



Case of primary hyperparathyroidism presenting with ADHD (Attention Deficit Hyperactivity Disorder)-like symptoms

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General Note



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ABSTRACT

The paper presents the case report of a 14-year-old adolescent boy initially presented to the psychiatric clinic with behavioral symptoms consistent with those associated with Attention Deficit Hyperactivity Disorder (ADHD) including inability to concentrate, hyperactivity, and poor school performance. Based on DSM-IV-TR (The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision) criteria, ADHD diagnosis was confirmed and he was started on medication treatment without a significant improvement of symptoms. More than two years later, an elevated parathyroid hormone, hypercalcemia, and hypophosphatemia led to a diagnosis of Primary Hyperparathyroidism. After clinical, laboratory and radiological examination, Adenoma of the right inferior parathyroid gland was successfully diagnosed and surgically removed. Upon regulating the patient's calcium levels, his mood, concentration, and cognitive function were back to baseline 6 months post operation. The common theme of resolving ADHD symptoms upon regulating the calcium levels, highlights the importance of careful evaluation of all possible secondary causes of

Attention Deficit Hyperactivity Disorder (ADHD) during the Initial psychiatric assessment and at each follow-up visit, especially when multiple medications have been ineffective or poor response is noticed.

Keywords: Primary Hyperparathyroidism, Hypercalciemia, Attention Deficit Hyperactivity Disorder, Parathyroid Adenoma

Abbreviations: DSM-IV-TR -The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; MEN1-Multiple Endocrine Neoplasia Type 1, MEN2-Multiple Endocrine Neoplasia Type 2.

1. INTRODUCTION AND RATIONALE

Psychiatric syndromes have consistently been described or documented in endocrine diseases. Historically, several authors have speculated about the role of hormones and endocrine disorders in relation to psychiatric conditions. Particular attention has been devoted to the role of hormones in relation to control and feedback processes in neural structures. Recent improvements in diagnosis and treatment of the hormonal disorders resulted in most severe psychiatric syndromes in endocrine diseases are not as frequent as in the past, yet, a high prevalence of psychiatric disturbances has been reported in most endocrine conditions, including adrenal, pituitary, pancreas, thyroid and parathyroid diseases. This paper is focused on Primary Hyperparathyroidism (PHPT) due to posing a real clinical challenge for psychiatrists working in general hospitals (liaison or psychosomatic psychiatrists). Some of the challenges posed by Primary Hyperparathyroidism (PHPT) include that :

1. Primary Hyperparathyroidism it is a rare condition in pediatric population and not commonly encountered in a variety of clinical settings. Other than several isolated case reports over the past few decades [1,2,3,4] , there are relatively few modern literature documentations regarding epidemiology of psychopathology in hyperparathyroidism. Also, none of the standard pediatric texts or recent clinical reviews mention Primary Hyperparathyroidism or Hypercalciemia as either a cause of ADHD or having symptoms similar to those of ADHD [5,6,7].
2. The symptoms of Primary Hyperparathyroidism may be associated with a wide range of psychological symptoms as it original as occurred in our case: a boy who presented with symptoms of ADHD with only partial response to stimulants for 2 years, before developing endocrine symptoms that led to the diagnosis of PHPT.

2. BACKGROUND

Attention Deficit/Hyperactivity Disorder (ADHD) is a neuropsychiatric disorder that begins in childhood that affects 3–5% of the population or more [5,6,7]. According to the current criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text-revision (DSM-V-TR), ADHD is defined as persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, has symptoms presenting in two or more settings (e.g. at home, school, or work; with friends or relatives; in other activities), and negatively impacts social, academic or occupational functioning. Several symptoms must have been present before age 12 years [8]. The disorder is probably heterogeneous in origin although genetics appear to play an important role [9]. Family, twin, adoption, segregation analysis, and molecular genetic studies show that it has a substantial genetic component that involves norepinephrine and dopamine receptors in certain brain regions, mainly the prefrontal cortex and basal ganglia. Untreated ADHD is associated with significant impairment in multiple domains of patient's daily living and can lead to serious Neuropsychiatric and Medical consequences. Growing body of data suggests that ADHD is associated with considerable morbidity and poorer outcomes later in life.

Primary Hyperparathyroidism (PHPT) is an endocrine disease that occurs when the parathyroid glands lose the ability to regulate Parathyroid Hormone (PTH) secretion via a negative feedback mechanism with calcium. PHPT occurs in 112 of every 100,000 persons with highest incidence in the sixth and seventh decade of life and average age at diagnosis is 55 years[10, 11]. Primary Hyperparathyroidism is the most common cause of

Primary hyperparathyroidism

The symptom of Primary hyperparathyroidism is classically summarized by the mnemonic "stones, bones, abdominal groans, and psychiatric overtones". These symptoms occur secondary to hyperparathyroid disease-induced hypercalcemia

1. "Stones" refers to kidney stones or Nephrolithiasis
2. "Abdominal groans" refers to gastrointestinal symptoms of constipation, indigestion, nausea and vomiting.
3. "Bones" refers to bone-related complications that are the result of abnormal bone remodeling due to overproduction of PTH.
4. "Psychiatric overtones" refers to depression symptoms that may occur in the presence of persistently elevated serum calcium levels.

hypercalcemia[12]and the leading sign of disease is Hypercalcemia with hypophosphatemia. However, serum phosphate levels are regulated by many factors, including dietary intake. Serum phosphate levels sometimes remain in the normal range in patients with primary hyperparathyroidism. The most common cause of Primary Hyperparathyroidism is parathyroid adenoma, followed by hyperplasia, and carcinoma only in 1 to 2% of cases. The sole purpose of the parathyroid hormone is to control blood calcium within a very tight range between 8.5 mg/dL and 10.5 mg/dL. Any decrease in the normal levels of calcium in the blood causes the parathyroid gland to secrete more Parathyroid Hormone which acts primarily on bone, kidney, and intestines. It increases calcium absorption from bone and intestine and decreases calcium excretion by kidneys.(13) The classical symptoms and signs of Primary Hyperparathyroidism reflect the combined effects of increased PTH secretion and hypercalcemia. These are known as the "bones, stones, abdominal moans, and psychic groans." The abnormalities directly associated with hyperparathyroidism are nephrolithiasis and bone disease; both are due to prolonged PTH excess[14,15]. Symptoms attributable to hypercalcemia include

anorexia, nausea, constipation, polydipsia, and polyuria. The Psychiatric presentations of hyperparathyroidism (PHPT) are the result of hypercalcemia. It includes cognitive dysfunction, affective disorders, psychosis, lethargy, and decreased social interaction. PHPT could be associated with significant psychiatric diagnoses like anxiety, depression, and psychosis. Delirium or dementia, lethargy or apathy, and stupor or even coma can be observed in people with this endocrinopathy[16]. The exact prevalence of such abnormalities is not well defined due to the lack of rigorous assessment for symptoms in many studies.

Multiple Endocrine Neoplasia Type 1 (MEN1):

It is an autosomal dominant familial tumor syndrome (also termed Wermer syndrome) in which persons develop tumors of the parathyroid glands, the enteropancreatic neuroendocrine system, the anterior pituitary gland, and the skin (1,2)

1. Guideline] Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab.* 2012 Sep. 97(9):2990-3011. [Medline].
2. Carroll RW. Multiple endocrine neoplasia type 1 (MEN1). *Asia Pac J Clin Oncol.* 2013 Dec. 9(4):297-309. [Medline].

3. CASE REPORT

A 14-year-old adolescent boy was referred to the general psychiatric clinic due to decreased school performance, behavioral and attention difficulties in school. Patient's medical and family history were unremarkable. There was no family history of ADHD, Anxiety, depression, psychosis or suicide attempts, and no previous psychiatric hospitalizations. The patient was the product of normal spontaneous full term planned pregnancy. Normal prenatal and post natal course. The patient was born at 38 weeks and had normal developmental milestones. His parents described him as active like other normal boys. The patient was the eldest of three siblings of a stable parental marital relationship and socio-economic status. He did not consume alcohol or smoke and denied using drugs.

Parents reported that patient's problems started when he was 12 years old, and that they have gotten worse over the following 2 years in the context of no obvious stressors. He had difficulty listening in class and did not complete his work properly. The school had him tested and he did not qualify for special education services. His neuropsychological test showed some auditory processing disorder but the overall score was average.

Before age 12-year-old, the patient did not appear to have any academic or behavioral problems, was an average academic school performer and active in the school cadets, and computer class. The Patient had his first psychiatric evaluation in April 2012 when he was referred to the general psychiatric clinic due to behavioral and attention difficulties in school. He presented with irritable mood, loss of interest in school, deteriorating academic performance, and difficulty concentrating, particularly in school. The diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) was made based on DSM-IV-TR criteria and

he was started on medication treatment. He failed a trial of methylphenidate (Concerta) 18 MG because of side effects (tachycardia and sleeping difficulties) as he was not able to sleep more than 3 hours per day. In June 2012, few weeks after Methylphenidate (Concerta) was discontinued, the patient was started on Amphetamine/ Dextroamphetamine Immediate Release (Adderall IR) 5 MG daily, which was well tolerated. The Amphetamines IR (Adderall IR) dose was titrated up total of 20 MG per day over a period of 8 months. In December 2012, the patient was on Amphetamines IR (Adderall IR) 10 MG in the morning and 10 MG in the afternoon with good academic and behavioral responses. In September 2013, the patient's parents reported that some of his initial symptoms had returned (declining grades, hyperactivity, and inability to complete and turn-in homework). The decision was made to increase his morning dose of Amphetamines IR from 10 MG to 20 mg. He continued on the same afternoon dose, Adderall IR 10 MG. In December 2013, the patient reported continued improvement in attention and concentration on the higher dose Amphetamines IR in the morning, however, he felt that the medication's effect was lasting for only 3 hours in his system as he had to take his afternoon dose earlier. Because the extended-release form of the Adderall has a longer duration, up to 12 hours per day, The decision was made to change his morning medication's preparation from Adderall Immediate-Release 20 MG to Adderall Extended-Release 20 MG. He continued on the same afternoon dose and form, Adderall IR 10 MG. The following six months, the patient continued to make grade-appropriate progress in school with no behavioral or emotional issues. In June 2014, the patient reported that some of his ADHD symptom (Poor concentration and Short attention span) had gradually gotten worse. He felt that his afternoon dose of Amphetamines IR 10 mg was not helping to stay focused and complete his homework at home. Medication adjustment was done and his morning dose of Amphetamine XR was increased to 30 mg daily with a good response that lasted for 8 weeks. In August 2014, another medication adjustment was done due to inadequate response. The decision was made to change his afternoon medication's preparation from Adderall Immediate-Release 10 MG to Adderall Extended-Release 20 MG and as needed dose of Amphetamine IR 10 mg was added to be used in the later afternoon. He continued on the same Morning dose and form, Adderall XR 30 MG. In March 2015, the patient was admitted to the emergency room with complaints of general weakness, vomiting, polyuria and polydipsia. He was hospitalized and his physical examination at that time was unremarkable. Mental State Examination revealed a well-kempt adolescent with no perceptual disturbance. He was orientated to time, place and person. Laboratory data on admission were as follows: Hemoglobin and hematocrit were 12.4g/dl and 32.6%; white cell count was 8,600/mm³; serum electrolytes were 128mEq/L for sodium, 4.0mEq/L for potassium, 111mEq/L for chloride, 100 mg/dl for random blood glucose, 13.7mg/dl for calcium and 5.3mg/dl for phosphorus; Parathyroid hormone (PTH) was elevated 110 pg/ml. BUN 22mg/dl, Creatinine 1.4mg/dl; Alkaline phosphatase 110U/L, liver function tests were normal; urine analysis was normal. Given the acute presentation, the patient was admitted to the hospital. During the first few days of hospitalization, the patient underwent conservative management with intravenous fluid. Because his high PTH level, the major concern was a possible parathyroid tumor. Multiple endocrine Neoplasia was ruled out by normal results of endocrine laboratory examinations. An ultrasound scan of his neck revealed a 2 cm well-defined oval hypoechoic mass posterior and inferior to right thyroid lobe. Ten days after admission, the patient underwent a neck exploration. During the exploration, the right inferior gland was found to be large, cystic, soft, and of a brown colour. Pathological examination revealed that the chief cells had proliferated homogeneously with a trabecular pattern and an alveolar pattern. This finding was compatible with parathyroid adenoma. There was no evidence of

local invasion and no lymphadenopathy. As such, a diagnosis of adenoma was made. The right inferior parathyroid gland was excised. The right superior parathyroid gland was normal, and the contralateral neck was not explored. Postoperative period was uneventful. Laboratory test showed calcium levels and parathyroid hormone within normal ranges at the time of discharge. The Amphetamine doses were gradually tapered off over 4 weeks. The patient's moods, concentration, and cognition function were back to baseline 6 months post operation.

Multiple Endocrine Neoplasia Type 2 (MEN2):

It is a rare familial cancer syndrome caused by mutations in the RET proto-oncogene. Patients may present with symptoms related to medullary thyroid carcinoma, hyperparathyroidism, or pheochromocytoma (1). The genetic defect in MEN2 is on chromosome 10 (10q11.2) and has also been identified both for MEN2A and MEN2B (3,4).

1. Richards ML et al, Type 2 Multiple Endocrine Neoplasia, Medscape, Apr 2011
2. Multiple Endocrine Neoplasia Type IIA; MEN2A, Online Mendelian Inheritance in Man (OMIM)
3. Multiple Endocrine Neoplasia Type IIB; MEN2B, Online Mendelian Inheritance in Man (OMIM)

4. CASE DISCUSSION

Primary hyperparathyroidism is most frequent in the sixth decade of life in postmenopausal women. This disease is rare in children and might be caused by several endocrinopathies with a genetic basis, such as MEN type 1 or 2 [12]. In our patient, results of endocrinological investigations ruled out MEN.

In pediatric population, the diagnosis of this disease is commonly delayed mainly because the initial clinical presentation of primary hyperparathyroidism (PHPT) are signs and symptoms of nonspecific diagnosis like irritable bowel syndrome, fibromyalgia, or stress reaction. and Psychiatric symptoms may be the most prominent manifestation of PHPT for years as occurred in our case: a boy who presented with symptoms of ADHD with only partial response to stimulants for 2 years before developing endocrine symptoms that led to the diagnosis of PHPT.

Psychiatrists must be mindful of the possibility of organic disease masking as ADHD like symptoms because symptoms like inattention or deterioration in school performance can be a sign of multiple medical and psychiatric problems. It is very important to evaluate all of the possible secondary causes of ADHD during the initial psychiatric assessment and at each follow-up visit, especially when multiple medications have been ineffective or poor response is noticed. Data showed that 70% of children who have ADHD have a positive response to stimulants such as methylphenidate. An additional 20% respond to the alternative class of stimulant medications. Poor response to these medications could possibly suggest the presence of a comorbid disorder. In general, it is very important that Psychiatrists should have a good general understanding of the signs and symptoms associated with elevated or decreased hormone levels because it can assist them in making the correct diagnosis and ultimately increases the likelihood that a patient receives appropriate treatment in a timely manner

5. CONCLUSION

1. Common themes in this case was the symptoms of ADHD resolving after calcium levels were regulated highlights the importance of the careful evaluation of all possible secondary causes of ADHD during the initial psychiatric assessment and at each follow-up visit, especially when multiple medications have been ineffective or poor response is noticed.
2. Our case highlights two important aspects of parathyroid disease that we would like to explore further. First, the difficulty in diagnosis Primary Hyperparathyroidism in pediatric patients and how important is to conduct Comprehensive Metabolic Panel. Second, the importance of the evaluation of secondary causes of ADHD during the initial psychiatric assessment and at each follow-up visit especially when multiple medications have been ineffective or symptoms are out of the ordinary for ADHD. In conclusion, we offer this uncommon case to demonstrate possibility of Primary Hyperparathyroidism as a cause of ADHD.

SUMMARY

In summary, adolescent boy with PHPT presented primarily with behavioral symptoms similar to those of ADHD. Tumor resection resulted in complete resolution of all of these symptoms. Although organic etiologies such as parathyroid adenoma are rarely identified in ADHD, one should be suspicious if the age of onset is atypical or if the patient has signs or symptoms not usually associated with ADHD or when poor response to treatment is noticed.

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