Robert Listernick, MD, and colleagues discuss hard-to-diagnose cases.

A 12-Year-Old Boy with Increasing Verbal Aggression

Robert Listernick, MD

A 12-year-old boy was referred by his school to a partial hospitalization program for increasing verbal aggression over the past 4 to 6 months. He had absolutely no symptoms. His history and family history were unremarkable.

On exam, he was a tall, healthy-appearing boy. His weight and height were greater than the 95th percentile. Blood pressure was 118/69 mm Hg. His physical exam was normal.

On the "standard medical evaluation" by the psychiatrist, the total serum calcium was 17 mg/dL. Ionized calcium at our institution was 2.75 mEq/L. Serum phosphorus was 3.6 mg/dL (normal).

Robert Listernick, MD, moderator: Is there a standard medical evaluation that a psychiatrist performs when confronted with an adolescent who has psychiatric symptoms?

James MacKenzie, DO, child psychiatrist: Obviously there's no "standard approach." Probably the most important thing that I do is sit down and try not to jump to conclusions. I don't even want to think about primary psychiatric disorders until I'm sure that all the physiologic categories are covered. I try to look for either historical or physical clues that suggest an underlying medical problem rather than a primary psychiatric disorder. One of the more common causes of acute psychiatric symptoms in children is medication side effects. For instance, we see a disproportionate number of children who have adverse anticholinergic reactions to diphenhydramine. Beyond that, I let the history and physical be my guide as to any diagnostic testing. Even if a child has psychotic symptoms, I try to resist diagnosing major mood disorders or schizophrenia until I'm sure that the child hasn't been physically or sexually abused.

Dr. Listernick: Is hypercalcemia likely to cause verbal aggression?

Donald Zimmerman, MD, pediatric endocrinologist: It is exceedingly common to have a variety of psychiatric presentations related to hypercalcemia ranging from confusion to frank psychosis. This behavior may well be related to hypercalcemia. We'll only know when the hypercalcemia is fixed.

Dr. Listernick: How should we approach the differential diagnosis of hypercalcemia?

Laura Torchen, MD, pediatric endocrinologist: The combination of elevated calcium and low phosphorus brings hyperparathyroidism to the top of the list. Once we know the parathyroid hormone (PTH) level, we could proceed with the differential diagnosis. His PTH was significantly elevated, particularly in the face of severe hypercalcemia.

Dr. Listernick: Just for the record, if his PTH were low, what are the other causes of hypercalcemia that could be considered in pediatrics?

Dr. Torchen: Approaching the diagnosis logically, the next step would be to measure vitamin D metabolite levels. Vitamin D toxicity can occur if children receive high doses through supplements. Elevated levels of 1,25 dihydroxy vitamin D may be seen in granulomatous diseases, such as sarcoid. Certain malignancies, such as lymphomas, clear cell carcinoma of the ovary, or Wilms tumor, can secrete a protein called PTH-related peptide that acts like PTH and causes hypercalcemia.

One would expect high levels of calcium in the urine in someone with hypercalcemia. However, if there were low levels, this would suggest familial hypocalciuric hypercalcemia, which is due to a loss of function mutation in the calcium-sensing receptor in the parathyroid glands and the kidneys. Other miscellaneous causes of hypercalcemia would be Williams syndrome or subcutaneous fat necrosis in infants, severe immobilization, and diffuse cancer metastases to the bones.

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Dr. Listernick: So what's the next step in the evaluation?

Dr. Torchen: We need to see a full set of electrolytes, urinalysis, urine calcium and creatinine, repeat ionized calcium, phosphorus, PTH, and vitamin D panel. The results clearly showed that the child had hyperparathyroidism.

Dr. Listernick: What is the differential diagnosis of hyperparathyroidism?

Dr. Zimmerman: One caveat to mention before Laura gives the differential diagnosis of hyperparathyroidism. In familial hypocalciuric hypercalcemia, the PTH may be mildly (inappropriately) elevated for the degree of hypercalcemia. In this condition, the parathyroids can't sense the serum calcium so they are churning out PTH, whereas the kidney is trying to conserve calcium because its job is to retain calcium in the face of what it perceives as low blood calcium.

Dr. Torchen: Approximately 90% of cases of primary hyperparathyroidism are due to adenomas. The remaining cases are either due to parathyroid gland hyperplasia or the rare parathyroid carcinoma. There are, of course, numerous cases of secondary hyperparathyroidism in children with chronic kidney disease. The next step would be to perform an ultrasound of the neck looking for an adenoma.

Mary Wyers, MD, pediatric radiologist: Unfortunately, the ultrasound was negative. The next step was a sestamibi scan. Technetium labeled-sestamibi is more avidly taken up by a hyperfunctioning parathyroid gland than by normal parathyroid tissue. It's not helpful in identifying diffuse parathyroid hyperplasia. Although the numbers across studies vary, the sensitivity of sestamibi imaging to detect parathyroid adenomas is approximately 60%. During the scan, we perform imaging at 30 minutes and 3 and 5 hours. Initially, the radionuclide is absorbed by the parathyroid glands, thyroid gland, and salivary glands. By 5 hours, only the hyperfunctioning parathyroid should retain the tracer. The scan of this patient was also negative.

Dr. Listernick: So now what? Since you don't have an identifiable target lesion on ultrasound or sestamibi scanning, what do you do?

Anthony Chin, MD, pediatric surgeon: The surgeon has to plan for a four-gland exploration, starting with one side and moving onto the contralateral side if nothing is found. The newest addition to our armamentarium is the use of intraoperative PTH testing. We no longer have to wait for the pathologist to examine the removed gland to see if we found the adenoma. The half-life of PTH is between 12 and 18 minutes. So within 10 to 15 minutes you should see a rapid drop-off in PTH levels if the adenoma has been removed. We receive the PTH results within 20 minutes.

Eric Grossman, MD, pediatric surgeon: There's actually controversy within the surgical community as to the best way to approach the surgery itself. Twenty years ago, everyone performed a four-gland exploration for what was presumed to be a parathyroid adenoma. With the advent of nuclear medicine and ultrasound imaging, there was a big push for focused, minimally invasive parathyroidectomies targeting the presumed adenoma. A large retrospective series published in *Annals of Surgery* last year calls into question this practice given a significant incidence of second adenomas on the contralateral side; the authors recommend exploring and identifying all four glands so as to not miss a second adenoma.

Panelists

Robert Listernick, MD
Moderator

James MacKenzie, DO
Child Psychiatrist

Donald Zimmerman, MD
Pediatric endocrinologist

Laura Torchen, MD
Pediatric endocrinologist

Mary Wyers, MD
Pediatric radiologist

Anthony Chin, MD
Pediatric surgeon

Marleta Reynolds, MD
Pediatric surgeon

(Not pictured: Nitin Wadhwani, MD, pediatric pathologist; and Eric Grossman, MD, pediatric surgeon)

All panelists practice at The Ann and Robert H. Lurie Children's Hospital of Chicago, IL, where this discussion, part of a weekly series, was recorded and transcribed for *Pediatric Annals*.

Dr. Torchen: Another aspect of preoperative planning is the identification of hyperparathyroidism predisposition syndromes in which second endocrinopathies might be present. These

would include both multiple endocrine neoplasia MEN-1 (parathyroid adenomas, pituitary tumors, and pancreatic islet cell tumors) and MEN-2A (parathyroid adenomas, pheochromocytoma and medullary carcinoma of thyroid). It's most important to preoperatively identify pheochromocytomas, as their presence would create a huge surgical risk. Plasma metanephrines and urine catecholamines in this child were normal. Finally, hyperparathyroidism-jaw tumor syndrome is an autosomal dominant disease characterized by solitary parathyroid adenomas, multiple ossifying fibromas of the mandible and maxilla, and a variety of malignancies, including Wilms' tumor and pancreatic adenocarcinoma.

Dr. Zimmerman: There's a dramatic difference between hyperparathyroidism that occurs in children and adolescents compared with that which occurs in adults. Approximately half of the cases of hyperparathyroidism in children and adolescents are associated with one of these genetic syndromes. This makes it extremely important to identify the MEN syndromes preoperatively. Additionally, the vast majority of these syndromal cases of hyperparathyroidism are associated with multiple gland involvement. Physicians differ about whether they call this parathyroid hyperplasia or multiple adenomas.

Dr. Listernick: How did the surgery proceed?

Marleta Reynolds, MD, pediatric surgeon: People can have anywhere from four to 11 parathyroid glands, making identification extremely challenging. Without imaging guidance, this became a much more difficult procedure. We searched both sides unsuccessfully, identifying what we thought were normal parathyroid glands. In addition, we looked in very unusual locations such as the back wall of the esophagus as well as the thymus (which was removed). We were concerned that we might have to remove 3.5 parathyroid glands and potentially reimplant one; however, ultimately we identified a clear adenoma on the right side beneath the middle thyroidal vessels. The PTH levels dropped precipitously following its removal.

Nitin Wadhwani, MD, pediatric pathologist: Parathyroid adenoma was confirmed histologically. In general, if we see compressed, normal parathyroid tissue, we label it an adenoma; if not, we would probably call this parathyroid hyperplasia. Parathyroid carcinoma is extremely rare in the pediatric population. It's not even a pathologic diagnosis so much as a surgical diagnosis. In cases of parathyroid carcinoma, the surgeon will find that the tumor is adherent to adjacent structures or difficult to dissect off the adjacent thyroid gland. The surgeon and the pathologist need to work very closely together in these cases.

Dr. Listernick: What are the issues relating to postoperative management?

Dr. Reynolds: As the PTH plummets, we expect postoperative hypocalcemia, which is normally seen during the first 16 hours. Given the difficulty of this operation and our manipulation of the parathyroid glands, we checked ionized calcium levels earlier. However, the patient didn't develop hypocalcemia until 72 hours after surgery, following discharge from the hospital.

Dr. Zimmerman: There are two main reasons for postoperative hypocalcemia. The first is hypoparathyroidism due to the remaining atrophied parathyroid glands that need time to "wake up" in response to hypocalcemia. His delayed hypocalcemia is probably due to the phenomenon of "bone hunger." Due to long-standing hyperparathyroidism, the bones have been leeched of calcium; once the PTH stimulus is removed, the osteoid begins to avidly absorb calcium from the blood.

Dr. Listernick: Did his psychiatric symptoms resolve following surgery?

Dr. Torchen: Too early to say, although I doubt that they will.

Dr. Listernick: Thank you everyone. ■

Key Learning Points

1. Hypercalcemia may lead to a variety of psychiatric complaints, ranging from confusion to frank psychosis.
2. Familial hypocalciuric hypercalcemia is due to a loss-of-function mutation in the calcium-sensing receptor in the parathyroid glands and the kidneys.
3. Identification of children with multiple endocrine neoplasia MEN-1 (parathyroid adenomas, pituitary tumors, and pancreatic islet cell tumors) and MEN-2A (parathyroid adenomas, pheochromocytoma and medullary carcinoma of thyroid) is important for preoperative planning.
4. Postoperative hypocalcemia should be anticipated following removal of parathyroid adenoma.