Investigation of a young woman with craniopharyngioma and hypopituitarism

VIRAL CHIKANI MB BS, FRACP
WARRICK J. INDER MB ChB, MD, FRACP

The investigations in endocrinology section uses case scenarios to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

ENDOCRINOLOGY TODAY 2013; 2(1): 28-30

Dr Chikani is a Clinical Research Fellow in the Department of Diabetes and Endocrinology at the Princess Alexandra Hospital, Brisbane. Associate Professor Inder is a Senior Staff Specialist in the Department of Diabetes and Endocrinology at the Princess Alexandra Hospital, Brisbane; and Associate Professor at The University of Queensland, Brisbane, Qld.

SERIES EDITOR: Dr Bernard Champion BEc, MB BS, BSc(Med)(Hon 1), FRACP, MMedEd is a Lecturer at Sydney Medical School Nepean and The University of Sydney; and Head of Department at Endocrinology & Diabetes, Nepean Blue Mountains Local Health District, Sydney, NSW.

Tammy is a 25-year-old woman with a history of craniopharyngioma (Figure). She was diagnosed at the age of 9 years when she presented with visual disturbance. She underwent transsphenoidal resection of the tumour. Subsequently she developed panhypopituitarism including diabetes insipidus and was commenced on hormone replacement therapy. Growth hormone (GH) therapy was commenced approximately one year after her diagnosis, and was ceased after she attained final adult height and bone age of more than 13 years. She underwent puberty induction, beginning at the age of 12 years, with oral oestradiol followed by a progestogen.

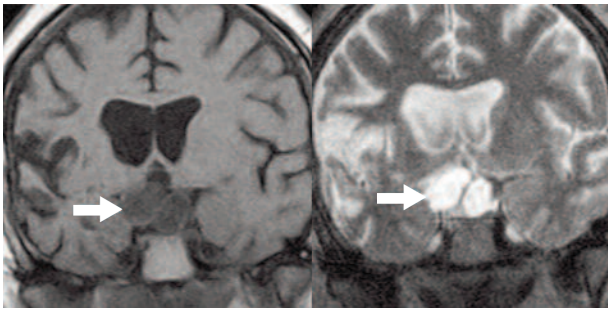
She is currently taking the following:

- hydrocortisone 20 mg in the morning and 10 mg at 3 pm
- ethinyloestradiol 30 µg plus levonorgestrel 150 µg oral contraceptive pill (OCP)
- desmopressin intranasal spray 20 µg twice daily
- thyroxine 100 µg once daily in the morning.

Her most recent 8 am blood results are:

- GH <0.5 mIU/L
- insulin-like growth factor-1 (IGF-1) 6 nmol/L (normal range: 10–50 nmol/L)
- luteinising hormone (LH) <1 IU/L (normal range: 2–10 IU/L)
- follicle-stimulating hormone (FSH) <1 IU/L (normal range: 2–10 IU/L)
- oestradiol 40 pmol/L (low, consistent with oral contraceptive use)
- cortisol (before morning hydrocortisone dose) 128 nmol/L (normal range: 150–600 nmol/L)
- adrenocorticotropic hormone (ACTH) <10 ng/L (normal range: 10–50 ng/L)
- thyroid-stimulating hormone (TSH) 0.01 mIU/L (normal range: 0.3–4.5 mIU/L)
- free thyroxine (T_4) 13 pmol/L (normal range: 7–17 pmol/L)
- free triiodothyronine (T_3) 4.2 pmol/L (normal range: 3.5–6.0 pmol/L)
- prolactin 48 mIU/L (normal range: 71–566 mIU/L).

Tammy gives a history of gradual weight gain of 7kg over the past two years and she has recently been diagnosed with glucose intolerance. On examination, her blood pressure is 138/90 mmHg. She is 155 cm tall and weighs 67 kg (BMI 27.8 kg/m^2). She has truncal obesity and bruising on her lower limbs.



T1 weighted T2 weighted

Figure. Preoperative MRI showing the classic 'popcorn' appearance of craniopharyngioma with mixed cystic and solid lesion in the suprasellar space (arrows).

Question 1. *Concerning Tammy's glucocorticoid replacement, which three of the following statements are correct?*

a. She has clinical features of glucocorticoid excess
b. Her glucocorticoid replacement dose may be contributing to her glucose intolerance
c. Lowering her current hydrocortisone dose is dangerous and puts her at risk of an adrenal crisis
d. Her current hydrocortisone dose is associated with an increased risk of mortality

Discussion

Daily estimated cortisol production rate in normal adults is between 5.7 and 11 mg/m^2/day, which is lower than originally thought.[1,2] Recent studies have shown that the conventionally used corticosteroid replacement dose (hydrocortisone 30 mg/day or cortisone acetate 37.5 mg/day) achieves supraphysiological cortisol levels and is also associated with increased mortality.[3] Optimal dosing of hydrocortisone is probably lower than 0.25 mg/kg/day,[3] which equates to

a total daily dose of approximately 16 mg for Tammy. This could be achieved using a three times a day regimen of 8 mg on waking, 4 mg at 12 pm, and 4 mg at 4 pm.

Weight gain, truncal obesity, bruising, proximal myopathy, low bone mineral density and impaired glucose tolerance are all signs of hypercortisolism, therefore, indicating over-treatment.

Efficacy of the replacement is mainly assessed on clinical grounds as there are no reliable laboratory parameters currently available.

Answers: a, b, d.

Tammy's hydrocortisone dose is lowered to a total daily dose of 16 mg.

Tammy returns for a routine review 6 months later. She complains of feeling more tired lately. She denies any change in the dose of her medications in the past year, except for a reduction in hydrocortisone dose at her last clinic visit. On asking specifically, she tells you that four months ago, when her aunt was diagnosed with osteoporosis, she started taking calcium supplements each day on waking.

Her blood pressure is 120/80 mmHg without any postural drop and her systemic examination is unremarkable. Her biochemistry results are:

- free T_4 6.9 pmol/L (normal range: 7–17 pmol/L)
- free T_3 3.0 pmol/L (normal range: 3.5–6.0 pmol/L)
- TSH <0.05 mIU/L (normal range: 0.3–4.5 mIU/L)
- morning cortisol (before morning hydrocortisone) 108 nmol/L (normal range: 150–600 nmol/L).

Question 2. *Which one of the following therapeutic changes would most likely improve her clinical and biochemical picture?*

a. Recommend that she take the calcium supplement separately from the thyroxine
b. Increase the hydrocortisone dose
c. Reduce her thyroxine dose because she has a suppressed TSH level
d. Add T_3 to her treatment regimen

Discussion

Tammy has symptoms of hypothyroidism that are likely to be mainly secondary to poor absorption of thyroxine due to concomitant use of calcium supplements. Thyroxine absorption can be decreased in patients with malabsorption from gastrointestinal disorders or previous small bowel bypass surgery. Several drugs including iron and calcium supplements, cholestyramine, aluminium hydroxide gel, sucralfate and dietary soy have all been reported to interfere with thyroxine absorption.[4]

Tammy should be encouraged to optimise her dietary calcium intake if possible, and if a supplement is necessary it should be taken at a different time from the thyroxine. In contrast to primary thyroid disease, measurement of basal TSH level is not useful for monitoring secondary hypothyroidism because it remains usually low or inappropriately normal despite a low free T_4 concentration. Hence, dose adjustment should be based on the serum free T_4 level with a goal of a free T_4 in the high normal range. The morning cortisol level was taken before Tammy's hydrocortisone dose and is low as expected. This should not prompt a dose increase in hydrocortisone.

Answer: a.

On a routine visit, Tammy asks you if there are any benefits from taking GH replacement as an adult. She is feeling better after the changes in her therapy introduced after her previous two consultations, but still does not feel quite right. Her energy levels are generally poor and, although she has lost 2 kg, she is still conscious of some truncal adiposity. She has no evidence of tumour recurrence on recent MRI imaging.

Question 3. *Which one of the following is correct about GH therapy in adults?*

a. Tammy would need an insulin tolerance test or other stimulation test to confirm GH deficiency before GH replacement therapy could be commenced
b. GH therapy significantly reduces fat mass and increases lean body mass
c. GH therapy may cause hyperlipidaemia
d. Men with GH deficiency need a higher dose of GH than women

Discussion

As per current diagnostic criteria, adults with three or more other hormone deficits, together with a low IGF-1 level, do not require a stimulation test to confirm GH deficiency.[5] Several studies have shown that long-term GH replacement reduces fat mass and increases lean body mass.[6] GH has a favourable effect on lipid profile, decreasing LDL-cholesterol and total cholesterol levels. Women with GH deficiency need higher doses of GH than men due to a higher concentration of circulating oestrogen.[7]

Answer: b.

Tammy decides to self-fund GH therapy, which is approved by the TGA for adult GH deficiency and can be obtained on a private prescription (there is currently no subsidy on the PBS). She is having regular withdrawal bleeds while taking the OCP (ethinyloestradiol 30 µg plus levonorgestrel 150 µg).

Question 4. *With regards to her sex hormone replacement, which one of the following statements is correct?*

a. The OCP is safer than hormone replacement therapy preparations
b. The hormone replacement therapy should be changed from ethinyloestradiol 30 µg plus levonorgestrel 150 µg to transdermal oestradiol plus a cyclical progestogen to reduce her GH dose requirements
c. Hormone replacement therapy should not be prescribed for more than five years due to an increased risk of breast cancer
d. In women with panhypopituitarism, the OCP is the best preparation for hormone replacement

Discussion

Tammy should be changed from the OCP to a cyclical transdermal oestradiol/progestogen preparation. If the patches are not tolerated, oestradiol may be given transdermally in the form of a gel with a cyclical oral progestogen for 12 days a month. Transdermal oestradiol with cyclical or continuous progestogen is the treatment of choice in women with hypopituitarism rather than the OCP because of reduced synthesis of procoagulatory factors and sex hormone binding globulin, and lower GH dose requirements.[8]

Physiological oestrogen and progestogen replacement (i.e. not the oral contraceptive pill that provides supraphysiological oestrogen) in premenopausal women should not increase the risks of breast cancer or cardiovascular disease beyond that of the normal population.

After the age of 50 years, the risks and benefits of continued use should be re-evaluated as in any other menopausal woman.[9]

Answer: b.

Several months later, Tammy comes to your clinic with her partner because they wish to have a child.

Question 5. ***Tammy would like to know what her chances of conceiving are. What initial advice should you give her? Choose one correct answer.***

a. Try to conceive naturally for six months
b. Consider adoption because she is infertile
c. Take clomiphene as an initial agent of choice for ovulation induction
d. Recommend immediate referral to a fertility specialist for gonadotrophin ovulation induction with or without in vitro fertilisation (IVF)

Discussion

Gonadotrophin deficiency in women with hypopituitary women leads to infertility. However, fertility can be achieved by ovulation induction with exogenous gonadotrophins or assisted reproductive technologies such as IVF.

Recombinant FSH is administered as a daily injection to promote ovarian follicle formation under ultrasound monitoring, with a single injection of human chorionic gonadotrophin to stimulate ovulation. Postovulation, progesterone support is also required to prepare the endometrium for implantation.[10] In Tammy's case, she would need a 30 to 50% increase in her thyroxine dose on confirmation of a positive pregnancy test (as would any woman with hypothyroidism) and close monitoring of her blood glucose status in view of her previous diagnosis of glucose intolerance.

Clomiphene citrate requires an intact hypothalamic–pituitary–gonadal axis and is ineffective in patients with hypogonadotrophic hypogonadism.

Answer: d.

Tammy subsequently attends your clinic at short notice because she has had persistent nausea, vomiting and diarrhoea. She has been taking her medications during this illness but has had difficulty keeping them down. On examination, her blood pressure is 110/70 mmHg in the supine position and 90/60 mmHg on standing. Her temperature is 37.8°C. She has some mild abdominal tenderness without signs of peritonism.

Question 6. ***With regard to Tammy's management, which course of action would you suggest? Choose one correct answer.***

a. Prescribe metoclopramide and loperamide for symptomatic relief
b. Triple her usual dose of oral hydrocortisone until she recovers
c. Give her an immediate dose of intravenous hydrocortisone 100 mg and refer her to the emergency department of your local hospital
d. Organise supine and erect abdominal x-rays

Discussion

Patients with ACTH deficiency do not respond with increased cortisol secretion in the case of infections, illness, trauma or surgery. Patients and their family members should be educated on increasing the oral glucocorticoid two- to three-fold during illness. However, vomiting or diarrhoea may prevent adequate absorption of oral doses and parenteral administration of hydrocortisone is required. The patient should carry an appropriate medical identification (e.g. a medic alert bracelet or necklace) at all times.[11]

Answer: c.

Two months after her bout of gastroenteritis, Tammy presents with a three-day history of headache and nausea (without vomiting). She has increased her usual oral hydrocortisone dose as instructed but this has made little difference. She mentions that her desmopressin nasal spray has been misfiring and subsequently she has often used three or four sprays at each dose. To prevent herself getting dehydrated, she has been making sure she drinks at least 3 L of water a day. She is clinically euvolaemic.

Her biochemistry results are:

- sodium 120 mmol/L (normal range: 135–145 mmol/L)
- potassium 3.6 mmol/L (normal range: 3.5–5.0 mmol/L)
- urea 1.2 mmol/L (normal range: 2.5–6.5 mmol/L)
- creatinine 65 µmol/L (normal range: 50–100 µmol/L)
- urine osmolality 890 mosmol/kg.

Questions 7. ***Regarding her current presentation, which of the following statements is correct? Choose the best answer.***

a. The clinical and biochemical picture is consistent with an overdose of desmopressin
b. Her headache and nausea are due to cerebral oedema, not her past craniopharyngioma
c. Substituting the desmopressin nasal spray with oral desmopressin will reduce the likelihood of this recurring in the future
d. All of the above are correct

Discussion

The aim of diabetes insipidus management is to minimise polyuria and polydipsia while avoiding hyponatraemia due to overtreatment. Desmopressin is the drug of choice and is available as a tablet, nasal spray and injection. Mucosal atrophy, nasal congestion and sinus disease can affect the intranasal absorption whereas use of desmopressin tablets reduces the incidence of hyponatraemia. Patients with an intact thirst mechanism should be advised to drink to thirst to avoid excess water retention. In this scenario, the patient developed symptomatic hyponatraemia due to an overdose of desmopressin and over hydration. Hyponatraemia presents with a wide spectrum of neurological manifestations ranging from mild symptoms (headache and nausea) to delirium, neurological deficit, seizure and coma. This is due to a decrease in plasma osmolality leading to fluid shift in the brain causing cerebral oedema.

Answer: d. **ET**

References

A list of references is available on request to the editorial office.

COMPETING INTERESTS: Dr Chikani: None. Associate Professor Inder has acted on advisory boards for Pfizer and Ipsen and received speaker honoraria from Ipsen and Novo Nordisk; all three companies are suppliers of human GH in Australia. He is also on a joint taskforce set up by the Endocrine Society of Australia and the Australasian Paediatric Endocrine Group, aiming to submit an application to the Pharmaceutical Benefits Advisory Committee for the funding of human GH in adults with GH deficiency.

Investigation of a young woman with craniopharyngioma and hypopituitarism

VIRAL CHIKANI MB BS, FRACP
WARRICK J. INDER MB ChB, MD, FRACP
ENDOCRINOLOGY TODAY 2013; 2(1): 28-30

References

1. Esteban NV, Loughlin T, Yergey AL, et al. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 1991; 72: 39-45.
2. Kraan GB, Dullaart RPF, Pratt JJ, et al. The daily cortisol production reinvestigated in healthy men. The serum and urinary cortisol production rates are not significantly different. J Clin Endocrinol Metab 1998; 83: 1247-1252.
3. Zueger T, Kirchner P, Herren C, et al. Glucocorticoid replacement and mortality in patients with nonfunctioning pituitary adenoma. J Clin Endocrinol Metab 2012; 97: E1938-E1942.
4. Roberts CG, Ladenson PW. Hypothyroidism. Lancet 2004; 363: 793-803.
5. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1587-1609.
6. Hazem A, Elamin MB, Bancos I, et al. Body composition and quality of life in adults treated with GH therapy: a systemic review and meta-analysis. Eur J Endocrinol 2012; 166: 13-20.
7. Burman P, Johansson AG, Siegbahn A, Vessby B, Karlsson FA. Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. J Clin Endocrinol Metab 1997; 82: 550-555.
8. Leung KC, Johannsson G, Leong GM, Ho KK. Estrogen regulation of growth hormone action. Endocr Rev 2004; 25: 693-721.
9. Armitage M, Nooney J, Evans S. Recent concerns surrounding HRT. Clin Endocrinol 2003; 59: 145-155.
10. Hirshfeld-Cytron J, Kim HH. Treatment of infertility in women with pituitary tumors. Expert Rev Anticancer Ther 2006; 6(Suppl 9): S55-S62.
11. Jung C, Inder WJ. Management of adrenal insufficiency during the stress of medical illness and surgery. MJA 2008; 188: 409-413.