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CLINICAL VIGNETTE

Acromegaly Uncovered by West Nile Meningoencephalitis

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Case Report

A 63-year-old Hispanic male with hypertension, type II diabetes mellitus, and bilateral knee osteoarthritis presented with acute onset of severe headache, fever, fatigue, and light-headedness. He was born in Mexico and immigrated to Southern California decades prior. His only medication was ibuprofen for osteoarthritis. He lived with his wife and previously worked as a gardener.

The patient's blood pressure was 119/84 mmHg, heart rate 140 beats per minute, respiratory rate 23 breaths per minute, and temperature 40ºC. He was obese with oily, diaphoretic skin, coarse facial features, frontal bossing, prognathism, large hands with thick fingers, and a deep, resonant voice. There were no neurological deficits and negative Kernig and Brudzinski signs.

Initial studies revealed a lactic acid level of 2.5 mmol/L (upper limit of normal (ULN) 2.2 mmol/L) and normal complete blood count and renal and liver studies. Blood glucose was 184 mg/dL. Brain CT was normal except for an incidental enlarged 12 mm pituitary gland (**Figure 1**). Blood cultures and HIV test were negative; urine culture grew greater than 100,000 colony-forming units of *E Coli*. A lumbar puncture had an opening pressure of 28 cm H_20 with cerebrospinal fluid (CSF) showing 4 WBC/μL, 22 RBC/μL, glucose 89 mg/dL, protein 87 mg/dL, and a negative gram stain.

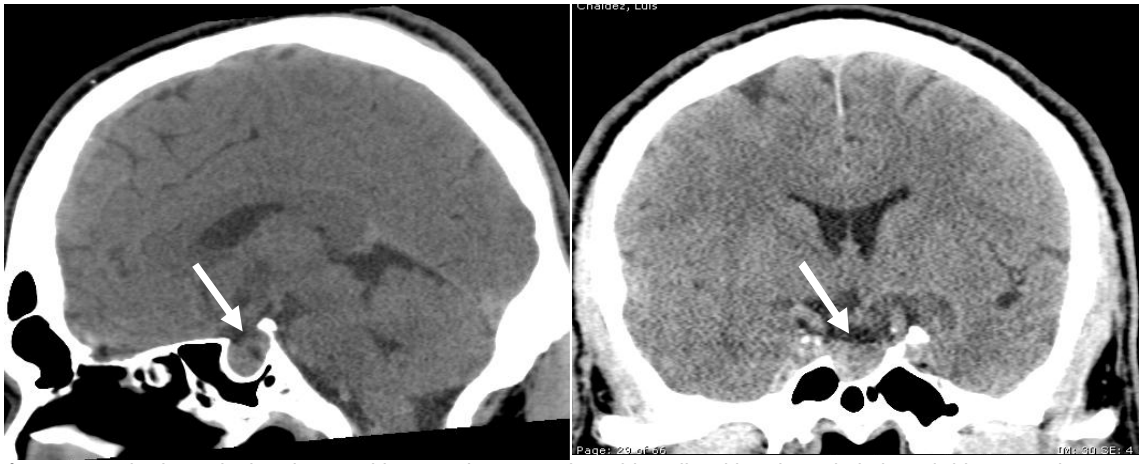

Figure 1. CT brain sagittal and coronal images demonstrating wide sella with enlarged pituitary (white arrows).

Acyclovir and empiric antibiotics for meningitis were begun. The patient's headache and fever resolved on day three. CSF bacterial and fungal cultures were negative. CSF viral polymerase chain reaction analysis was positive for West Nile virus (WNV). Empiric antibiotics were discontinued and he was discharged on day six.

Pituitary function assessment showed low testosterone 103 ng/dL (lower limit of normal 241 ng/dL), elevated insulin-like growth factor-1 (IGF-1) 650 ng/mL (ULN 228 ng/mL), and normal levels of growth hormone (GH, 7.0 ng/mL, ULN 10 ng/mL), prolactin, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, free T4, and adrenocorticotropic hormone. A cosyntropin stimulation test was normal. Hemoglobin A1C was 6.5%. The patient was started on intramuscular testosterone 200 mg every 2 weeks.

Outpatient brain magnetic resonance image (MRI) showed a large T1 hypointense, hypoenhancing intrasellar mass measuring 12.5 x 16 x 12.2 mm, consistent with a pituitary macroadenoma (at least 1 cm, **Figure 2**). At an outpatient Endocrinology evaluation, the patient denied changes in ring or shoe size, but stated he has had sweaty, oily skin and that 7 of his 8 children also have coarse facial features. Formal visual field evaluation elicited bilateral superior hemianopia. Repeat labs revealed an IGF-1 of 1084 ng/mL and a normal random GH. A diagnosis of acromegaly and hypogonadotropic hypogonadism was established. The patient was referred to neurosurgery for pituitary macroadenoma resection.

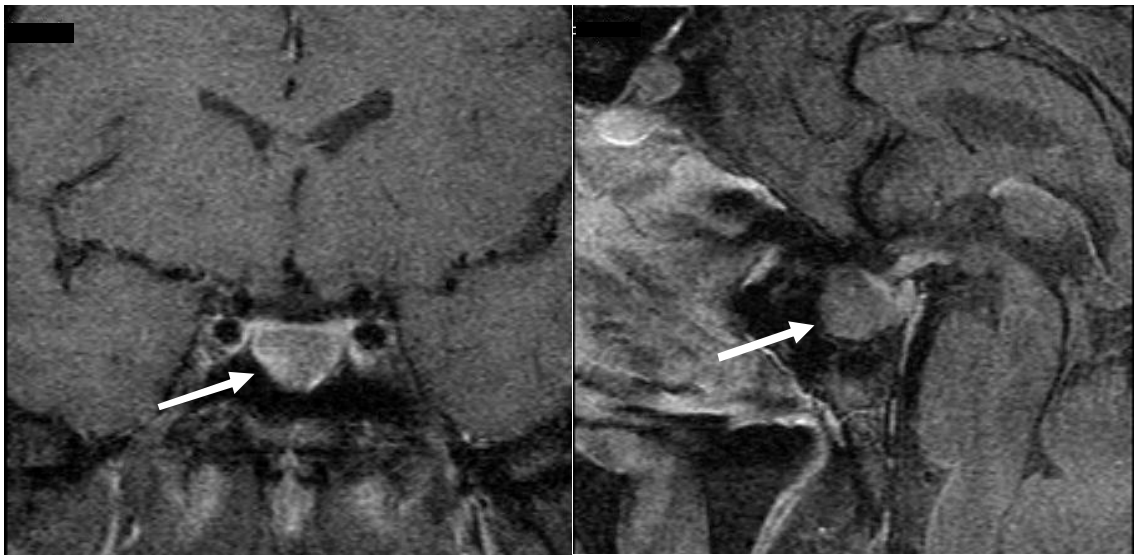

Figure 2. MRI brain sagittal and coronal images demonstrating wide sella with enlarged pituitary (white arrows).

Discussion

Acromegaly is a rare endocrine disorder, with over 90% of cases secondary to a benign monoclonal GH-secreting pituitary adenoma.[1] Excessive GH release stimulates the liver to produce excess IGF-1, which binds to muscle, cartilage, bone, lung, liver, renal, and nerve cell receptors, stimulating cell growth and multiplication and inhibiting apoptosis.[1] The incidence and prevalence are roughly 3 and 60 cases per million, respectively.[2] Acromegaly occurs equally in men and women, with a mean age of diagnosis around 45 years. The diagnosis has been made in all age groups; the equivalent pediatric condition is gigantism.

Diagnosis

Acromegaly is often diagnosed by primary care physicians who suspect the condition based on acral bone growth, skin thickening, coarse facial features, diaphoresis, or the metabolic syndrome.[1,2] Because physical changes occur insidiously, patients often must be asked whether they have outgrown several ring, shoe, or hat sizes or look different from past photos. More than half of cases are diagnosed by subspecialists after evaluation for arthralgia, visual field deficits suggestive of a pituitary mass, refractory hypertension, congestive heart failure, abnormal bite and dentition, diabetes, obstructive sleep apnea, or menstrual dysfunction.[1-3] **Table 1** summarizes organs affected and their phenotypic and physiologic consequences.

The diagnosis is occasionally suspected after an incidental finding of a pituitary lesion on brain CT or MRI. "Incidentalomas" occur in 3.1% to 22.5% of the population and typically represent a benign condition without hormonal hypersecretion.[4,5] Nevertheless, incidentalomas may hypersecrete pituitary hormones; 2% to 3% of macroademonas[6] hypersecrete GH.

Acromegaly can be confirmed by several biochemical studies. It has classically been diagnosed by lack of GH suppression following an oral glucose tolerance test (OGTT). This has grown out of favor as it is cumbersome and not

Table 1 – Effects of Excess Growth Hormone on Various Physiologic Systems

Local Mass Effects

Effect on production of pituitary hormones other than GH • Adrenal insuffiency (decreased ACTH) • Galactorrhea (increased prolactin resulting from decreased dopamine inhibition) • Goiter/thyromegaly (decreased TSH) • Hypogonadism (decreased FSH and LH) • Menstrual abnormalities (decreased FSH and LH)
Headache
Spontaneous cerebrospinal fluid (CSF) rhinorrhea from extension into sphenoid sinuses
Visual changes: • Abnormal color vision • Abnormal pupillary light reaction • Bitemporal hemianopsia or bitemporal superior quadrantanopsia • Decreased visual acuity (monocular or binocular) • Ophthalmoplegia, diplopia, or ptosis from cavernous sinus compression • Optic nerve atrophy

Systemic Growth Hormone Effects

System	Pathology
Cardiovascular	Cardiomyopathy, Congestive heart failure Hypertension, Left ventricular hypertrophy
Endocrine	Diabetes mellitus Hypertriglyceridemia Impaired glucose intolerance Low renin/increased aldosterone Low thyroxine-binding-globulin Multiple endocrine neoplasia type 1
Gastrointestinal	Colon cancer, Colon polyps Hepatosplenomegaly
Integument	Acral enlargement. Hyperhidrosis (increased perspiration) Oily skin, Skin tags
Musculoskeletal	Arthalgia, Arthritis, Frontal bossing Gigantism, Myopathy (proximal) Spinal stenosis
Oral/Dental	Glossomegaly, Malocclusion, Prognathism Separation of lower jaw teeth
Neurologic	Carpal tunnel syndrome Neurogenic claudication (from spinal stenosis) Radiculopathy
Renal	Renomegaly
Respiratory	Sleep apnea

very sensitive for acromegaly. In addition, other processes, such as diabetes mellitus, puberty, pregnancy, hepatic and renal disease, and anorexia nervosa also lack GH suppression.[7] The OGTT has been replaced by direct serum IGF-1 assays, which correlate better with acromegaly signs and symptoms. However, up to 30% of patients may have biochemical assays inconsistent with the patient's signs and symptoms; acromegaly has been reported in the presence of a normal OGTT or IGF-1 level.[7,8] In such cases, both the OGTT and IGF-1 levels should be measured to confirm the diagnosis of acromegaly; if both are negative, another cause of the patient's symptoms should be explored. Once suspected on the basis of clinical or hormonal evaluation, the pituitary should be imaged, preferably by MRI.[9]

Early diagnosis of acromegaly is important, as much of the morbidity and two-fold mortality compared with the general population can be reduced or eliminated with adequate treatment. Cardiovascular diseases (coronary artery disease, congestive heart failure, and stroke) are the most common acromegaly-associated causes of death.[10] Patients also have a higher incidence of colon polyps and up to 14-fold increase in colon cancer and 2.5-fold increase in colon cancer mortality.[11] The morbidity and increased mortality associated with acromegaly are largely related to duration of exposure to elevated serum IGF-1 and GH levels; early detection and treatment can limit many complications.[2,12] Unfortunately, acromegaly usually goes undiagnosed for quite some time, with an average 8-year latency from the onset of symptoms or changes in photographic appearance to the time of diagnosis.[2]

Treatment

Treatment goals of acromegaly include age-adjusted normalization of IGF-1 levels and post-OGTT nadir GH levels less than 1.0 µg/L, levels at which recurrence is unlikely.[1,2] First-line treatment is surgical for most patients. The transsphenoidal approach is most common and is particularly useful for microadenomas and decompression of mass effect on the optic tracts.[1] Outcomes following surgery are good, with relapse rates of roughly 10%, which is thought to be related to residual tumor.[1] The main surgical complications[1] are hypopituitarism (30%) and diabetes insipidus (3%). Surgery may not be first-line therapy if full resection is unlikely (e.g. - cavernous sinus invasion) or when surgery is unsafe.[1]

Alternatives to surgery include traditional external beam radiotherapy and the gamma knife. Normalization of serum IGF-1 levels may take years following radiation therapy; only 30% to 35% of patients fully respond after 10 years[1] and 50% will develop hypopituitarism within 10 years. For these reasons, radiation therapy is largely reserved for recurrent pituitary tumors following surgery or inpatients who cannot tolerate medical therapy.

Medical therapy consists of somatostatin analogs (octreotide and lanreotide) which, through selective receptor binding, act on the pituitary to suppress GH production.[1] These agents are highly effective, with 80% of patients experiencing normalization of IFG-1 and GH levels and improved symptoms. In addition, tumor bulk decreases in 50% of patients treated with somatostatin analogs.[1] Despite the efficacy and safety of these agents, somatostatin analogs are largely reserved for patients who have failed surgery or radiation, have large extra-sellar tumors, or cannot undergo surgery.[1] These agents are expensive and must be used for life, secondary to recurrence of symptoms and tumor bulk following drug discontinuation.

Successful treatment improves local mass effects and systemic health, particularly cardiovascular function, including reducing left ventricular mass, lowering heart rate and blood pressure, and increasing ejection fraction.[13] Patients should undergo earlier and more frequent colonoscopic screening than the general population, starting at age 40 and repeated every 3 years if an ademona is discovered or IGF-1 levels are above age-adjusted ULN, or every 5 years if colonoscopy is negative or reveals a hyperplastic polyp.[11] With appropriate management, patients can achieve a mortality risk similar to the general population.[14] However, adequate treatment is still associated with long-term morbidity, including a 22% incidence of hypertension and arthropathy.[2]

Acromegaly patients require lifelong evaluation. Yearly testing of both IGF-1 and post-OGTT nadir GH levels is important, as elevation in either assay is associated with higher recurrence rates and should be treated.[1] Pituitary hormones should be assessed 6 to 12 weeks after surgery or initiating medical treatment, as IGF-1 may take several

months to normalize.[14] Following surgery or radiotherapy, patients should have periodic imaging, visual field evaluation, and global pituitary hormone assessment; hypopituitarism should be treated accordingly. After radiotherapy, long-term hormone evaluation is required to assess efficacy and the development of pituitary failure.

Conclusion

This patient's acromegaly went undiagnosed for many years and his morphologic changes were unnoticed due to the gradual nature of the disease. There also seems to be a familial propensity towards coarse facial features amongst the patient's children, so changes in his appearance may have simply been attributed to normal aging. The patient's knee pain was probably dismissed as arthritis secondary to years as a gardener.

This case highlights how a thorough history and physical examination can reveal additional important conditions separate from a presenting, apparent life-threatening condition. As it turned out, WNV meningoencephalitis was not this patient's most concerning condition; most cases without focal neurologic deficits resolve without sequellae.[15] Acromegaly, in contrast, confers significant long-term morbidity and mortality risk. It is likely that WNV meningoencephalitis was a blessing in disguise, granting him access to health care and the appropriate treatment that will likely extend his life by years.

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