ID: 16-0054; November 2016
DOI: 10.1530/EDM-16-0054

# Growth of a progesterone receptor-positive meningioma in a female patient with congenital adrenal hyperplasia

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## Summary

Meningioma growth has been previously described in patients receiving oestrogen/progestogen therapy. We describe the clinical, radiological, biochemical and pathologic findings in a 45-year-old woman with congenital adrenal hyperplasia secondary to a defect in the 21-hydroxylase enzyme who had chronic poor adherence to glucocorticoid therapy with consequent virilisation. The patient presented with a frontal headache and marked right-sided proptosis. Laboratory findings demonstrated androgen excess with a testosterone of 18.1 nmol/L (0–1.5 nmol) and 17-Hydroxyprogesterone >180 nmol/L (<6.5 nmol/L). CT abdomen was performed as the patient complained of rapid-onset increasing abdominal girth and revealed bilateral large adrenal myelolipomata. MRI brain revealed a large meningioma involving the right sphenoid wing with anterior displacement of the right eye and associated bony destruction. Surgical debulking of the meningioma was performed and histology demonstrated a meningioma, which stained positive for the progesterone receptor. Growth of meningioma has been described in postmenopausal women receiving hormone replacement therapy, in women receiving contraceptive therapy and in transsexual patients undergoing therapy with high-dose oestrogen and progestogens. Progesterone receptor positivity has been described previously in meningiomas. 17-Hydroxyprogesterone is elevated in CAH and has affinity and biological activity at the progesterone receptor. Therefore, we hypothesise that patients who have long-standing increased adrenal androgen precursor concentrations may be at risk of meningioma growth.

### Learning points:

- Patients with long-standing CAH (particularly if not optimally controlled) may present with other complications, which may be related to long-standing elevated androgen or decreased glucocorticoid levels.
- Chronic poor control of CAH is associated with adrenal myelolipoma and adrenal rest tissue tumours.
- Meningiomas are sensitive to endocrine stimuli including progesterone, oestrogen and androgens as they express the relevant receptors.

## Background

Congenital adrenal hyperplasia (CAH) is the most common adrenal disorder diagnosed in children and is secondary to a defect in the 21-hydroxylase enzyme in more than 95% of cases. Virilisation of affected female children occurs in both the salt-losing and simple virilising forms of CAH. In normal adrenal steroidogenesis,

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ACTH promotes the production of pregnenolone from cholesterol, which is then converted to progesterone and 17-hydroxyprogesterone (17OHP) and cortisol. In the absence of 21-hydroxylase enzyme activity, production of cortisol (and to a varying extent aldosterone) is reduced, leading to increased ACTH secretion due to a decrease in negative feedback by cortisol at the level of the pituitary and hypothalamus. In 21 hydroxylase deficiency, steroid precursors are diverted into androgen synthesis pathways leading to testosterone, androstenedione and 17OHP excess. The major treatment goals in adults with CAH include avoidance of adrenal crisis, prevention of adrenal and gonadal hyperplasia and neoplasia, the prevention of long-term consequences of adrenal replacement therapies and optimisation of fertility (if required).

Meningiomas are the most common primary brain tumours in adults (1). The higher prevalence of meningiomas in women suggests a link between sex steroids and meningiomas (1). Meningiomas commonly express the progesterone receptor (PR) and less commonly, oestrogen and androgen receptors (1).

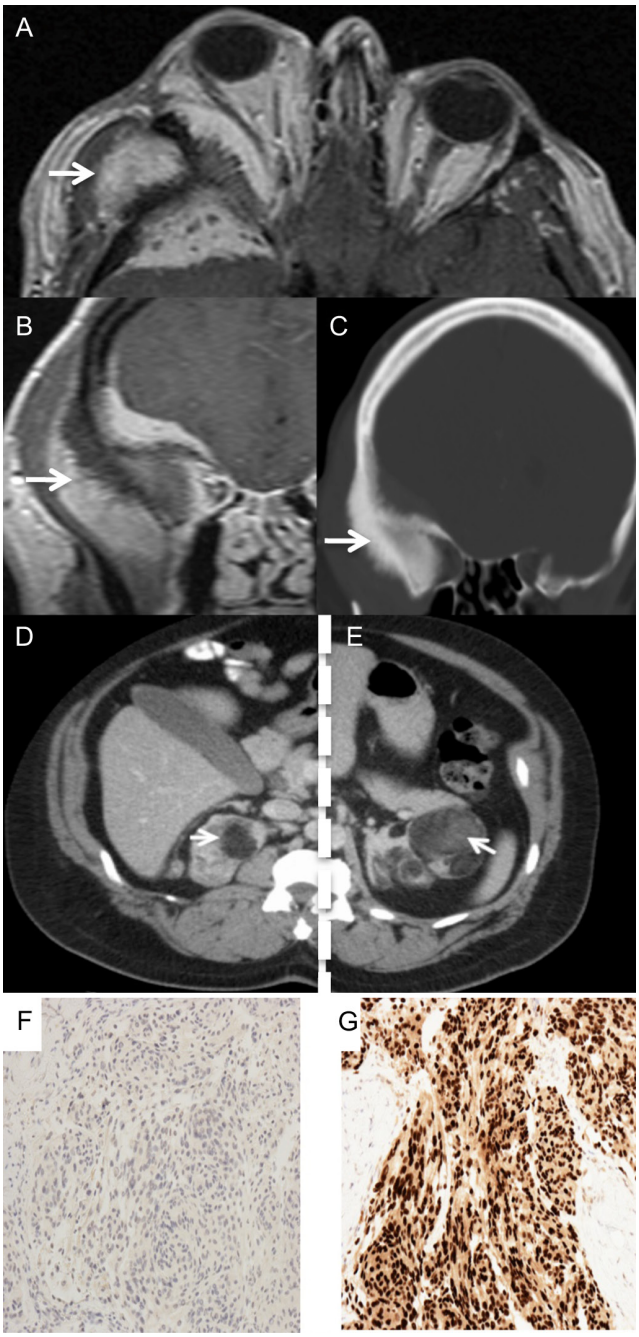


**Figure 1**
(A) Axial gadolinium contrast-enhanced MRI demonstrating an intensely enhancing 4.3 × 4.6 cm soft tissue mass centred upon the right greater wing of sphenoid (arrow), expanding into the middle cranial fossa, lateral orbit and infra-temporal fossa, with a marked right proptosis. There is a spiculated periosteal reaction involving the lateral orbital wall. (B) Coronal contrast-enhanced MRI demonstrates an enhancing soft tissue mass centred upon the right greater wing of sphenoid, measuring 6.0 cm in craniocaudal extent, with the involvement of the squamous part of the temporal bone (arrow). An extra-axial intracranial component shows typical features of a meningioma, with homogenous intense enhancement and a dural tail. (C) Coronal CT head (bone windows) showing the spiculated 'sunray' periosteal reaction of the right greater wing of sphenoid (arrow). (D) and (E) – CT abdomen showing large bilateral adrenal myelolipomata up to 4.5 cm (arrows). (F) and (G) histology from meningioma specimen showing negative oestrogen receptor expression (F) and positive progesterone receptor expression (G).

## Case presentation

### Case report

A 45-year-old woman was diagnosed with CAH secondary to a defect in 21-hydroxylase (non-salt wasting, simple virilising) in childhood, at which time she presented with premature adrenarche and virilisation. Glucocorticoid therapy was initiated, but adherence throughout childhood and adolescence was suboptimal. Menarche was never achieved, and the patient was lost to follow-up. At the age of 45 years, the patient was hospitalised because of severe frontal headaches, increasing in intensity over the preceding three years. Her height was 148 cm; body mass index 27 kg/m$^2$; and cardiovascular, respiratory and gastrointestinal system examinations were unremarkable. On examination, the patient was virilised. Right-sided proptosis, but no diplopia, was evident but visual acuity was preserved, and focal neurological deficits were not apparent.

Laboratory investigations confirmed significant hyperandrogenaemia with testosterone 18.1 nmol/L (reference range 0–1.5 nmol/L) and 17-Hydroxyprogesterone (17-OHP) levels greater than the upper limit

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of detection of the assay at >180 nmol/L (reference range <6.5 nmol/L). ACTH concentration for this patient was 519 pg/mL (reference range 0–46 pg/mL). CT and MRI imaging (Fig. 1A, B and C) revealed a solid enhancing mass (measuring 4.3 × 4.6 cm) centred upon the greater wing of the right sphenoid bone, expanding into the middle cranial fossa, orbit and infra-temporal fossa associated with an aggressive periosteal reaction and a dural tail. There was significant mass effect on the right orbit, with proptosis and stretching of the right lateral rectus muscle and optic nerve, but no evidence of increased intracranial pressure from a radiological or clinical perspective. She also complained of an increase in abdominal girth, and CT imaging of the abdomen (Fig. 1D and E) revealed bilateral adrenal masses characteristic of adrenal myelolipoma in keeping with radiological evidence of chronic ACTH hyperstimulation (2), but no other pathology was evident.

The patient underwent debulking neurosurgery with stress dose intravenous hydrocortisone as perioperative cover. Histology demonstrated a meningioma (WHO Grade 1), which stained strongly positive for progesterone receptors and negative for oestrogen receptors (Fig. 1F and G). Improved adherence with glucocorticoid therapy was advised.

Periodically, glucocorticoid dosage was increased as high as 35 mg of hydrocortisone/24 h. On glucocorticoid therapy, the patients' most recent androstenedione concentrations were >30.0 nmol/L (reference range 1.7–16.4), 17-OHP 705 nmol/L (reference range <6.5 nmol/L) and testosterone 9.5 nmol/L (reference range 0–1.5 nmol/L). Plasma renin activity was consistently within the normal range with the last assessment being 3.7 ng/mL/h (erect reference range 1.0–4.2). Plasma aldosterone concentration was also normal on the last assessment 794.7 pmol/L (erect reference range 194–970 pmol/L). Renal profile and electrolytes were normal on the last review. The patient opted for a lower dose of glucocorticoid replacement of 15 mg of hydrocortisone/24 h as she felt higher doses were contributing to weight gain.

## Investigation

Laboratory investigations confirmed significant hyperandrogenaemia with testosterone 18.1 nmol/L (reference range 0–1.5 nmol/L), androstenedione >30 nmol/L (reference range 1.7–16.4) and 17-Hydroxyprogesterone (17-OHP) levels greater than the upper limit of detection of the assay at >180 nmol/L (reference range <6.5 nmol/L). ACTH concentration for this patient was 519 pg/mL (reference range 0–46 pg/mL). CT and MRI imaging (Fig. 1A, B and C) revealed a solid enhancing mass centred upon the greater wing of the right sphenoid bone, expanding into the middle cranial fossa, orbit and infra-temporal fossa associated with an aggressive periosteal reaction and a dural tail. There was significant mass effect on the right orbit, with proptosis and stretching of the right lateral rectus muscle and optic nerve. She also complained of an increase in abdominal girth, and CT imaging of the abdomen (Fig. 1D and E) revealed bilateral adrenal masses characteristic of adrenal myelolipoma in keeping with radiological evidence of chronic ACTH hyperstimulation (2), but no other pathology was evident.

## Treatment

The patient underwent debulking neurosurgery, and post-operatively, the tumour dimensions had decreased from 4.3 × 4.6 cm to 3.5 × 2.1 cm. Histology demonstrated a meningioma (WHO Grade 1), which stained strongly positive for progesterone receptors and negative for oestrogen receptors (Fig. 1F and G).

## Outcome and follow-up

Improved adherence with glucocorticoid therapy was advised. Periodically, glucocorticoid dosage was increased as high as 35 mg of hydrocortisone/24 h; however, during subsequent follow-up, her 17OHP and androstenedione levels remained markedly elevated. The patient opted for a lower dose of glucocorticoid replacement of 15 mg of hydrocortisone/24 h as she felt higher doses were contributing to weight gain. The meningioma was stable with no clinically significant growth after debulking after 4-year follow-up, and the patient was under neurosurgical follow-up who deemed there was no indication for further surgical intervention at present.

## Discussion

Meningiomas occur twice as frequently in women as in men. This gender difference has been attributed to the expression of sex steroid receptors by meningiomas; approximately 68% of meningiomas express receptors for progesterone (PR), whereas a smaller number express oestrogen receptors and androgen receptors (1).

To date, there have been two reported cases of growth of PR-expressing meningiomas in patients with

congenital adrenal hyperplasia (3, 4). Our patient also has evidence of bilateral giant adrenal myelolipomas, which is likely due to chronic ACTH hyperstimulation. These findings have never been reported in combination and suggest a link between poorly controlled CAH and development of these tumours. In patients with CAH and inadequate glucocorticoid replacement, stimulation of meningioma growth may possibly be influenced by elevated adrenocorticotrophin hormone (ACTH) or to elevated androgens and their precursors. Occurrence of these 2 meningiomas in CAH and further reports of meningioma growth in postmenopausal women receiving post-menopausal hormone replacement therapy, long-acting reversible contraceptives and pregnancy, suggest that progesterone or its precursors may play a role in the growth and pathogenesis of meningiomas; however, the data are conflicting. Indeed, epidemiological studies of factors associated with increased prevalence and accelerated growth of meningiomas have confirmed a link with exogenous sex steroids but cannot prove causality (5, 6).

In our patient, 17OHP concentrations were significantly elevated and most likely had been so for some time as evident by the bilateral adrenal myelolipomas and clinical features. Adrenal myelolipomas are rare benign adrenal tumours, which are composed largely of mature fat and can be identified by this characteristic on imaging studies (2). They have increasingly been reported in patients with poorly controlled CAH and have been hypothesised to occur as a result of chronic stimulation of the adrenal gland by high levels of adrenocorticotropic hormone (ACTH).

17OHP has been shown to have affinity for and bind to the progesterone receptor (varying binding affinities have been reported) (7). To our knowledge, the binding affinity of 17OHP to progesterone receptors in situations of supraphysiological levels of 17OHP in female patients with CAH has not been addressed. Estrone and testosterone also interact with human PR (8), both of which are also elevated in patients with poorly controlled CAH. Small *in vitro* studies have shown some growth of meningioma cells in the presence of progesterone, perhaps by the modulation of epidermal growth factor (9). In recent years, it has been increasingly recognised that adult patients with CAH are underrepresented in adult endocrinology clinics and are known to face multiple problems in adulthood including reduced fertility rates, greater rates of metabolic disease and osteopenia and subjectively reduced quality of life (10).

The growth of meningioma in our patient with CAH is an association (given the relative frequency of CAH and meningioma) and therefore routine imaging is not recommended in all patients with CAH. We hypothesise that the prolonged supraphysiologic exposure to 17OHP levels in our patient reported here may have accelerated meningioma growth by stimulation of the PR. Whether patients with poorly controlled CAH with elevated levels of 17OHP are at greater risk for meningioma growth or whether 17OHP accelerates meningioma growth needs further study. Similarly, whether reducing 17OHP will have an effect on tumour growth requires further study.

**Declaration of interest**
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

**Funding**
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

**Patient consent**
The patient has given informed written consent for the publication of this manuscript and has reviewed the manuscript prior to submission.

**Author contribution statement**
All authors were involved in writing and reviewing the manuscript. T O S, R K C, J G and M S were involved in the endocrine clinical management of patient. P G and J F were involved in radiological investigations. S Mc N and M F were involved in the neurosurgical aspects of the case.

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**Received in final form** 20 September 2016
**Accepted** 25 October 2016