CASE REPORT

Roux-en-Y gastric bypass in the treatment of non-classic congenital adrenal hyperplasia due to 11-hydroxylase deficiency

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SUMMARY

Non-classic adrenal hyperplasia (NCAH) has been associated with insulin resistance (IR). Therapies such as metformin, thiazolidinediones and lifestyle alterations improve IR and also ameliorate the biochemical and clinical abnormalities of NCAH, much as they do in polycystic ovarian syndrome (PCOS). More recently, bariatric surgery, such as Roux-en-Y gastric bypass (RYGBP), has also been associated with improvement in IR and amelioration of PCOS and may, therefore, be beneficial in NCAH. We report a case of a 39-year-old, deaf-mute, obese woman with NCAH due to 11-hydroxylase deficiency who underwent RYGBP followed by improvement of NCAH manifestations. She was initially treated with metformin and pioglitazone, which lowered serum 11-deoxycortisol from 198 ng/dl (<51) to 26 ng/dl. Five weeks after undergoing RYGBP her body mass index fell from 44.18 kg/m² to 39.54 kg/m² and, despite not taking metformin or pioglitazone, serum 11-deoxycortisol remained normal at <40 ng/dl. Concurrently and subsequently, her NCAH symptoms, for example, alopecia, hirsutism and irregular menses normalised as well. We conclude that RYGBP, like other interventions that reduce IR, may be another way of treating non-classic 11-hydroxylase deficiency in selected patients.

BACKGROUND

Congenital adrenal hyperplasia (CAH) is a disorder resulting in inadequate cortisol production, due to a quantitative or functional deficiency of one or more of the enzymes involved in adrenal steroidogenesis. More than 90% of the cases are due to 21-hydroxylase deficiency, while 11-hydroxylase deficiency accounts for approximately 5–8% of cases.^{1–2} The defect is in the final step of cortisol synthesis, in which 11-hydroxylase is required to convert 11-deoxycortisol to cortisol. These cortisol precursors are produced in excess due to increased adrenocorticotrophic hormone (ACTH) secretion and are converted to cortisol more slowly, allowing them to be siphoned off into androgen production, resulting in hyperandrogenism.

Depending on the severity of the quantitative or qualitative defect of the affected enzyme or the interference with its expression, patients with CAH are categorised into two groups. In the classical form of CAH, findings are evident at birth with pseudohermaphroditism in women and virilisation and hypertension in both boys and girls.³ The non-classical form is due to a milder mutation or to a

heterozygous expression of a functionally more severe mutation and does not become apparent until mid-childhood or adulthood with findings such as precocious pubarche, irregular menses, infertility, acne and hirsutism.⁴ 11-Hydroxylase deficiency is reported as being due to mutations in CYP11B1.⁵ CAH is also associated with metabolic abnormalities such as obesity and insulin resistance (IR).⁶

RYGBP is the most common surgery performed worldwide in the treatment of obesity. It consists of anastomosis of a small stomach pouch to the middle portion of the jejunum, thus bypassing the rest of the stomach, duodenum and upper jejunum. It has been shown to be superior to other surgical procedures for achieving sustained weight loss.⁷ After RYGBP excess body weight decreases substantially, and there is also evidence of significant improvement in IR and insulin secretion.⁸ Furthermore, the improvement in insulin sensitivity is an early manifestation and appears before significant weight loss and is greater than expected for the change in body mass index (BMI)⁹; thus providing evidence that the improvement of IR is not solely the result of the weight loss. For example, one study demonstrated that 1 month after surgery, IR was reduced by more than half.¹⁰ Although several studies have demonstrated the benefits of bariatric surgery on disorders associated with IR such as type 2 diabetes mellitus (DM)^{11–14} and PCOS,^{15–16} to our knowledge the effects of bariatric surgery on CAH have not been reported previously. In this case report, we will discuss what appears to be the first reported case of non-classical 11 hydroxylase deficiency (OHD) ameliorated post RYGBP.

CASE PRESENTATION

A 39-year-old woman with morbid obesity (BMI=45 kg/m²) and deafness/mutism who communicates with the aid of a sign language interpreter was referred to us by her primary care provider for an elevated serum thyroid-stimulating hormone (TSH) level and symptoms consistent with hypothyroidism. She was found to have Hashimoto's thyroiditis based on a TPO antibody titre of 9144.1 U/ml (<60) by chemiluminescence and started on l-thyroxine, but subsequently was non-compliant with medication and follow-up appointments. Eighteen months after her initial visit, the patient presented to clinic with palpitations, weight and hair loss, and oligomenorrhoea, despite admitting to non-compliance with her l-thyroxine 3 months prior to presentation. Repeat

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thyroid function tests confirmed a suppressed TSH, with elevated free thyroxine by chemiluminescence, elevated titre of thyroid-stimulating immunoglobulin (TSIG) by bioassay and a thyroid scan and radioactive iodine uptake consistent with Graves' disease. Also noted at that time was impaired glucose tolerance found on routine laboratory tests and a slightly elevated haemoglobin A1c by high-performance liquid chromatography (HPLC). She weighed 127.9 kg with BMI=44.18 kg/m². On review of systems, she reported, via sign language interpreter, an increase in facial and body hair. Methimazole was initiated for the newly diagnosed hyperthyroidism and miglitol prescribed for her impaired glucose tolerance. Over the succeeding months, her glucose intolerance progressed to type 2 diabetes and her hirsutism worsened, leading to further workup for a possible adrenal or ovarian disorder. She was noted to have bald areas on her scalp in a male pattern distribution, and scant facial hair over the chin area. Her thyroid was slightly enlarged, but non-tender, and without palpable nodules. She was noted to have combined dyslipidaemia and had a history of sarcoidosis.

INVESTIGATIONS

These included serum TSH by electro-chemiluminescence (ECLIA), thyroid peroxidase antibody (TPO) by ECLIA, thyroglobulin antibody by immunochemiluminometric assay (ICMA), dehydroepiandrosterone-sulfate (DHEA-S) by ECLIA, DHEA by liquid chromatography/mass spectroscopy (LC/MS), androstenedione by LC/MS, 17-OH-progesterone by LC/MS, 17-OH-pregnenolone by radioimmunoassay (RIA), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by immunoassay, 11-deoxycortisol by LC/MS, deoxycorticosterone by mass spectrometry (MS), glycated (glycosylated) haemoglobin with HPLC. Her LH was 16.42 mIU/ml (follicular phase 1.9–12.5 and luteal phase 0.5–16.9) and FSH was 9.52 mIU/ml (follicular phase 2.5–10.2 and luteal phase 1.5–9.1) and transvaginal pelvic ultrasound showed normal ovaries. Both 17-hydroxypregnenolone and 17-hydroxyprogesterone levels were within normal limits and the patient's baseline 11-deoxycortisol levels were very elevated at 147, 115 and 198 ng/dl (normal <51) supporting the diagnosis of non-classic 11OHD. Cosyntropin stimulation testing was not performed because the baseline serum 11-deoxycortisol levels were already 2–4 times the upper limit of normal.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included: PCOS, hyperandrogenism, insulin resistance, acanthosis nigricans (HAIRAN) syndrome, NCAH, subclinical hypercortisolism and hair shedding due to hyperthyroidism.

OUTCOME AND FOLLOW-UP

The patient was originally started on metformin titrated to 2 g daily and her 11-deoxycortisol levels improved to 45 ng/dl, later pioglitazone 45 mg/day was added and her levels were further improved to 26 ng/dl. However, given her morbid obesity (BMI=45), her frustration with past attempts at sustained weight loss, and co-morbidities, the patient was a candidate for gastric bypass surgery, which she received on 12/7/2010. At postoperative week 5, off metformin and pioglitazone, her DHEA was 31 ng/dl (102–1185), DHEA-S was 8.37 µg/dl (139.7–484.4) and androstenedione was 47 ng/dl (follicular phase 35–250 and luteal phase 30–235). Preoperative levels of these metabolites were not performed. Her serum 11-deoxycortisol was in the normal range of <40 which is in

Figure 1 Patient's 11-deoxycortisol (ng/dl) levels at baseline, with metformin+pioglitazone, and post-RYGBP surgery. The solid line indicates the upper limit of normal value for 11-deoxycortisol (<51 ng/dl).

the same range previously achieved with medication (figure 1). It has been maintained in the reference range to date without medication with parallel and subsequent improvement in alopecia, hirsutism and oligomenorrhoea. As our patient was not interested in fertility we did not assess luteal phase serum progesterone levels after normalisation of her menstrual cycle. She has achieved and maintained euglycaemia without the use of any oral hypoglycaemics, insulin or glucagon-like peptide-1 agonists.

DISCUSSION

Congenital adrenal hyperplasia includes a group of disorders that result in the overproduction of one or more steroids due to a quantitative or functional deficiency of an enzyme found downstream along the synthetic pathways of cortisol, and aldosterone or to an interference with the expression of such an enzyme. The most common form of this disorder results from 21OHD¹⁷; however, a less common form resulting from 11OHD was first described in the 1950s³ and is described in this case report. In the general population the incidence of 11OHD is 1/100 000 births, although it can be as high as 1/5000–7000 births in highly inbred populations such as Moroccan Jews.⁵ The mutation is found in the CYP11B1 gene, which is located on chromosome 8q22, and is transmitted in an autosomal dominant mode of inheritance with variable penetrance.¹⁸ CYP11B1 is responsible for the final step of cortisol production and is under strict control of ACTH.¹⁹ Thus far, there have been over 50 mutations identified resulting in 11-hydroxylase deficiency.^{19–22}

Clinically, the classical form of 11OHD often presents in infancy with ambiguous genitalia and hypertension, while the non-classical form appears in childhood, adolescence and early adulthood as precocious pubarche, virilisation, insulin resistance and menstrual abnormalities in females. Metabolically, baseline ACTH may be elevated with concomitant elevations in ACTH-stimulated precursors to cortisol, for example, 11-deoxycortisol as well as their urinary metabolites. Serum androgen levels and their urinary metabolites are also likely to be elevated. This is due to the accumulation of precursors

which are redirected into the androgen pathway. ACTH stimulation testing may be used for further confirmation when the diagnosis remains questionable. For our patient, the diagnosis of 11-hydroxylase deficiency was made based on a very elevated baseline serum 11-deoxycortisol levels as well as her progressive hirsutism, alopecia and oligomenorrhoea. She also had a modestly elevated LH/FSH ratio of 1.7, which is more supportive of NCAH than PCOS in which the ratio often exceeds 2.5. Furthermore, pelvic ultrasound showed normal ovaries making a PCOS diagnosis less likely. It should be remembered that NCAH patients frequently have polycystic ovaries on ultrasound which gradually normalise in appearance with glucocorticoid treatment. Baseline serum 11-deoxycortisol levels have not been reported to be elevated in PCOS patients although they may show an increased response to metyrapone.²³ Free and total testosterone levels had been ordered twice in the clinic, but never collected by the laboratory.

It is also intriguing that the diagnosis of 11OHD was made after the onset of Graves' disease. It has been shown that elevated thyroid hormone levels in the setting of Graves' disease can unmask previously undiagnosed NCAH.^{24–25} Elevated thyroid hormone can increase the turnover of cortisol and consequently an occult NCAH may become symptomatic, or even lead to adrenal crisis. Takasu *et al*²⁴ have reported Graves' disease causing adrenal crisis in a 75-year-old patient with previously unrecognised non-classical 21-hydroxylase deficiency. Also Kim *et al*²⁵ reported a case of thyrotoxic periodic paralysis with Graves' disease leading to a late diagnosis of non-classic 11 β -hydroxylase deficiency. It is well known that thyroxine therapy without adrenal steroid replacement in patients with hypothyroidism and subclinical adrenocortical insufficiency can cause adrenal crisis, as the adrenal glands may not be able to keep up with the newly increased cortisol requirement.

The mainstay of conventional treatment of 11OHD is replacement/suppression with glucocorticoids, which inhibit central secretion of ACTH and corticotrophin-releasing hormone (CRH), resulting in reduction of the elevated precursor steroids and causing a decrease in androgen synthesis. Although glucocorticoid replacement has historically been the main method of treatment, our group has focused on using insulin sensitisers to improve insulin sensitivity.^{26–28}

Bariatric surgery has been gaining favour in the treatment of obesity, especially when accompanied by comorbidities such as type 2 DM which is characterised by IR.^{11–14} Early studies have consistently shown a resolution of diabetes post-RYGBP surgery in the range of 80%,^{29–31} with one study demonstrating an even more impressive normalisation of glucose control in 150 of 152 patients with abnormal glucose tolerance (98.7%).³⁰ In addition to weight reduction and improvement in IR, the added benefits have also been seen with resolution of other comorbidities including hypertension, dyslipidaemia and obstructive sleep apnoea.^{29–32} The metabolic improvement seen postbariatric surgery has led to its investigation for treatment of other disorders associated with IR.

It is well known that PCOS is associated with insulin resistance and PCOS patients have been reported to benefit from the metabolic effect of bariatric surgery. Studies have also shown that post-bariatric surgery there is normalisation of the menstrual cycle,³³ an increase in sex hormone binding globulin, and a decrease in serum androgen levels in PCOS patients.^{34–36} A reviewed outcome of 24 women with PCOS who underwent RYGBP showed that after 2 years more than 50% of patients had resolution of their hirsutism and all of them had normalised their menstrual cycles; and interestingly 5 of the women were

able to conceive without clomiphene.¹⁵ In another study, Escobar-Morreale *et al*³⁶ were able to follow 12 obese women with PCOS who underwent bariatric surgery and reported significant reduction in IR, and serum testosterone, androstenedione and dehydroepiandrosterone sulfate.

It has been reported that CAH, like polycystic ovarian syndrome (PCOS) is associated with insulin resistance.^{6 37–40} Charmandari *et al*³⁹ studied 18 children with CAH and compared them to normal children matched for BMI and found that insulin resistance is a regular feature of both 21-hydroxylase deficiency and 11-hydroxylase deficiency. Kelly *et al*⁴¹ have demonstrated in vitro that hyperinsulinemia may direct adrenal steroidogenesis toward androgen production and away from cortisol production.

Gastric bypass surgery has been increasingly used for obesity and diabetes, and is reported to ameliorate PCOS.¹⁶ We believe that this procedure may ultimately prove to be an alternative treatment for 11-hydroxylase deficiency in selected patients. This case provides yet another demonstration of the efficacy of ameliorating insulin resistance in the treatment of NCAH. Needless to say, larger randomised, prospective trials of bariatric surgery are needed to assess its efficacy in patients with NCAH. We conclude that RYGBP may ameliorate disorders involving insulin resistance, such as NCAH in selected patients.

Strengths of this report include the dramatic reduction in serum 11-deoxycortisol using either a combination of insulin-sensitising medications and maintenance of normal levels of this metabolite following RYGBP without medication accompanied and followed by improvements in oligomenorrhoea and features of androgen excess. Limitations of our report include non-measurement of preoperative, pretreatment serum gonadotrophins, androstenedione, DHEA and DHEA-S and failure of the laboratory to perform the ordered free/total testosterone determinations.

Learning points

- ▶ Insulin resistance appears to underlie non-classic adrenal hyperplasia (NCAH) as it does diabetes mellitus type 2, gout, non-alcoholic fatty liver disease and polycystic ovarian syndrome.
- ▶ Increased thyroid hormone with its increased cortisol requirements can unmask features of NCAH.
- ▶ Roux-en-Y gastric bypass has been associated with improved insulin sensitivity.
- ▶ Roux-en-Y gastric bypass might have ameliorated this patient's NCAH by improving her insulin sensitivity.

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Competing interests None.

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