Index of Suspicion
Barbara Marshall, Karen Chernoff and Paul Saenger
Pediatrics in Review 2008;29;243
DOI: 10.1542/pir.29-7-243

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/29/7/243

Data Supplement (unedited) at:
http://pedsinreview.aappublications.org/content/suppl/2008/06/30/29.7.243.DC1.html
The reader is encouraged to write possible diagnoses for each case before turning to the discussion. We invite readers to contribute case presentations and discussions. Please inquire first by contacting Dr. Deepak Kamat at dkamat@med.wayne.edu.

**Author Disclosure**

Drs Marshall, Saenger, Mytinger, Blackman, Goodkin, Kit, and Franceschini and Ms Chernoff have disclosed no financial relationships relevant to these cases. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

**Frequently Used Abbreviations**

- ALT: alanine aminotransferase
- AST: aspartate aminotransferase
- BUN: blood urea nitrogen
- CBC: complete blood count
- CNS: central nervous system
- CSF: cerebrospinal fluid
- CT: computed tomography
- ECG: electrocardiography
- ED: emergency department
- EEG: electroencephalography
- ESR: erythrocyte sedimentation rate
- GI: gastrointestinal
- GU: genitourinary
- Hct: hematocrit
- Hgb: hemoglobin
- MRI: magnetic resonance imaging
- WBC: white blood cell

---

**Case 1 Presentation**

A 9-year-old girl has experienced projectile vomiting, upset stomach, and a 9-lb weight loss over a 3-week period. After GI evaluation reveals no abnormalities, her pediatrician consults a pediatric neurologist, who orders an MRI that reveals a 1.6×1.6×1.0-cm homogeneously enhancing pituitary macroadenoma. The tumor elevates the optic chiasm minimally. A neuro-ophthalmologic evaluation demonstrates no evidence of optic neuropathy, cranial nerve palsy, or chiasmal syndrome.

Physical examination reveals weight loss and decreasing height velocity (1.53 cm/y) over the preceding 3 years, resulting in a drop from the 95th percentile to the 10th percentile in height.

CBC, blood chemistries, liver function tests, insulin-like growth factor (IGF-1), and cortisol values are normal. Prolactin is elevated at 94.7 ng/mL (4,117.4 pmol/L). Pituitary macroadenoma is diagnosed, and the patient is referred to the pediatric endocrinologist for pre-operative evaluation.

**Case 2 Presentation**

A 23-month-old girl is referred to a pediatric neurologist for evaluation of generalized hypotonia and global developmental delay. She was born at term after a normal pregnancy and delivery. Breastfeeding failed because of poor latch and weak suck. Bottle feeding was possible only by widening the nipple holes. At birth, her weight was at the 25th percentile and her length and head circumference were at the 10th percentile.

At 6 months of age, the baby showed no interest in her environment, could not sit without support, was not bearing weight, and was not reaching for or holding toys. Evaluation at that time yielded normal findings on MRI of the brain and laboratory studies (creatine kinase, acylcarnitine profile, serum amino acids, urine organic acids, karyotype, fluorescence in situ hybridization for Prader-Willi syndrome).

At 23 months of age, there has been little developmental gain, with the exception of the ability to sit briefly without support and minimal babbling. There has been no regression.

On physical examination, the child’s growth percentiles, including head circumference, have remained steady since birth. She responds briefly to a bell but does not babble. She demonstrates generalized hypotonia with some weakness but is able to sit briefly without support. The child does not hold or reach for objects, nor does she bear weight on her legs. Muscle stretch reflexes are obtained easily. She displays nearly continuous choreoathetotic movements of her tongue and fingers.

**Case 3 Presentation**

A 15-year-old boy who has well-controlled, mild, intermittent asthma presents to the ED with a 5-hour history of chest pain and shortness of breath. He denies fever, wheezing, vomiting, cough, rhinorrhea, or recent trauma. A recent ankle injury has precluded excessive physical exertion, but he has been well otherwise. He denies the use of illicit drugs.

Physical examination reveals a well-developed white male in no distress. His temperature is 98.6°F (37°C), heart rate is 72 beats/min, and respiratory rate is 18 breaths/min. The room air oxygen saturation is 98%. His lungs are clear, breath sounds are symmetric, and all other findings are normal.

Chest radiograph shows a pneumomediastinum without associated
pneumothorax; CT of the chest confirms the pneumomediastinum but yields no other findings. The patient is admitted to the observation unit for supplemental oxygen and pain control. 

An additional piece of history leads to a procedure that reveals the source of the problem.

**Case 1 Discussion**

**The Suspected Condition**

Pituitary adenomas are rare in children, accounting for 2.7% of all supratentorial tumors. Such tumors can be subdivided on the basis of size into macroadenomas (10 mm or greater in diameter) and microadenomas (<10 mm in diameter). The female-to-male ratio is 3.3:1. Nearly half (41.7%) of all pituitary adenomas are prolactin-secreting tumors, or prolactinomas, with 93% of such tumors occurring in children older than 12 years of age.

Patients who have prolactinomas generally present with headaches, visual problems, or growth disturbance. Additionally, girls may fail to enter puberty at the expected time or may fail to progress in their pubertal development. Hypogonadism, galactorrhea, and menstrual disturbances may be presenting signs. Gadolinium-enhanced MRI is the suggested procedure for detecting a pituitary adenoma. Microadenomas take up gadolinium more slowly than the rest of the pituitary and, therefore, do not enhance as strongly as the surrounding tissue. Plasma prolactin concentrations tend to be in the range of 145.0 to 3,300.0 ng/mL (6,304.3 to 143,477.4 pmol/L) in macro- and 70.0 to 500.0 ng/mL (3,043.5 to 21,739.0 pmol/L) in microadenomas (normal range, 3.0 to 24.0 ng/mL [130.4 to 1,043.5 pmol/L]).

**The Actual Condition**

All cases of pituitary adenoma require a full neuroendocrine evaluation, which includes studies of thyroid function. In this girl, the decrease in growth velocity also prompted thyroid function tests. The thyroxine (T4) concentration was undetectable (<1.0 mcg/dL [12.9 nmol/L]), with a thyroid-stimulating hormone (TSH) concentration of 1,350.0 U/mL. Thyroid peroxidase antibodies (anti-TPO) were positive at 37.9 U/mL. These findings were consistent with primary hypothyroidism.

Hypothyroidism is defined as underactivity of the thyroid gland, resulting in abnormally low concentrations of free T4 and high concentrations of TSH. Among patients who have hypothyroidism, primary hypothyroidism accounts for 99% of cases, with fewer than 1% caused by TSH deficiency (secondary hypothyroidism). In North America, the most common cause of goiter and hypothyroidism in children older than 6 years of age is chronic thyroiditis. In the developing world, iodine deficiency is the most common cause.

Other causes of primary hypothyroidism include transient hypothyroidism due to inflammatory or viral conditions, thyroid injury after radioactive iodine treatment or thyroid surgery, and some drugs (eg, amiodarone, interferon-alfa, stavudine). This patient had a positive TPO antibody consistent with Hashimoto thyroiditis.

Hypothyroidism affects all the major organ systems and can cause a variety of signs and symptoms, depending on the age of onset and degree of hormone deficiency. The manifestations might be due to a direct hormonal effect, overlap in the pituitary feedback mechanism, or hyperplasia of the pituitary gland.

Pituitary hyperplasia resulting from longstanding primary hypothyroidism has been described in adults and children. Hypothyroidism triggers the feedback loops to increase production of TSH in the pituitary and thyrotropin-releasing hormone (TRH) in the hypothalamus. Excess TRH can lead to lactotroph hyperplasia and resultant hyperprolactinemia. Lactotroph hyperplasia can be mistaken for a prolactinoma, due to similarities in presentation, including headaches, endocrinopathy, and a homogenous pituitary mass.

Because TRH and gonadotropin-releasing hormone have similar structures, excess TRH also can lead to increased concentrations of luteinizing hormone and follicle-stimulating hormone, resulting in precocious puberty.

Pituitary hyperplasia due to hypothyroidism has been reported to resolve in weeks to months after initiation of thyroxine therapy for the primary hypothyroidism and does not require surgical intervention. In this patient, autoimmune inflammation of the thyroid gland led to markedly decreased T4 values, stimulating very high concentrations of TSH, which caused pituitary hyperplasia mimicking a tumor.

The girl was started on oral thyroxine therapy, and T4, TSH, and prolactin values all normalized within 6 months. Follow-up MRI 5 months after the initiation of therapy revealed a normal pituitary size, and the girl no longer had headaches and vomiting. Growth velocity also increased to 5.6 cm/y. She continues to receive oral thyroxine therapy with careful follow-up of thyroid hormone concentrations and growth.

**Lessons for the Clinician**

Hypothyroidism can present in many different ways and can mimic other
diseases. A decrease in growth velocity on a growth curve often is one of the first signs, and frequently the onset of hypothyroidism can be traced back to when the growth velocity began to decline. Insufficient thyroxine production leads to a decrease in growth hormone and IGF-1 concentrations, which delays the bone maturation. Thyroid function tests always should be part of an evaluation for failure of normal growth. In this case, after the correction of hypothyroidism, the patient’s normal growth velocity resumed, and she continues to grow between the 10th and the 25th percentile.

It also is important to remember that primary hypothyroidism can cause pituitary hyperplasia and release of hormones other than thyroid hormones. Therefore, thyroid function tests should be obtained any time pituitary enlargement or abnormalities of other pituitary hormones are suspected. In this case, correction of the hypothyroidism spared the girl unnecessary surgery. (Barbara Marshall, MD, Karen Chernoff, BS, Paul Saenger, MD, Montefiore Medical Center, Bronx, NY)

Case 2 Discussion

Hypotonia, a decrease in the muscle’s postural tone, can result from a wide range of disorders of the brain, spinal cord (spinal muscular atrophies, spinal cord injury), nerves (hereditary motor-sensory neuropathies, congenital hypomyelinating neuropathy), neuromuscular transmission (infantile botulism, myasthenia gravis), or muscles (congenital myopathies and muscular dystrophies, metabolic myopathies such as acid maltase deficiency) (Table). In this child, the combination of hypotonia, developmental delay, and other findings on neurologic examination such as continuous choreoathetotic movements and preserved muscle stretch reflexes was most consistent with CNS dysfunction.

CNS causes of hypotonia and developmental delay include cerebral malformations; acquired cerebral injury that may occur with hypoxia, ischemia, or infection; genetic disorders such as Prader-Willi syndrome; and several metabolic disorders, including disorders of the peroxisomes, lysosomes, and mitochondria. Rarely, hypotonia and developmental delay are the combined result of a pathophysiologic process that affects both the brain and muscles, such as observed with a subset of the congenital muscular dystrophies (eg, Fukuyama type).

The absence of purposeful hand skills in this girl afflicted with both hypotonia and developmental delay led to the consideration of Rett syndrome, which was confirmed by the identification of a mutation in the MeCP2 gene by sequence analysis. Genetic testing for this syndrome most likely was not included in the initial evaluation because of the early onset of the developmental delay, the absence of true regression, and preserved head growth velocity.

The Disorder

Rett syndrome is an X-linked dominantly neurodegenerative disorder occurring primarily in females. Its incidence is between 1 in 10,000 and 1 in 22,000 individuals. Although previously believed to be lethal in males, male variants have been reported.

Diagnosis of classic Rett syndrome presumes a normal prenatal and perinatal course, normal psychomotor development through the first 5 months after birth, and normal head circumference at birth. Subse-

Table. Selected Neurologic Causes of Hypotonia

<table>
<thead>
<tr>
<th>Central Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>– Injury: Hypotonic cerebral palsy</td>
</tr>
<tr>
<td>– Chromosomal: Angelman syndrome, Prader-Willi syndrome, Rett syndrome, trisomy 21</td>
</tr>
<tr>
<td>– Metabolic: Leukodystrophies (eg, metachromatic leukodystrophy*), peroxisomal disorders (eg, neonatal adrenoleukodystrophy*), GM1 and GM2 gangliosidoses (eg, Tay-Sachs disease), organic acidemias</td>
</tr>
<tr>
<td>– Other: Cerebral malformations, benign central hypotonia, autism</td>
</tr>
<tr>
<td>Spinal cord</td>
</tr>
<tr>
<td>– Injury: Hypoxic-ischemic myelopathy, trauma</td>
</tr>
<tr>
<td>– Anterior horn cell: Spinal muscular atrophies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peripheral Nervous System (Motor Unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerves: Hereditary motor-sensory neuropathies, acute inflammatory demyelinating neuropathy (Guillain-Barré syndrome), congenital hypomyelinating neuropathies</td>
</tr>
<tr>
<td>Neuromuscular Transmission: Infantile botulism, myasthenic syndromes (eg, familial infantile myasthenia)</td>
</tr>
<tr>
<td>Muscle: Muscular dystrophies (eg, Duchenne muscular dystrophy, Fukuyama congenital muscular dystrophy*), congenital myopathies (eg, central core disease), metabolic myopathies (eg, acid maltase deficiency)</td>
</tr>
</tbody>
</table>

*May have features of both central and peripheral nervous system involvement.
quently, the rate of head growth slows (ages 3 months to 4 years), resulting in an acquired microcephaly, and a period of regression (ages 9 months to 4 years) results in psychomotor retardation, with the loss of language and social skills. Impairment in language and social capabilities provides the rationale for placing Rett syndrome under the pervasive developmental disorders classification in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition. Another characteristic is the loss of purposeful hand skills (ages 9 months to 2.5 years), with replacement by stereotyped hand movements (ages 1 to 3 years). Such movements are variable but include wringing, washing, clapping, and patting motions.

Other features include screaming fits; episodes of inconsolable crying; bruxism; GI dysfunction; disordered sleep; and autonomic instabilities, including breathing irregularities, reduced variability in the heart rate, and a prolonged QT interval. Epilepsy also is a common feature. Although the seizures can start at any age, the median age of onset is approximately 4 years. Both partial and generalized seizures can occur and frequently are difficult to treat.

In its early stages, Rett syndrome may be difficult to differentiate from autism and other causes of developmental delay or regression. In addition, genetic disorders such as Angelman syndrome and metabolic disorders such as infantile neuronal ceroid lipofuscinosis. Of note, children who have infantile neuronal ceroid lipofuscinosis also may develop stereotyped hand movements reminiscent of those associated with Rett syndrome. Rett-like symptoms also have been described in children afflicted with tuberous sclerosis complex.

Genetic Testing
In 1999, the MeCP2 gene defect responsible for most cases of Rett syndrome was identified. This gene is located on the Xq28 locus, and normal MeCP2 expression may regulate the expression of other genes.

Sequence analysis of the entire MeCP2 coding region and mutation scanning analysis can detect disease-causing mutations in approximately 80% of patients who have classic Rett syndrome. In a small percentage of mutation-negative patients, quantitative polymerase chain reaction or multiplex ligation-dependent probe amplification may be required to detect large deletions.

Prognosis and Treatment
After the period of regression, there is a period of relative stability (ages 2 to 10 years) that can be followed by additional late motor impairments (>10 years of age). Although more longitudinal studies are needed to understand the long-term outcome in Rett syndrome, a recent epidemiologic study has suggested that most girls who have classic Rett Syndrome survive past the age of 25 years. (1)

Rett syndrome is associated with an increased risk of unexpected sudden death that is posited to result from the associated autonomic dysfunction and epilepsy. Although the cause of death often is difficult to determine, a large Australian series identified the most frequent causes to be pneumonia, respiratory failure, and aspiration/asphyxiation. (1)

Treatment largely is supportive. Children afflicted with Rett syndrome should receive baseline ECG. Medications that prolong the QT interval should be avoided. Physical therapy is used to strengthen and improve flexibility. Patients should be monitored for scoliosis, which is common. A gastrostomy tube sometimes is indicated because many children fail to take adequate nutrition. A swallow study revealing aspiration also may indicate the need for gastrostomy feeding. Frequently, a laxative is required for the treatment of constipation. Antiepileptic drugs are needed for seizures. For parents, there are several excellent Internet sources, including the International Rett Syndrome Association website (http://www.rettsyndrome.org/).

Lessons for the Clinician
It is critical to understand that Rett syndrome is a clinical diagnosis that is aided by genetic testing, and a broad range of phenotypes is associated with mutations of the MeCP2 gene. Atypical female and male variants of Rett syndrome have been described. The most common variant is the “forme fruste” variant, which is a milder presentation than classic Rett syndrome and rarely is diagnosed before the age of 10 years. In addition, children who have autism and mental retardation without the additional signs of classic Rett syndrome have been found to have MeCP2 mutations. The severity of the phenotype may depend on the location of the mutation within the gene.

Congenital Rett syndrome, which is the appropriate designation for this girl, is rare but has been described previously. Affected children do not display the period of normal development after birth that is seen in the classic presentation. As with this patient, the early onset of hypotonia and poor feeding are typical of congenital Rett syndrome.

It is important to consider Rett syndrome in children who demonstrate developmental delay, even in those who do not have a period of normal development after birth. Similarly, variants must be considered when dealing with older children who display multiple signs and symptoms suggestive of Rett syn-
Pediatric cases of SPM are due to asthma and respiratory infections, although some occur following the Valsalva maneuver or forceful vomiting. Pneumomediastinum due to inhalation drug use has been reported in recent years.

Patients who experience pneumomediastinum present most commonly with chest pain, shortness of breath, and subcutaneous emphysema. The presence of crepitations over the precordium is known as Hamman sign and is strongly suggestive of the diagnosis. The crepitus is heard best during systole and may obscure the heart sounds. Diagnosis is made with chest radiography in 98% of cases. Lateral views are associated with higher yields. Chest CT scans yield the diagnosis when the radiograph appears normal.

Complications of pneumomediastinum are rare, including pneumopericardium and pneumothorax, and generally resolve without any intervention. Severe respiratory distress, stridor, and tamponade almost never occur. When these more serious complications do occur, they usually are seen in patients who are receiving mechanical ventilation or in those who have severe underlying disease.

Treatment is supportive and includes bed rest, analgesics, and avoidance of the Valsalva maneuver. The patient may be treated on an outpatient basis if the underlying cause is identified and controlled. Follow-up is recommended within 24 to 48 hours. Oxygen therapy often is instituted in hospitalized patients in an effort to speed reabsorption of the pneumomediastinum, although no conclusive evidence indicates that oxygen is beneficial. Repeat radiographs are not necessary unless the patient deteriorates clinically.

When managing pneumomediastinum, the primary condition to consider other than SPM is esophageal perforation. In cases in which an underlying cause for a pneumomediastinum is not identified or in which the history is suggestive, additional evaluation may be warranted to rule out esophageal perforation.

**The Underlying Cause**

Esophageal perforation is a rare but serious cause of pneumomediastinum in the pediatric population. Perforation results most often from foreign body ingestion, trauma, or a medical procedure. Rarely, it may occur after forceful vomiting associated with either binge drinking or eating, known as Boerhaave syndrome. Described first in 1724 by Hermann Boerhaave, the esophageal perforation in this syndrome results from increased intra-abdominal pressure transmitted to the esophagus against the closed glottis. Complications of an esophageal perforation include mediastinitis, emphysema, and pneumothorax. Mediastinitis can be fatal.

Signs and symptoms of esophageal perforation can include chest pain, abdominal pain, subcutaneous emphysema, neck pain, dyspnea, and sore throat. Patients in whom diagnosis and treatment are delayed may exhibit respiratory distress or signs of shock.

Radiologic evaluation generally begins with plain radiographs of the chest and soft tissue of the neck, followed by esophagography. Plain radiographs often appear normal, but suggestive findings include subcutaneous emphysema, pneumomediastinum, and mediastinal widening. Although esophagography with barium-containing contrast has the highest sensitivity for identifying an esophageal perforation, extravasation of barium into the mediastinum may lead to a fibrosing mediastinitis. Some experts, there-
fore, recommend beginning with esophagography that employs water-soluble contrast. If that study is not diagnostic, barium-containing contrast is used.

Treatment of esophageal perforation generally requires coordination with a surgical team, although most children do not require operative intervention. Medical management usually consists of the cessation of oral intake, broad-spectrum antibiotics, and parenteral nutrition.

Lessons for the Clinician
Esophageal perforation is a rare but serious condition that may present initially with pneumomediastinum. A thorough history must be obtained, focusing particularly on the circumstances surrounding the onset of symptoms. In cases in which no underlying cause of pneumomediastinum can be identified, esophagography may be warranted. (Brian Kit, MD, Betina Franceschini, MD, Children’s National Medical Center, Washington, DC, and Anne Arundel Medical Center, Annapolis, MD)

To view Suggested Reading lists for these cases, visit pedsinreview.org and click on Index of Suspicion.

New Section Editor
Beginning July 1, 2008, the editing of “Index of Suspicion” will be handled by Dr Deepak Kamat of Children’s Hospital of Michigan and the Wayne State University School of Medicine. Inquiries regarding potential case submissions should be directed to Dr Kamat at dkamat@med.wayne.edu.
# Index of Suspicion

Barbara Marshall, Karen Chernoff and Paul Saenger

*Pediatrics in Review* 2008;29;243

DOI: 10.1542/pir.29-7-243

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pedsinreview.aappublications.org/content/29/7/243">http://pedsinreview.aappublications.org/content/29/7/243</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 1 articles, 0 of which you can access for free at: <a href="http://pedsinreview.aappublications.org/content/29/7/243#BIBL">http://pedsinreview.aappublications.org/content/29/7/243#BIBL</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s):</td>
</tr>
<tr>
<td></td>
<td><strong>Neurologic Disorders</strong> <a href="http://pedsinreview.aappublications.org/cgi/collection/neurologic_disorders">http://pedsinreview.aappublications.org/cgi/collection/neurologic_disorders</a></td>
</tr>
<tr>
<td></td>
<td><strong>Disorders of Cognition, Language, Learning, and Attention</strong> <a href="http://pedsinreview.aappublications.org/cgi/collection/cognition_language_learning_attention_disorders">http://pedsinreview.aappublications.org/cgi/collection/cognition_language_learning_attention_disorders</a></td>
</tr>
<tr>
<td></td>
<td><strong>Respiratory Disorders</strong> <a href="http://pedsinreview.aappublications.org/cgi/collection/respiratory_disorders">http://pedsinreview.aappublications.org/cgi/collection/respiratory_disorders</a></td>
</tr>
<tr>
<td></td>
<td><strong>Endocrine Disorders</strong> <a href="http://pedsinreview.aappublications.org/cgi/collection/endocrine_disorders">http://pedsinreview.aappublications.org/cgi/collection/endocrine_disorders</a></td>
</tr>
<tr>
<td></td>
<td><strong>Gastrointestinal Disorders</strong> <a href="http://pedsinreview.aappublications.org/cgi/collection/gastrointestinal_disorders">http://pedsinreview.aappublications.org/cgi/collection/gastrointestinal_disorders</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml</td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: /site/misc/reprints.xhtml</td>
</tr>
</tbody>
</table>
The following Suggested Reading lists are included online only for the “Index of Suspicion.”

**Case 1 Suggested Reading**


Sarlis NJ, Brucker-Davis F, Doppman JL, Skarulis MC. MRI-demonstrable regression of a pituitary mass in a case of primary hypothyroidism after a week of acute thyroid hormone therapy. *J Clin Endocrinol Metab.* 1966;82:808–811


**Case 2 Suggested Reading**


**Case 3 Suggested Reading**


