Alerts, Notices, and Case Reports

Chronic Atypical Seizure Disorder and Cataracts Due to Delayed Diagnosis of Pseudohypoparathyroidism

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PSEUDOHYPOPARATHYROIDISM is a genetic form of hypoparathyroidism that results from end-organ resistance to the action of parathyroid hormone (PTH). Hypocalcemia is responsible for many of the clinical features and potential adverse sequelae of this syndrome. We report the case of a patient with pseudohypoparathyroidism type Ib in whom the failure to suspect the presence of severe hypocalcemia delayed the diagnosis despite a history of atypical seizure disorder since childhood and the development of bilateral cataracts in early adulthood.

Report of a Case

The patient, a 27-year-old African-American man with a history of seizures since early childhood, was seen because of muscle twitching and increasing seizure frequency. Significant findings on examination were widely spaced teeth with a marbled appearance, hyperirritability with a strongly positive Chvostek's sign, and mild cognitive impairment. The rest of the findings, including neurologic, were within normal limits. He was 170 cm (67 in) tall and weighed 78 kg (172 lb). Features of Albright's hereditary osteodystrophy were not present. A typical "seizure" was observed, involving pronounced stiffening of all extremities and a coarse tremor without incontinence or loss of consciousness.

His medical history included transient postnatal apneic episodes and notably delayed motor and cognitive developmental milestones. He was considered to have mild mental retardation. At age 11 "spells" developed, often beginning with leg pain followed by flexion of the extremities. An electroencephalogram (EEG) demonstrated some disorganization and slowing, with no epileptiform activity. The diagnosis of convulsive disorder was made, and he was treated with phenytoin with slight improvement.

At 16 he was admitted to hospital for episodes of tingling followed by uncontrollable jerking movements of his extremities. An EEG was unremarkable, and a regimen of diazepam was prescribed with little improvement.

At 21 he was found to have dense subcapsular cataracts bilaterally. The patient underwent three ophthalmologic procedures under general anesthesia without incident. Continued jerking movements and seizure activity led to another medical evaluation at age 27, at which time marked hypocalcemia was found. There was no family history of seizure disorder, hypocalcemia, or skeletal abnormalities.

Initial laboratory findings included a serum calcium level of 1.25 mmol per liter (5.0 mg per dl), phosphorus 2.45 mmol per liter (7.6 mg per dl), albumin 45 grams per liter (4.5 grams per dl), magnesium 0.78 mmol per liter (1.9 mg per dl), blood urea nitrogen 6.8 mmol per liter (19 mg per dl), creatinine 88.4 μmol per liter (1.0 mg per dl), glucose 5.55 mmol per liter (100 mg per dl), free thyroxine index 2.5 (normal 1.6 to 5.2), and thyroid-stimulating hormone 2.5 mU per liter. The alkaline phosphatase level was minimally elevated at 137 U per liter (normal less than 128). A serum 25-hydroxyvitamin D_2 level was 190 nmol per liter (normal 22 to 130; 78 ng per ml), 1,25-dihydroxyvitamin D_3 was 55 pmol per liter (normal 40 to 144; 23 pg per ml), and intact PTH (immunoradiometric assay) was 8.2 pmol per liter (normal 1.0 to 6.9; 77 pg per ml), with a simultaneous serum calcium level of 1.25 mmol per liter. A second PTH value was 8.1 pmol per liter (76 ng per dl), with a simultaneous calcium level of 1.55 mmol per liter (6.2 mg per dl). An x-ray film showed thickening of the skull and salt-and-pepper granularity of the calvarium, possibly consistent with hypoparathyroidism. Intracranial calcifications were not noted. No subperiosteal resorption was demonstrable on hand films. Prior dental films were unobtainable, but roots of teeth appeared normal with intact lamina dura.

An infusion of synthetic human PTH, amino acids 1 to 34, resulted in an increment in nephrogenous cyclic adenosine monophosphate (cAMP) of only 7.4 nmol per liter glomerular filtrate at 30 minutes. Expected incremental responses in normal healthy persons and hypoparathyroid patients are 937 ± 518 and $1,512 \pm 707$ nmol per liter glomerular filtrate, respectively.[1] No phosphaturic response occurred. A thyrotropin-releasing hormone (TRH) stimulation test was normal. The diagnosis of pseudohypoparathyroidism type Ib was made.

Treatment with 1,25-dihydroxyvitamin D_3 (calcitriol) and oral calcium supplements caused a rapid rise in the serum calcium level, which became normal within three weeks. The patient is being maintained on 100,000 IU of vitamin D_2 (ergocalciferol) per day with a serum calcium level of between 1.99 and 2.12 mmol per liter (8.0 to 8.5 mg per dl). Levels of PTH were suppressed to 4.03 pmol per liter (38 pg per ml), within the normal range. The seizures resolved on correction of the hypocalcemia and did not recur over the next 18 months despite the cessation of anticonvulsant therapy. An EEG was repeated and was within normal limits. Cognitive function improved substantially, and the patient became successfully employed.

Discussion

A recent prospective study of patients evaluated in an emergency department for newly occurring seizure activity found metabolic abnormalities in 8% of patients, with hypocalcemia in only 1.5%. The conclusion was that, with the

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ABBREVIATIONS USED IN TEXT

cAMP = cyclic adenosine monophosphate
EEG = electroencephalogram
PTH = parathyroid hormone
TRH = thyrotropin-releasing hormone

exception of serum glucose measurements, further extensive laboratory workup was unnecessary except as indicated by the history and physical examination.[2] Unfortunately, in cases of pseudohypoparathyroidism and idiopathic hypoparathyroidism, the failure to suspect the diagnosis from a history and physical examination findings is often the crux of the problem.[3] Indeed, the most common misdiagnosis in hypocalcemic patients is "idiopathic seizure disorder."

Hypocalcemia may be responsible for a broad spectrum of central nervous system manifestations including lassitude, irritability, impaired cognitive function, and poor school performance. Psychotic behavior and extrapyramidal signs may be found in patients with calcification of the basal ganglia, which occurs in about 50% of untreated patients with hypoparathyroidism and pseudohypoparathyroidism.[4] Severe symptoms include seizures and seizure-like activity that are often precipitated by stress, vomiting, or respiratory alkalosis.

Hypocalcemic seizures can range from syncopal episodes and movement disorders to typical petit mal, grand mal, or focal seizures. Anticonvulsant therapy may delay the diagnosis because both phenytoin and phenobarbital therapy may diminish or eliminate the signs and symptoms of tetany.[5] Correcting the hypocalcemia results in symptomatic improvement regardless of the seizure pattern.

Cataract formation is associated with prolonged hypocalcemia and appears to be correlated with the duration of the abnormality.[6] The mechanism remains obscure.

Type I pseudohypoparathyroidism is a heterogeneous disorder characterized by blunting of the nephrogenous cAMP and phosphaturic responses to infused PTH.[7] Patients with type Ia have Albright's hereditary osteodystrophy and diminished Gs protein activity, ascribed to specific mutations in the genes encoding the G proteins.[8] This generalized defect may result in a decreased production of cAMP[9] and can cause resistance to multiple cAMP-mediated hormones, such as TRH and gonadotropin-releasing hormone.[10] Patients with type Ib do not have Albright's hereditary osteodystrophy, and their Gs activity is normal. Instead, they exhibit specific resistance to PTH, which is thought to result from a defect in the PTH receptor.[11] Our patient lacked Albright's hereditary osteodystrophy, failed to show a cAMP response to infused PTH 1 to 34, and had a normal TRH stimulation test, suggesting a diagnosis of pseudohypoparathyroidism type Ib.

Conclusion

Hypocalcemia due to pseudohypoparathyroidism or hypoparathyroidism may occur in the context of a vague or misleading history and in the absence of typical physical stigmata.[12] Given the potentially subtle manifestations and long-term morbidity from a delayed diagnosis, as evidenced in this patient, we suggest that all patients with presumptive seizure activity or premature cataracts be screened for hypocalcemia.

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Hypokalemia as a Cause of Tetany

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TETANY IS A condition characterized by sustained muscular contraction that often occurs in the acute care setting. We report a case of classic tetany with an uncommon, though significant, etiologic mechanism that to our knowledge has not been reported in the recent literature.

Report of a Case

The patient, a 28-year-old woman, was admitted to the Cedars-Sinai Medical Center (Los Angeles, Calif) for the evaluation of anorexia, nausea, and weakness. She was a vigorous, athletic woman who was reportedly in excellent health until ten weeks before admission when fatigue, nausea, and generalized weakness developed. In the five weeks before admission, she had intermittent episodes of uncontrollable, generalized, sustained muscular spasms of her extremities and trunk lasting as long as half an hour and occurring without apparent precipitating cause. She said she had not lost consciousness and did not have incontinence or tonic-clonic activity. She had been seen as an outpatient three times and had serum potassium levels ranging from 2.1 to 2.3 mmol per liter. The patient said that she took vitamins and levothyroxine but did not use cigarettes or alcohol or abuse drugs. There was no family history of neuromuscular disease.

Physical examination revealed no abnormalities. Her pulse rate was 70 beats per minute, and blood pressure was

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