASE REPORT

A ‘smart’ type of Cushing’s syndrome

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Abstract

Cushing’s syndrome results from lengthy and inappropriate exposure to excessive concentrations of either endogenous or exogenous glucocorticoids. This case report describes a patient with a novel type of Cushing’s syndrome due to the use of party drugs. A 35-year-old woman had gained 8 kg body weight in 5 months and complained of anxiety. She showed a Cushing-like appearance and mild hypertension (blood pressure, BP 150/95 mmHg). She reported daily use of increasing doses of γ -hydroxybutyric acid (GHB), a popular party drug. ACTH plasma levels were in the upper normal range (41 ng/l), with normal plasma cortisol (0.36 μ mol/l). She showed an abnormal overnight 1 mg dexamethasone suppression test (cortisol 0.38 μ mol/l). The urinary excretion of free cortisol in 24 h was also increased (0.47 μ mol/24 h). CT scanning of the abdomen showed normal adrenals. After stopping GHB intake she lost 7 kg body weight and her BP normalized (BP 135/80 mmHg). GHB is a popular party drug in the Netherlands, but it is also used as a narcotic and for the treatment of narcolepsy. We hypothesize that GHB may bind to the pituitary gland γ -aminobutyric acid-B receptors leading to ACTH overproduction.

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Introduction

Cushing’s syndrome results from a lengthy and inappropriate exposure to excessive concentrations of glucocorticoids (1). Cushing’s syndrome can be induced by either endogenous overproduction of cortisol or exogenous corticosteroids. A different classification is based on the difference between Cushing’s syndrome and Cushing’s disease. Furthermore, ectopic adrenocorticotrophin hormone (ACTH) production is also a well-known cause of Cushing’s syndrome (2–6). Less frequent causes are food-induced Cushing’s syndrome (7, 8), alcohol-induced pseudo-Cushing’s syndrome (2, 9), depression and obesity (2). In this case report, we describe a patient with a novel type of Cushing’s syndrome due to the chronic use of γ -hydroxybutyric acid (GHB).

Case report

A 35-year-old woman was admitted to our hospital with complaints of dyspnoea, fatigue, insomnia and weight gain. She had no medical history. She had gained 8 kg body weight in 5 months and she complained of anxiety. She reported of having frequent loose stools during the last few days before admittance to the hospital. Physical examination revealed a restless woman with a full moon face and slight central adiposity. Her height was 170 cm, and she weighed 76 kg. Her blood pressure (BP) was mildly elevated (150/95 mmHg) with a regular heart rate

of 70 beats per min. She reported a daily use of increasing doses of GHB for the last 2 years. The average dose was 50 ml per day. Besides the use of GHB, she also reported the consumption of three units of alcohol daily.

After administering 1 mg dexamethasone overnight, there was a lack of suppression of plasma cortisol (cortisol 0.38 μ mol/l; Table 1). The urinary excretion of free cortisol in 24-h urine was elevated. ACTH plasma levels were in the upper normal level. An abdominal CT scan showed normal adrenals. She was advised to stop using GHB, which she refused initially. The patient appeared to be highly dependent on GHB. After several consultations, she was able to stop GHB, but continued her daily use of alcohol. Thereafter, she became less restless, her BP normalized (BP 135/80 mmHg) and she lost 7 kg body weight. Furthermore, the urinary excretion of free cortisol in 24 h normalized (0.17 μ mol/24 h; Table 1).

Serum potassium at presentation was 2.4 mmol/l and following GHB withdrawal a normal level of 4.4 mmol/l was measured. However, at presentation she suffered from unrelated diarrhoea, most likely explaining the low serum potassium levels.

Methods

Both urinary free cortisol and serum cortisol were measured by a solid-phase competitive chemiluminiscent enzyme immunoassay with the Immulite 2000 from DPC.

Table 1 Laboratory results on and off γ -hydroxybutyric acid (GHB).

	On GHB	Off GHB	Reference values
ACTH (ng/l)	41	19	7–50
Free cortisol in urine (μ mol/24 h)	0.47	0.17	0.03–0.28
Serum cortisol (μ mol/l)	0.36	0.29	0.18–0.72
Serum cortisol after overnight 1 mg dexamethasone suppression test (μ mol/l)	0.38	ND ^a	<0.07

^aNot done.

ACTH levels were measured using a sandwich chemiluminiscent enzyme immunoassay with the Immulite 2500 from Diagnostic Products Corporation (DPC).

Discussion

To our knowledge, this is the first report describing Cushing’s syndrome induced by GHB abuse.

The diagnosis was established by the clinical presentation and the biochemical tests. In addition, withdrawal of GHB resulted in normalization of urinary free cortisol excretion and of the clinical signs and symptoms. Most likely, the low potassium level was caused by a self-limiting viral gastroenteritis, as the documented level of glucocorticoid excess is unlikely to impact on serum potassium.

In recent years, several unusual causes of Cushing’s syndrome have been reported (2–10). For example, food-induced Cushing’s syndrome is attributed to aberrant receptors in the adrenals for gastric inhibitory peptide (8). Other receptors have also been described, functionally linked to steroid genesis, such as receptors for vasopressin, catecholamine, luteinizing hormone/human chorionic gonadotropin (hCG) and serotonin (11). Recently, also receptors for angiotensin, leptin, glucagon, IL-1 and thyrotrophin have been described (11).

Our hypothesis is that GHB has a direct effect on pituitary ACTH production, since γ -aminobutyric acid (GABA)-B-receptors are also present on the pituitary gland (12). This may induce the release of cortisol, leading to Cushing’s syndrome. Baseline ACTH levels were in the normal range, in contrast to the usual suppression in the case of adrenal overproduction. However, an effect on the adrenal gland cannot be excluded, although it seems less likely due to the relatively high ACTH levels.

GHB is a short-chain fatty acid that occurs naturally in the mammalian brain and is formed primarily from the precursor GABA. The properties of GHB suggest that it has a neuromodulatory role in the brain and has the ability to induce several pharmacological and behavioural effects (13). GHB is also a well-known narcotic. Nowadays GHB is being used for the treatment of alcoholism and narcolepsy (13–14). It has a reversing effect on cataplexy. GHB binds to the GABA-B-receptor

and a distinct GHB-specific receptor (15). The maximum dose of GHB for the treatment of narcolepsy is 9 g (18 ml) per day.

GHB, also known as ‘liquid XTC’, has gained popularity over the last decade as a party drug in the Netherlands. The effect depends on the dosage and can be potentiated by combination with alcohol or other drugs. Regular GHB use can lead to physical addiction, resulting in fear, quivering and insomnia on withdrawal. Over the last few years, there has been an increase in the number of cases of acute GHB intoxication (16), but chronic use leading to Cushing’s syndrome has not been reported before.

In this case report, the hypercortisolism could not be explained by alcohol abuse, because of clinical normalization after stopping GHB and continuing alcohol intake.

The fact that the Cushing’s syndrome regressed completely both clinically and biochemically after stopping GHB is suggestive of GHB-induced hypercortisolism.

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