Synapse
a clinical resource
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Evaluation of Incidental Pituitary Adenomas

Michael Chan, MD

Pathophysiology

The most common type of pituitary mass is an adenoma. A microadenoma is less than 1 cm in diameter while a macroadenoma is larger than 1 cm. Adenomas fall into two categories, secreting and non-secreting adenomas. Most adenomas are non-secreting tumors and cause problems by compressing important structures nearby such as the pituitary gland (resulting in hormone disturbances) and the optic chiasm (with resultant visual loss). Secreting adenomas may be discovered via endocrinologic abnormalities, most commonly galactorrhea or infertility in the case of prolactin secreting tumors (prolactinomas) or gonadotrophin secreting tumors (gonadotrophin release factors). Rarely, pituitary adenomas can be malignant (less than 3%).

Presentation

Patients may present with loss of their peripheral vision, galactorrhea, infertility, or acromegaly. Endocrine disturbances can be vague and full work up must be attempted to define the disorder.

More commonly, the pituitary adenoma may be found incidentally on a brain scan performed for an unrelated indication such as headache, dizziness or trauma.

Differential Diagnosis

Pituitary lesions can sometimes be other tumors such as craniopharyngiomas, Rathke's cyst, arachnoid cyst, germinoma, or meningiomas. Metastatic carcinoma can also present as a pituitary lesion. Non-neoplastic lesions such as infections or aneurysms can also present as a pituitary mass and can create compression which can affect vision or decrease hormone production of the pituitary gland.

Diagnosis and Work Up

A formal pituitary lesion work up always includes a comprehensive endocrinological panel consisting of prolactin, cortisol, ACTH, TSH, T4, LH, FSH, GnRH, IGF1, growth hormone etc. Usually a referral to an endocrinologist is warranted since post-operative management of hormone status and supplementation may be required.

"More commonly, the pituitary adenoma may be found incidentally on a brain scan performed for an unrelated indication such as headache, dizziness or trauma."

Formal visual examination (Goldman Visual Field Examination) by an ophthalmologist is also recommended before and after treatment, especially if the patient has visual loss prior to treatment.

MRI brain with sellar protocol with and without contrast allows for high definition visualization of pertinent anatomy.

Consultation with neurosurgery is usually required for surgical options. The neurosurgeon will usually call in an ENT surgeon for assistance with the surgery. Rarely is an oncology consultation required.


Michael Chan, MD

Treatment

Small pituitary tumors <1 cm without symptoms can be followed with MRIs. If no significant growth is observed over a 10-year period, then the patient may be discharged.

continued on page 3

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Portable Monitoring for Obstructive Sleep Apnea

Robert Dias, MD

Portable monitoring (PM), or home/unattended/out-of-center sleep testing, is being increasingly utilized to more readily and cost-effectively diagnose a growing number of patients at high risk of obstructive sleep apnea (OSA). In North America, the prevalence of OSA is approximately 20-30% of males and 10-15% of females, with the risk increasing with age, and the risk in postmenopausal women approaches that of men. Untreated sleep apnea is associated with an increased risk of cardiovascular and cerebrovascular morbidity and mortality as well as cognitive impairment, underscoring the importance of early diagnosis and treatment.

The International Classification of Sleep Disorders (3rd Edition) states that the diagnosis of OSA in symptomatic adult patients requires five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals (RERAs)) per hour. In general, the AHI (Apnea-Hypopnea Index) or RDI (Respiratory Disturbance Index which includes RERAs in addition to apneas and hypopneas) can be used to classify the severity of OSA (mild = 5 to <15 events/hour; moderate = 15 to <30 events/hour; and severe ≥30 events per hour).

OSA may be diagnosed through in-laboratory polysomnography (PSG), the gold standard (Type I/attended study with oversight by a sleep technologist), or through various PM options. The most comprehensive is a Type II study which includes EEG, as well as monitoring of eye movements and muscle tone, to enable staging of sleep and scoring of RERAs in addition to the parameters included on the more common Type III study which monitors a minimum of four channels: airflow, respiratory effort, oxygen saturation, and heart rate. The American Academy of Sleep Medicine guidelines advise PM may be used as an alternative to PSG for the diagnosis of OSA in patients with a high pretest probability of moderate to severe OSA, in conjunction with a comprehensive sleep evaluation by a board-certified sleep specialist. Negative or technically inadequate PM results should prompt in-laboratory PSG, particularly given Type III studies are less sensitive without inclusion of EEG to enable scoring of RERAs.

Various sleep questionnaires may be utilized to identify patients at high risk for OSA for which PM may be considered, such as the STOP BANG questionnaire, where an answer of yes to three or more of the following questions has a sensitivity of 83.6% for AHI >5, 92.9% for AHI >15, and 100% for AHI >30 on PSG. The STOP BANG questions are:

1) Do you **S**nore loudly (louder than talking or loud enough to be heard through closed doors)?
2) Do you often feel **T**ired, fatigued, or sleepy during daytime?
3) Has anyone **O**bserved you stop breathing during your sleep?
4) Do you have or are you being treated for high blood **P**ressure?
5) Is your **B**MI >35?
6) Is your **A**ge >50?
7) Is your **N**eck circumference >40 cm (15.7 inches)?
8) **G**ender: Male?

continued on page 3

Portable Monitoring for Obstructive Sleep Apnea—continued from page 2

Additional risk factors for OSA include congestive heart failure, stroke, hypothyroidism, end-stage renal disease, chronic lung disease, polycystic ovarian syndrome, smoking, and diabetes. In a study by Foster et al, 87% of obese patients with Type 2 diabetes had OSA on PSG. Positive family history, ethnicity, and craniofacial risk factors (retrognathia, narrow oropharynx) may also raise the likelihood of OSA. For lesser degrees of obesity, Asians are at risk for a more severe degree of illness relative to Caucasians.

"In North America, the prevalence of OSA is approximately 20-30% of males and 10-15% of females, with the risk increasing with age, and the risk in postmenopausal women approaches that of men."

Contraindications for PM include chronic obstructive pulmonary disease, home oxygen, risk factors for central sleep apnea (such as congestive heart failure, opiate medication or stroke), parasomnias (sleepwalking, dream enacting behavior/REM Sleep Behavior disorder), concern for limb movements, or inability to perform home sleep testing due to cognitive impairment.

Sleep medicine evaluation is encouraged if the above comorbidities are present or if the diagnosis of OSA has been made by PM. Serial smartcard checks in clinic can be performed on current PAP (Positive Airway Pressure) devices to ensure ongoing optimal settings and clinical response.

For references, comments, or questions, please email DignityHealthNeuro@DignityHealth.org. ■

Robert Dias, MD

Evaluation of Incidental Pituitary Adenomas—continued from page 1

Treatment options for prolactinoma start with dopamine agonists such as carbergolin (Dostinex) and Bromocriptine, which can completely resolve the tumor. Growth hormone secreting adenomas can be treated with somatostatin analogs such as octreotide. Conventional chemotherapy is not the first line for adenomas. Radiation is not usually offered before surgery.

Recurrent or refractory prolactinomas and adenomas are treated primarily through surgical resection. Endoscopic approaches through the nose is a joint surgery between a neurosurgeon and an ENT surgeon. Opening up the sphenoidal sinus in the back of the nose allows access to the sella turcica where the pituitary tumors are located at the base of the brain. The tumor is resected through the nose. Risks include CSF leak, injury to cavernous sinus, and cavernous carotid arteries and loss of pituitary hormone function. Post-operative care is performed in the ICU and careful study of the patient's serum sodium levels, urine output, and urine specific gravity allows for treatment of post-operative diabetes insipidus, caused from surgical manipulation of the hypothalamus and the resultant ADH deficits.

Residual or recurrent tumors may be treated by surgical reexploration. External beam radiation treatment may also be an option after surgery. Follow-up MRIs are performed for up to 10 years after surgery.

Outcome

Ten year tumor-free progression can be up to 94%. Stable patients usually do not require MRI follow-up after 10 years. ■

Myelitis: Weakness and Numbness of Legs of Rapid Onset is an Emergency!

John Schafer, MD

Sensory symptoms and weakness of legs with onset over hours or a few days is a medical emergency, even when objective findings are mild. All too often patients with this presentation are sent home from the office visit or emergency room only to return soon, unable to walk.

Consider the case of a healthy 36 year old woman who three days ago noticed numbness and tingling in the soles of her feet while showering. Over the next 72 hours the sensory symptoms ascended her legs to her perineum. She had an episode of urinary incontinence, and she had difficulty walking because she could not feel her legs. She had no pain, and no sensory or motor symptoms were present in her face or arms. On examination, power was 5/5 in all limbs, knee jerks were 2+ and ankle jerks trace. Hypesthesia to pinprick was present to mid calf, and vibratory sensation on great toes was markedly reduced. The examining physician considered sending her home since she had no weakness and looked so good. The decision to admit her to the hospital was fortunate, because when she awakened the following morning she was unable to walk from her bed to the bathroom.

The main diagnostic considerations in this case are myelitis and Guillain Barre syndrome. Causes which are less likely include infection or compression mass by a mass lesion, such as abscess, hematoma or epidural metastatic tumor. All of these disorders will most likely get worse, and treatment is available which can greatly improve the course and shorten the period of recovery if started early. Therefore, this presentation is a medical emergency which mandates admission to the hospital and rapid evaluation and treatment.

Several clinical features may differentiate between myelitis and Guillain Barre syndrome in this patient. Restriction of symptoms to the lower body and legs, and especially paresthesias in the perineum, as well as her episode of urinary incontinence strongly suggest a spinal cord localization. In Guillain Barre syndrome the sensory symptoms are more likely to involve distal upper and lower extremities, and ankle jerks are usually (though not invariably) lost early.

An MRI scan of the spine should be the initial test. Commonly, but incorrectly, an MRI scan of the lumbar spine is ordered because the symptoms are in the legs. However, the perineal sensory and bladder symptoms are most likely caused by lesions in the spinal cord itself above the level of the lumbar scan. Also, the actual lesion is sometimes found at a higher level than expected based on the neuroanatomy of sensory levels. In this case an MRI of the cervical, thoracic and lumbar spine showed an area of hyperintensity and gadolinium enhancement in the low thoracic spinal cord, consistent with myelitis.

"Sensory symptoms and weakness of legs with onset over hours or a few days is a medical emergency, even when objective findings are mild. All too often patients with this presentation are sent home from the office visit or emergency room only to return soon, unable to walk."

The next test should be a lumbar puncture with tests for protein, glucose, cell count, culture (if cells are present), and a multiple sclerosis panel. Hallmark findings in Guillain Barre syndrome are high protein and few or no cells. Protein in myelitis may not be as high, and cells may be present. Very early after onset, the spinal fluid can be normal in any of the causes. Presence of oligoclonal bands signals a demyelinating process, which can include multiple sclerosis. Other causes of myelitis include other autoimmune disorders, neuromyelitis optica, sarcoidosis, lyme disease and some types of infection.

Treatment of myelitis begins with corticosteroids but may include plasma exchange or IVIG. Treatment for Guillain Barre syndrome is plasma exchange or IVIG. Both disorders tend to have long recovery, over many months in Guillain Barre syndrome, and delay by even a matter of hours could conceivably add weeks or months to recovery. ■

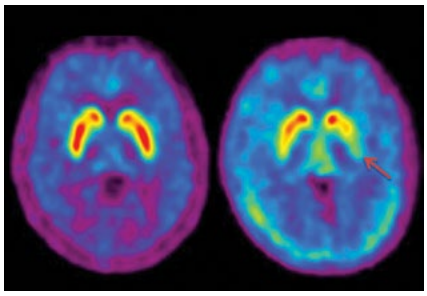
John Schafer, MD

Differentiating Tremors

Ehsan Hadi, MD

Tremor is the most common form of involuntary movement and a common reason for referral to neurology movement disorder clinics. Tremor is a hyperkinetic disorder, described as rhythmic oscillations of body parts, produced by alternating contractions of agonist and antagonist muscles. Since tremor can have very distinct associated characteristics, pattern recognition is important.

Tremors can be classified according to their phenomenology, distribution, frequency or etiology. Tremor can be seen in different positions, at rest and with action. Rest tremors are seen when the body part is fully supported against gravity, as in Parkinsonism. Action tremor is seen with voluntary movements and can be subdivided into postural, kinetic, task specific and isometric. Action tremor occurs with voluntary movements, as in essential tremor, task specific tremor or orthostatic tremor, which is tremor of the legs when standing. Tremors can involve a variety of anatomic locations, including but not limited to limbs, head or voice. Tremor can vary in frequency, the setting in which it occurs and body part involved. The frequency can range from less than 4Hz, as seen in Parkinsonism, to high frequency of greater than 7Hz, as seen essential tremor. Tremor can have many causes, ranging from enhanced physiologic tremor, tremor secondary to an offending medication such as antipsychotics, lithium, steroids etc., tremor associated with structural lesions, or peripheral neuropathy and tremor due to a variety of metabolic disorders, including copper metabolism (Wilson's disease), X-linked disorders (FXTAS), and neurodegenerative disorders with Parkinsonism and Spinocerebellar ataxias. Tremor can also be psychogenic. The most common type of tremor is essential tremor, which is five times more common than Parkinsonian tremor. Essential tremor typically has a strong family history, and several genes have been identified giving marked phenotypic and genetic heterogeneity.



SPECT scan: Normal versus Parkinsonism—decreased asymmetric dopamine uptake over the Putamen.

"Management of tremor is symptomatic, and depends on the underlying etiology and the extent to which it affects day-to-day functioning."

Diagnosis and characterization of tremor is typically made on clinical examination, and various criteria have been proposed for the diagnosis of Tremor, such as the *NIH Essential Tremor diagnostic criteria, UK Parkinson's disease Rating scale* and others. In unique, complex situations, radiotracer imaging, such as Dat Scan, can be helpful in differentiating essential tremor from tremor originating from pre-synaptic dopamine loss.

Management of tremor is symptomatic, and depends on the underlying etiology and the extent to which it affects day-to-day functioning. Treatment could be as simple as discontinuing caffeine or an offending medication or treating the underlying metabolic abnormality, to use of pharmacological agents such as Primidone, Propranolol, Topiramte, Gabapentin, Clonazepam, anticholinergics, Carbidopa-levodopa or botulinum toxin, depending on the etiology of tremor. Surgical option such as deep brain stimulation (DBS) can also be considered in medically intractable tremors and has proven to be quite effective. Tremors can be the cause of immense anguish for our patients, given its association with neurodegenerative disorders, its adverse effect on quality of life and even as a source of embarrassment. It is thus essential to be able to clearly delineate the various types of tremors and underlying etiologies accurately. Finding out that they don't have Parkinson's disease can bring immense relief for the patients, which is also satisfying to us as providers. ■

Ehsan Hadi, MD

Ten Key Points to Know About Non-Epileptic Spells

Edwin A. Cruz, MD

1. Non-Epileptic Spells (NES) are common. 25-30% of patients admitted to a tertiary level Epilepsy Center with presumed Intractable Epilepsy are ultimately diagnosed with NES.

2. NES mimic epileptic seizures, but are not due to abnormal brain activity, and have normal or non-epileptiform EEGs.

3. NES can be divided into:

   a. Psychogenic—malingering, somatization, conversion disorder

   b. Organic—sleep disorder (e.g. cataplexy); movement disorder (e.g. dystonia, non-epileptic myoclonus); complicated migraine; breath holding spells; syncope

4. Epidemiology:

   a. NES are more common in women than men (like most somatoform disorders)

   b. They typically begin in early adulthood, and one should be cautious in diagnosing NES when the onset is early childhood or old age

5. Historical Features—NES is often associated with recurrence of spells despite multiple antiepileptic drugs, seizures in presence of the doctor or an audience and a history of psychiatric illness or of sexual or physical abuse.

   NES can also occur in patients with traumatic brain injury, including veterans who are often treated as epileptics with lower index of suspicion for NES and longer delay to getting VEEG for definitive diagnosis of NES.

6. Semiology—NES have gradual onset, waxing and waning characteristic; asynchronous limb movements, pelvic thrusting, opisthotonus and also intact sensorium despite bilateral generalized convulsions.

   Clinical Pearl—NES are associated with Sustained Eye Closure, whereas eyes are usually open in epilepsy.

   Clinical Pearl—NES are associated with biting the tip of tongue, whereas the side of the tongue is usually injured in epilepsy.

7. Diagnosis is only possible with Simultaneous Video-EEG to document the abnormal behavior plus a normal or non-epileptiform EEG.

8. Prolactin Level—Check within 20 minutes after seizure onset and again 12 hours later, by which time levels should have returned to baseline after post-ictal elevation. A 3-fold increase in prolactin level is predictably seen after an isolated generalized or temporal lobe seizure. Patients with more than two seizures in 12 hours have progressively lower elevations, presumably because stored prolactin is exhausted. Seizures of non-temporal lobe origin may not lead to prolactin level elevation.

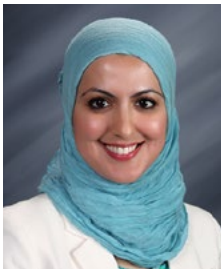
9. False positive diagnosis of epilepsy may be due to over interpretation of EEG or MRI. EEG normal variants, such as wicket spikes, mu rhythm, vertex waves, and even drowsy patterns, are often misinterpreted as being epileptiform. In patients with a past EEG report of "spikes," delay to diagnosis is 12.5 years as compared to 7.1 years in patients without an abnormal EEG report.

10. Treatment requires a multidisciplinary team. Anti-seizure medications are not necessary and can be harmful. Phenobarbital or benzodiazepines have to be tapered slowly to prevent drug withdrawal seizure. Behavioral modification therapy has been found to be most effective. It is also important to emphasize to the patient that "they are not crazy," that "it is not just in their mind," or that "they are making it up." It is important to educate the patient and the family that distress, fear, anger or a past traumatic experience can be channeled to an involuntary somatic response. Thus the underlying psychiatric illness has to be treated. ■

Edwin A. Cruz, MD

Brainwaves: Updates from Dignity Health Neurological Institute

Dignity Health Welcomes New Neurology Specialists



Sabeen Lulu, MD, MCR, a graduate of the Dubai Medical College in United Arab Emirates, is a diplomat of the American Board of Psychiatry and Neurology. She completed her residency in neurology at Wayne State University/Detroit Medical Center. She interned at Sinai Grace Hospital in Detroit and completed a fellowship in multiple sclerosis at University of California, San Francisco. Dr. Lulu's special clinical interests include multiple sclerosis and related disorders.

Dr. Lulu earned a master's degree in clinical research from University of California San Francisco. Dr. Lulu says she sees the physician and patient as a team, and as such she strives to involve patients in the decision-making process.

Howard Fan, MD, a graduate of the St. George University School of Medicine in Grenada, is board certified in neurology. He was chief resident at University of Texas Health Science Center at Houston. He interned at SUNY Downstate Long Island College Hospital in New York and completed a fellowship in neurocritical care at the UCLA David Geffen School of Medicine.

Dr. Fan's special clinical interests include traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke, status epilepticus, intracranial monitoring and therapeutic hypothermia.

Prior to attending medical school, Dr. Fan earned a master's degree in biomedical engineering from the UCLA Henry Samueli School of Engineering and Applied Science.

Today, both Dr. Lulu and Dr. Fan are proud to be serving the Greater Sacramento community as new additions to the team of renowned specialists comprising Dignity Health Neurological Institute of Northern California.

Dignity Health Telemedicine Network Continues to Thrive and Grow

The Dignity Heath Telemedicine Network (formerly the Mercy Telehealth Network) began in 2008 in the Northern California Sacramento service area, thanks to a generous charitable contribution from the Elliott Family Foundation. At the time there was no telemedicine network, and while Dignity Health had a strong stroke program at its Sacramento hospitals (Mercy General Hospital and Mercy San Juan Medical Center), Mercy Hospital of Folsom had limited neurology coverage. Out of the need for more rapid and available neurological consults, Dignity Health put in place robotic telemedicine (or remote presence technology) to bring the expertise from Mercy General Hospital and Mercy San Juan Medical Center to patients who needed it in Folsom and other hospitals.

During its first full year of service in 2009, the Mercy Telehealth Network provided 16 Telestroke Consults. By the end of the current fiscal year (ending June 2015), the Dignity Health Telemedicine Network (DHTN) will have performed more than 14,000 Telemedicine consults throughout 39 facilities in California, making the DHTN one of the largest acute care telemedicine networks in the country. The services with the highest volume are neurology, psychiatry, intensive care, and nephrology. Thanks to the dedication of the physician specialists and the DHTN team, patients are receiving highly specialized care in a timely fashion.

If you're interested in learning more about the Dignity Health Telemedicine Network, email DignityHealthNeuro@DignityHealth.org. ■

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CONTINUING MEDICAL EDUCATION 2015

Monthly Neuro Grand Rounds
Mercy San Juan Medical Center
Conference Rooms 2, 3 and 4
First Friday of each month at 12:30 p.m.

Epilepsy Case Conference
Mercy General Hospital
North Auditorium
Fourth Tuesday of each month at 6 p.m.

Acute Stroke and Neurocritical Care Case Conferences
Mercy San Juan Medical Center
Conference Room 2
Second Wednesday of each month at 5 p.m.

Multiple Sclerosis Case Conference
Mercy San Juan Physicians Plaza
Room 145
First Wednesday of each month at 5:30 p.m.

If you have any questions about upcoming opportunities, contact DignityHealthNeuro@DignityHealth.org or call 916.962.8751.