

## CLINICAL VIGNETTE

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# Secondary Adrenal Insufficiency with a Pituitary Macroadenoma

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A 48-year-old woman presented to the emergency department after she developed new onset headache four days prior. The pain was initially mild but worsened and was associated with progressively worsening double vision on the fourth day. She described the pain as dull, generalized and aching in character with nausea. She denied fever, chills, neck stiffness, photophobia or phonophobia. She had no gait changes, weakness, falls or dizziness and no recent or remote head trauma. She had no recent travel, insect bites, or breast change. Her previous medical history was notable for hypertension, prediabetes, hyperlipidemia, and polycystic ovarian syndrome. Her family history included coronary artery disease in her father and uncles. Her mother has dementia. Medications include rosuvastatin and valsartan. Her previous surgical history was remarkable for an appendectomy and a remote Caesarian section. She was compliant with her medications and a low carbohydrate diet. On exam, she was alert and orientated with blood pressure of 90/50 mmHg and a heart rate of 84 beats per minute with a regular rhythm. Her BMI was 31 kg/m<sup>2</sup>. She had a left ptosis and left pupillary dilation. Her left orbit was swollen with restricted extra ocular movements and complete left CN III palsy. She had normal visual fields by confrontation testing and 20:20 visual acuity. The palmar creases and buccal mucosa were not hyperpigmented. Her sensation, strength, tone and reflexes were normal, as was the clinical assessment of her cerebellum. Thyroid gland was without abnormalities and her lung, heart, and abdomen exam was unremarkable. Laboratory testing was remarkable for sodium 124 mmol/L, normal urine sodium (39 mmol/L) and osmolality (502 mOsm/Kg). Her 9 am serum cortisol was normal at 1.2 mcg/dL (morning draw: 8-25 mcg/dL), an ACTH of 3.6 pg/mL (4 - 48 pg/mL), TSH 0.838 mcIU/mL (0.3 - 4.7 mcIU/mL), Free T4 of 1.5 ng/dL. Serum prolactin was 3.3 ng/mL (3 - 23.1 ng/mL), luteinizing hormone level of 0.6 mIU/mL (N), follicle stimulating hormone level of 3 mIU/mL (N), and an estradiol level less than 5 pg/mL. Her human chorionic gonadotrophin level was undetectable. Her IGF-1 level was 118ng/dL (52 - 328 ng/mL). Brain magnetic resonance imaging (MRI) showed an enlarged pituitary gland measuring 1.5 x 2.6 x 1.5 cm with abnormal signal and enhancement consistent with a macroadenoma (see Figure 1). The mass extended to contact with the optic chiasm. There was no evidence of intra-mass bleeding.

The patient was evaluated by neurosurgery, ophthalmology and endocrinology. Her clinical presentation and imaging findings were consistent with a pituitary macroadenoma. Her low adrenocorticotropic hormone (ACTH), serum sodium and

early morning cortisol level were consistent with secondary adrenal insufficiency. She was started on hydrocortisone 50mg three times daily and rapidly tapered to a morning dose of 20 mg of hydrocortisone and 10 mg hydrocortisone in the evening by hospital discharge. Her blood pressure and re-measurement of ACTH and cortisol improved. At one-month outpatient follow up, her cranial nerve palsy was significantly improved and her diplopia had resolved. Repeat hypothalamo-pituitary-axis testing returned to the normal range. She will continue to have close endocrine and neurosurgical follow up in the coming months. She was counseled about the need for higher doses of steroids during times of stress and illness.

### Discussion

Nonfunctioning pituitary adenomas are difficult to recognize clinically until they reach a size large enough to cause symptoms. This is primarily by mass effect on the surrounding tissue. The most common presentations include visual symptoms based on compression of the optic chiasm, an incidental pituitary mass seen on an imaging study for unrelated indications or endocrine hypofunction due to compression of normal pituitary tissue by the adenoma.<sup>1</sup> The most common type of vision anomalies are visual field loss, typically in the temporal fields superior temporal quadrantanopia or temporal hemianopsia which has gradual onset, and may not be noticed by the patients.<sup>2</sup> One or both eyes may be affected. Reduced visual acuity occurs when the optic chiasm is significantly compressed. Interestingly diplopia induced by oculomotor nerve compression resulting from lateral extension of the adenoma is less common, and seen in less than fifteen percent of patients. The primary endocrine abnormality in our patient was the development of secondary adrenal insufficiency (AI) from tumor-induced reduction of adrenocorticotrophic hormone release. Although her presenting symptoms were vague (fatigue and nausea) the development of acute AI is potentially life threatening. Patients with slow onset AI usually complain of being chronically fatigued. They often report joint pain, lack of appetite, unintentional weight loss, abdominal pain, nausea, and diarrhea.<sup>3</sup> Although hyperkalemia is observed only in primary AI, hyponatremia can occur in secondary AI. This is due to reduced glomerular filtration rate from low blood pressure, increased antidiuretic hormone secretion (SIADH), and possible concomitant central hypothyroidism (which was not seen in our patient).<sup>4</sup> Our patient's normal urine electrolytes suggested an element of syndrome of inappropriate anti diuretic hormone. Hyponatremia in secondary AI corrects with cortisol

supplementation and volume repletion. This will inhibit ADH release and allow excess water to be excreted. The administration of saline alone is ineffective in the presence of isolated cortisol deficit (ACTH deficiency) since the elevated ADH levels and consequent impairment in water excretion will persist.<sup>5</sup> Our patient's presentation made the diagnosis of secondary AI straight forward, as there was evidence of a pituitary mass on imaging in addition to a low morning cortisol and ACTH levels. Her symptoms responded quickly to hydrocortisone supplementation and there was no need for cosyntropin stimulation testing to confirm the diagnosis of secondary adrenal insufficiency. As in all cases of symptomatic pituitary lesions, laboratory tests to assess the hypothalamic-pituitary axis were ordered and all except cortisol and ACTH were normal. Macroadenomas often present with evidence of biochemical hypopituitarism. Rarely, gonadotroph adenomas present with hormonal hypersecretion that causes ovarian hyperstimulation or precocious puberty.<sup>6</sup> Our patient had a diagnosis of polycystic ovarian syndrome but this was likely unrelated to the pituitary mass as her FSH and LH were within the normal range. Gonadotroph adenomas, can occur as part of the multiple endocrine neoplasia type 1 (MEN1) syndrome.<sup>7</sup> This rare genetic syndrome can present with tumors of the parathyroid gland, anterior pituitary, and pancreatic islet cells. Fortunately, this was not found in our patient. When patients are symptomatic from nonadenomatous cell compression by the macroadenoma in the pituitary gland, symptoms tend to be nonspecific, fatigue and lethargy are not the primary reason that the patient seeks care, as was the case in our patient. The most common hormone deficiency seen is hypogonadism and is more likely to manifest in premenopausal females.<sup>8</sup> In men with nonfunctioning pituitary adenomas, nearly forty percent had low serum gonadotropins causing low serum testosterone, reduced libido, and erectile dysfunction. About one third of the women of reproductive age had menstrual irregularities.<sup>9</sup> Based on several studies, the most commonly seen biochemical pituitary hormone deficiency in non-functional macroadenomas is growth hormone (GH) deficiency.<sup>9</sup> This is assessed by checking IGF-1 (insulin like growth factor one) which is a more reliable assay than GH. Low LH and FSH (hypogonadotropic hypogonadism) are seen in just over seventy percent of those tested. Low ACTH, as seen in our patient, was only seen in thirty percent of patients in population studies. Likewise, low TSH levels from central hypothyroidism was seen in less than twenty-five percent.<sup>9</sup>

This case demonstrates the acute presentation of a neuro-ophthalmologic emergency that presented to an internist for management based on secondary adrenal insufficiency. Hospitalists in close consultation with endocrine, ophthalmology and neurosurgery provided her non-operative management. After extensive assessment and emergent steroid treatment, her acute life and vision threatening symptoms resolved.

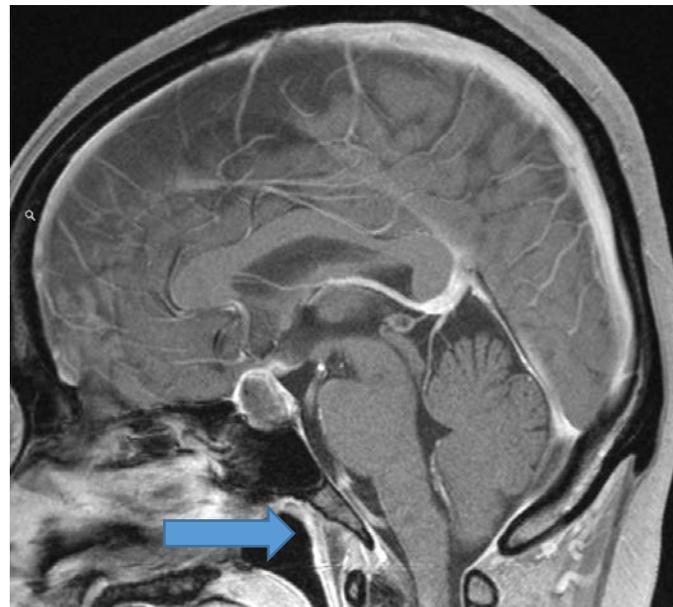


Figure 1. Magnetic resonance imaging (MRI) of the brain with an enlarged pituitary gland measuring 1.5 x 2.6 x 1.5 cm with abnormal signal and enhancement in keeping with a macroadenoma (Arrow). The mass extended to contact with the optic chiasm. There is no evidence of intra-mass bleeding.

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