Index of Suspicion
Eyal Cohen, Oscar M. Navarro, Erica Reynolds, Robert P. Schwartz and Padmini Venkataramani
Pediatr. Rev. 2007;28;419-425
DOI: 10.1542/pir.28-11-419

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/cgi/content/full/28/11/419
Case 1 Presentation
An 18-month-old girl presents with a 6-month history of intermittent fevers, 5 lb weight loss, and mild respiratory distress. A chest radiograph demonstrates bibasilar infiltrates. Despite treatment with parenteral antibiotics, the symptoms persist and the radiographic changes worsen. She has had no cough, vomiting, food aversion, change in appetite, contact with tuberculosis, or foreign travel. Born at term, she previously was healthy and developing normally.

The girl's weight is 20 lb (<3rd percentile), and her height is 31 in (10th to 25th percentile). Her respiratory rate is 30 breaths/min and oxygen saturation is 91% in room air; she is afebrile. Mild intercostal retraction are noted, and crackles are heard bilaterally. There is no clubbing, organomegaly, or rash. Her neurologic findings are normal. Her WBC count is 15.6 × 10^9/mL (15.6 × 10^9/L) with normal differential count, pH is 7.42, bicarbonate concentration is 20 mEq/L (20 mmol/L), carbon dioxide partial pressure is 32 mm Hg, and base excess is -3 mEq/L. Blood cultures are sterile, and a tuberculin skin test is nonreactive. A sweat test yields normal results. Twenty-four-hour esophageal pH monitoring does not show gastroesophageal reflux disease (GERD). An additional bedside clinical assessment followed by radiologic confirmation reveals the diagnosis.

Case 2 Presentation
The parents of a 3½-year-old boy notice that he has grown pubic hair recently, but has no body odor or acne. He has had no headaches, seizures, visual problems, polyuria, or polydipsia. His growth and development have been normal.

Physical examination reveals a muscular child whose height is at the 90th percentile, where it has been for 6 months, and whose weight is above the 95th percentile. His gonads are prepubertal in size, measuring 2.1 × 0.9 cm on the right and 2.0 × 0.8 cm on the left. His penis is 5.2 cm in length, and there is sparse pubic hair (Sexual Maturity Rating 2). The remainder of the physical findings are normal.

Laboratory evaluation includes a complete metabolic profile that is within normal limits. His testosterone concentration is 64 ng/dL (2.22 nmol/L) (normal prepubertal range, 3 to 10 ng/dL [0.1 to 0.35 nmol/L]) and androstenedione, dehydroepiandrosterone sulfate (DHEAS), and 17-hydroxyprogesterone values are normal. An 11-hydroxylase deficiency screen also yields normal results. Serum gonadotropin concentrations are in the prepubertal range. His bone age is 6 years. Ultrasonography of the abdomen and testes shows normal findings. Additional history reveals the diagnosis.
is at the 3rd percentile, and his weight is below the 3rd percentile. He has no cyanosis and is not pale. His heart rate is 82 beats/min, with normal cardiac findings and peripheral pulses, and his temperature, blood pressure, and respiratory rate are normal. Examination of his chest shows no tenderness or skin lesions. All other findings are normal.

The boy’s oxygen saturation is 98%. Echocardiography shows a normal heart. Results of CBC, peripheral blood smear, and electrolyte measurement are normal. A simple investigation gives a clue to the diagnosis, which is confirmed by another test.

Case 1 Discussion
A bedside feeding assessment by an occupational therapist revealed increased congestion and upper airway sounds without cough during feeding. Subsequently, asymptomatic (“silent”) aspiration was confirmed during a videofluoroscopic swallow study (VFSS). Endoscopic evaluation of the upper airway and MRI of the head yielded normal findings. Treatment was initiated with thickening of feedings, which resulted in weight gain and resolution of the fever, pulmonary signs, and radiographic abnormalities.

The Condition
Silent aspiration describes aspiration without cough or obvious acute distress. (1) Infants and young children afflicted with this disorder are at increased risk of developing aspiration-induced chronic lung disease, malnutrition, and neurodevelopmental problems. Pulmonary failure due to chronic aspiration is a leading cause of death in children who have severe neurologic impairment. Silent aspiration commonly is associated with aspiration from below (due to GERD). Investigations such as 24-hour pH monitoring can be helpful in excluding this condition.

Silent aspiration can be due to aspiration from above (related to dysphagia) and often is associated with underlying conditions such as prematurity, global neurologic dysfunction, or anatomic anomalies of the upper aerodigestive tract. These conditions put the child at risk for aspiration by interfering with the complex neuromuscular and airway coordination involved in swallowing. However, several studies have suggested that aspiration can occur from oropharyngeal dysfunction in children who have none of these risk factors. Most affected children develop symptoms in the first postnatal year, and many outgrow the condition by the preschool years. (2) Radiographic aspiration in children who aspirate while in a supine position (infants, neurologically impaired children) frequently affects the upper lobes or perihilar regions, but bilateral basilar findings can occur in children who aspirate while in an upright position.

Diagnosis
Silent aspiration should be considered in children who experience unexplained recurrent chest infections or who have a history of wheezing or congestion after feedings. Aspiration also should be considered in children who have respiratory symptoms and a history suggestive of GERD. Less commonly, silent aspiration can present with recurrent undiagnosed fevers, perioral cyanosis or vocal changes with feedings, failure to thrive despite adequate nutritional intake, feeding aversion, or poor control of secretions.

A comprehensive clinical assessment that involves a history, risk factors, and a bedside feeding evaluation by an experienced occupational therapist or speech-language pathologist has been shown to have 92% sensitivity and an 89% negative predictive value for diagnosing aspiration of fluids in children. (3) This assessment can prevent the need for the radiation exposure and cost of additional radiologic assessment in many children. It should be noted, however, that the accuracy of the evaluation depends on the experience of the specialist; speech pathologists or occupational therapists who are highly trained in this area are not immediately available in all locations.

VFSSs are dynamic radiographic examinations of food passing from mouth to pharynx and are considered the “gold standard” for diagnosing aspiration from above in patients who have a positive screening assessment. Findings from the VFSS also can help clinicians identify safe feeding strategies if the child only aspirates foods of certain consistencies.

Management
Recommended management depends on the underlying cause of the aspiration. For children who have GERD, optimal medical management is successful in many patients and often includes the use of acid suppression with histamine-2 receptor antagonists or proton pump inhibitors. Occasionally, prokinetic agents can be helpful, although the evidence for the effectiveness of many of these drugs is weak. Surgical options such as fundoplication and enterostomy tube insertion are viable alternatives for patients who cannot be managed medically.

If the primary problem is dysphagia, a variety of dietary modifications can be employed. Thickening of liquids often is helpful. Other therapies include changing the feeding position (upright versus reclined), slowing the pace of feedings, and al-
morning and slept without a shirt at night. The boy often slept with his parents. After this discovery, the father switched to a testosterone patch and began wearing a shirt before going to bed. Follow-up examination of the boy 4 months later showed Sexual Maturity Rating 1 pubic hair and a phallus measuring 4.2 cm. The testosterone concentration had decreased to a normal prepubertal value (4.5 ng/dL [0.16 nmol/L]), confirming the diagnosis of exogenous androgen exposure.

Differential Diagnosis
Precocious puberty is defined as the onset of physical signs of sexual development prior to the accepted age of sexual maturation. True precocious puberty consists of the development of secondary sexual characteristics together with increased growth velocity and advanced bone age. For boys of any ethnic background, development before age 9 years is considered precocious. For girls, pubertal onset previously was considered precocious prior to the age of 8 years, but recent studies suggest an earlier onset, especially in African-American and Mexican-American girls.

Early sexual development can be categorized into several subtypes. Premature pubarche, characterized by isolated pubic hair growth, adult body odor, and acne, often is used interchangeably with the term early adrenarche. Increased adrenal androgens, such as dehydroepiandrosterone (DHEA) and DHEAS in girls and adrenal and gonadal androgens in boys, cause pubarche. Premature thelarche is isolated breast development in girls and typically is benign.

The etiology of precocious puberty can be subdivided into central or peripheral causes. Central or gonadotropin-dependent precocious puberty is caused by premature activation of the hypothalamic-pituitary-gonadal axis. Central precocious puberty is idiopathic in 90% of girls, but a CNS cause is detected more frequently in boys. CNS causes include hypothyroidism hamartoma, other CNS tumors, infection, head trauma, hydrocephalus, third ventricle cyst, neurofibromatosis, and cranial radiation. The differential diagnosis for peripheral or gonadotropin-independent early pubertal changes includes congenital gonadal hypoplasia, adrenal tumors, gonadal tumors, McCune-Albright syndrome, familial male precocious puberty (testotoxicosis), and exogenous androgens.

Diagnostic Evaluation
Evaluation of early pubertal changes should begin with a history investigating the onset and progression of puberty, exposure to hormones, presence of CNS symptoms, and family history. Physical examination should include blood pressure measurement and evaluation of the skin and fundi as well as developmental staging of the genitalia. Testicular volume is increased in central precocious puberty, as it is in normal puberty. The testes usually are prepubertal in size if there is an extragonadal source of androgens. A gonad may be enlarged unilaterally if a tumor is present. The growth chart should be studied for increasing growth velocity. A bone age radiograph typically is advanced more than 2 years beyond the chronologic age in true precocious puberty. Initial laboratory studies should include measurement of follicle-stimulating hormone, luteinizing hormone, estradiol (for females), testosterone (for males), androstenedione, and DHEAS. DHEA and DHEAS concentrations may be elevated markedly in adrenal tumors. Patients

Lessons for the Clinician
Silent aspiration should be considered in children who have pulmonary symptoms of unclear cause, particularly those who have risk factors such as GERD, prematurity, or global neurologic dysfunction. Prompt identification can lead to simple therapies that can reduce the degree of aspiration. (Eyal Cohen, MD, Oscar M. Navarro, MD, The Hospital for Sick Children, Toronto, Ontario, Canada)

References

To view a video clip showing aspiration during feeding, visit pedsinreview.org and click on Index of Suspicion.
who experience isolated premature pubarche have normal bone ages and growth rates as well as early adrenarchal concentrations of DHEA, DHEAS, and androstenedione. To rule out congenital adrenal hyperplasia, 17-hydroxyprogesterone should be measured. Additional evaluation may include an MRI if central precocious puberty is suspected as well as abdominal and pelvic or testicular ultrasonography.

The Offending Agent

Physicians must be aware of the many hormone-containing products that can be obtained without a prescription. Androgen-containing products are used for many different indications, such as body building and treatment of hair loss. They are taken by some individuals to increase libido and energy and to slow aging.

Many prescription and nonprescription sources of estrogen are available as well, such as hair products. There are case reports of such products causing precocious puberty in female children and gynecomastia in male children. Many parents do not consider these products medications and may not mention their use if not asked directly. Parents should be counseled to use these products correctly; elevated testosterone concentrations have been demonstrated in sexual partners of men using testosterone gel as well as in exposed female children and gynecomastia, 17-hydroxyprogesterone should be measured. Additional evaluation may include an MRI if central precocious puberty is suspected as well as abdominal and pelvic or testicular ultrasonography.

Lessons for the Clinician

This case illustrates the importance of taking a thorough history. A comprehensive diagnostic evaluation served to rule out many possible causes of this patient’s pubic hair growth, but a detailed history was necessary to make the correct diagnosis. (Erica Reynolds, MD, Robert P. Schwartz, MD, Wake Forest University School of Medicine, Winston-Salem, NC)

Case 3 Discussion

This boy’s constellation of symptoms warranted the performance of an ECG, which showed a corrected QT interval (QTc) of 0.464 seconds. The T wave was generated slowly and notched. Twenty-four hour ambulatory ECG monitoring showed that the maximum QTc was 0.548 seconds, and the incidence of average QTc intervals of more than 0.45 seconds was 59%. He was diagnosed as having long QT syndrome (LQTS) and was started on propranolol. He became symptom-free and is followed regularly. His biologic family was not available for history or screening.

Lessons for the Clinician

LQTS, a condition in which the QTc is prolonged, occurs in both congenital and acquired forms. QTc is calculated by using the Bazett formula: observed QT interval (in seconds) ÷ square root of the previous RR interval (in seconds).

The QT interval represents the period of activation and recovery of the ventricular myocardium. When recovery is prolonged from electrical excitation, some part of the myocardium might be refractory to subsequent depolarization. This physiologic state predisposes to circus reentrant rhythm and polymorphic ventricular tachycardia (torsade de pointes), leading to ventricular fibrillation and ineffective ventricular contraction (Figure). This abnormal rhythm may resolve spontaneously but also can progress to sudden death. Sudden cardiac death is the
The Congenital Form
Mutations of the cardiac sodium, potassium, and calcium ion channel genes cause LQTS. There are six variants of the autosomal dominant form of LQTS, known as Romano-Ward syndrome, two other rare syndromes, and two types of the autosomal recessive form, known as Jervell and Lange-Nielsen syndrome (JLNS) (Table 1).

The prevalence of congenital LQTS is estimated to be 1 in 5,000 to 10,000 individuals, with no racial predilection. Approximately 33% of patients who have congenital LQTS are asymptomatic but still are at risk for sudden death. The other 67% have symptoms, predominantly syncope, seizures, and palpitations, often triggered by rigorous exercise, swimming, emotional stress, or abrupt auditory stimuli, but sometimes occurring spontaneously or during sleep. Episodic dizziness, light-headedness, blackouts, or loss of consciousness followed by a seizure suggest LQTS. The findings on physical examination may be unremarkable, although some patients may have bradycardia.

Seventy-five percent of asym-
tomotic patients are diagnosed during a family screening when another member has been diagnosed as having LQTS or because there is a family history of recurrent syncope, epilepsy, sudden infant death syndrome, sudden death, cardiac arrest, unexplained fatal accidents, or death due to drowning. There may be a history of hearing loss in a patient or family members when JLNS is present.

**LQTS in Neonates**

The QTc of neonates and infants are slightly longer. There is a physiologic increase in QTc during the second postnatal month that peaks between the second and third months, declining to birth values by about 6 months. The upper limit of normal (98th percentile) values for QTc during the first week after birth is 0.47 seconds, and in early infancy, 0.45 seconds. Some of the published data suggest that compound heterozygotes or those having two mutations in different genes are likely to have severe forms of LQTS, with early and serious manifestations.

**The Acquired Form**

A large number of drugs have been associated with lengthening of the QTc and include antiarrhythmic medications, antiarrhythmics (quinidine, amiodarone, dofetilide), antimicrobials (erythromycin, cotrimoxazole), anti fungal agents (fluconazole, ketoconazole), antidepressants (amitriptyline), antihistamines (astemizole, terfenadine), antipsychotics (haloperidol, risperidone), lipid-lowering agents (probufol), oral hypoglycemic agents (glibenclamide), organophosphates, and promotility agents (cisapride). This is a representative but not exhaustive list.

Electrolyte abnormalities such as acute hypokalemia, chronic hypokalemia, hypocalcemia, and hypomagnesemia can prolong the QTc interval. Medical conditions associated with LQTS include complete atrioventricular block, congestive heart failure, myocarditis, hyperparathyroidism, hypothyroidism, pheochromocytoma, encephalitis, head trauma, stroke, subarachnoid hemorrhage, alcoholism, and anorexia nervosa.

**Diagnosis**

The first step in evaluating a child suspected of having LQTS is to obtain an ECG. Indications for ECG are as follows: emotional or exer tional syncope; being a first-degree relative of a person who has been diagnosed as having LQTS; family history of individuals having symptoms as described previously; unexplained bradycardia; fetal bradycardia; and syndactyly, which occurs in Andersen-Tawil and Timothy syndromes.

Standard ECG recordings that focus on the QTc and T wave are most useful. A QTc greater than 0.46 seconds has a predictive value of more than 90%. For those younger than age 15 years, a QTc of 0.44 to 0.46 seconds is considered borderline. Twenty-four hour ambulatory ECG monitoring or stress ECG is essential to confirm the diagnosis. Approximately 10% to 15% of gene positive patients who have LQTS may present with normal QTcs. Females have a slightly higher upper limit of normal for QTc than do males.

The following T-wave abnormalities may be seen in LQTS: wide-based, slowly generated T; wide-based, double-hump, notched T; low-amplitude deflection on descending limb; indistinct termination of T wave (T-U complex); sinusoidal, slowly generated T wave; and T waves inscribed after prolonged ST segment. Some variation occurs in the T-wave patterns on ECG among the different subtypes of LQTS.

The scoring system of Schwartz and associates for determining the probability of LQTS being present is presented in Table 2. As in this case, 24-hour ECG monitoring or stress ECG often is needed to give a complete picture of the patient’s rhythm pattern.

If a standard ECG does not demonstrate an arrhythmia but one is suspected, 24-hour ECG monitoring might reveal abnormalities, as in this case. An exercise ECG is a good test for eliciting the signs of LQTS, and some cardiologists follow borderline ECG or nondefinitive monitoring findings with an exercise test.

Serum concentrations of potassium, calcium, and magnesium should be measured. Echocardiography is performed to exclude structural abnormalities. Appropriate tests may be undertaken to rule out other medical conditions based on the clinical findings. A detailed drug history is essential.

Genetic testing provides additional insight into the underlying condition, but may identify only 50% of affected patients. A negative result does not rule out LQTS.

**Management**

Beta-blockers such as propranolol, nadolol, atenolol, and metoprolol can prevent cardiac events in about 70% of patients who have LQTS. In high-risk patients, implantation of cardioverter-defibrillators, with or without left cervicothoracic stellectomy, may be successful. Treatment reduces the 10-year mortality from 50% to 5%. The safety of gene specific therapy is under evaluation.

It is important for affected patients to avoid offending drugs; a Web site sponsored by the University of Arizona provides a comprehensive list of
QT-prolonging drugs (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm). Electrolyte abnormalities also should be avoided. Competitive sports are discouraged. A buddy system may be used when the child goes out to play or swim.

Genetic counseling and education of patients, their families, and school personnel are essential.

Table 2. 1993 LQTS Diagnostic Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG Findings</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>QTc&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>480 msec</td>
<td>3</td>
</tr>
<tr>
<td>460 to 470 msec</td>
<td>2</td>
</tr>
<tr>
<td>450 msec (males)</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T wave in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Clinical History</strong></td>
<td></td>
</tr>
<tr>
<td>Syncope&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>Syncope with stress</td>
<td>1</td>
</tr>
<tr>
<td>Syncope without stress</td>
<td>0.5</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td></td>
</tr>
<tr>
<td>Family history&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>A. Family members who have definite LQTS&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>B. Unexplained sudden cardiac death among immediate family members younger than 30 y</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Scoring: ≤1 point, low probability of LQTS; 2 to 3 points, intermediate probability; and ≥4 points, high probability.

<sup>*</sup>In the absence of medications or disorders known to affect these ECG features.

<sup>1</sup>QTc calculated by using formula of Bazett.

<sup>2</sup>Mutually exclusive.

<sup>3</sup>Resting heart rate below 2nd percentile for age.

<sup>4</sup>The same family member cannot be counted in A and B.

<sup>5</sup>Definite LQTS is defined as an LQTS score of ≥4 points.


QT-prolonging drugs (http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm). Electrolyte abnormalities also should be avoided. Competitive sports are discouraged. A buddy system may be used when the child goes out to play or swim.

Genetic counseling and education of patients, their families, and school personnel are essential.

**Lessons for the Clinician**

LQTS is a potentially fatal condition that must be considered when a child presents with syncope, palpitations, cardiac arrest, or seizures or when there is a family history of sudden death, sudden infant death syndrome, congenital deafness, unexplained accidents, or epilepsy. In this case, symptoms unusual for LQTS suggested a rhythm disturbance, which was confirmed by additional evaluation.

ECG is an important initial investigation, but even if the ECG appears normal, a stress ECG or 24-hour ambulatory ECG monitoring should be obtained when LQTS is suspected. Genetic testing may be done, if available. Prompt institution of therapy and lifelong follow-up are necessary.

(Padmini Venkataramani, MD, formerly Faculty of Medicine & Health Sciences, Universiti Malaysia Sarawak, Kuching, Malaysia, currently Oman Medical College, Sohar, Sultanate of Oman)

The author acknowledges with gratitude the UNIMAS medical students and the staff in Sarawak General Hospital and UNIMAS library who assisted in the management of this boy and provided references on time, respectively.

To view Suggested Reading lists for these cases, visit pedsinreview.org and click on Index of Susicion.
Index of Suspicion
Eyal Cohen, Oscar M. Navarro, Erica Reynolds, Robert P. Schwartz and Padmini Venkataramani
DOI: 10.1542/pir.28-11-419

Updated Information
& Services
including high-resolution figures, can be found at:
http://pedsinreview.aappublications.org/cgi/content/full/28/11/419

Supplementary Material
Supplementary material can be found at:
http://pedsinreview.aappublications.org/cgi/content/full/28/11/419/DC1

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://pedsinreview.aappublications.org/misc/Permissions.shtml

Reprints
Information about ordering reprints can be found online:
http://pedsinreview.aappublications.org/misc/reprints.shtml