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A Saudi Girl with Familial Glucocorticoid Deficiency Presented with Visual Hallucinations as a Sign of Adrenal Insufficiency Crises: Case Report and Literature Review

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Abstract

Introduction: Familial glucocorticoid deficiency (FGD) is a disease of ACTH resistance in which the cells of the zona fasciculata within the adrenal cortex fail to respond appropriately to stimulation by ACTH to produce cortisol. Genetic testing is essential in patients presented with familial isolated glucocorticoid deficiency (FGD)/ACTH resistance demonstrates mutations in the ACTH receptor gene melanocortin two receptors (MC2R), which indicates an apparent probability for causing primary adrenal insufficiency. FGD is manifested by glucocorticoid deficiency alone.

Case description: 12 years old female who was in regular follow-up with an endocrinologist as a case of adrenal insufficiency and query IMAGe syndrome. The patient presented to the emergency department with a history of confusion state, frontal headache, blindness, visual hallucination, and vomiting. After presenting to ER, the patient was treated with corticosteroid, and she dramatically regained her level of consciousness and improved. Whole exome sequencing (WES) was sent and revealed a homozygous mutation in the melanocortin two receptors (MC2R) gene, indicating familial glucocorticoid deficiencies.

Conclusions: Adrenal insufficiency should be suspected in a child with familial glucocorticoid deficiency who presents to the hospital with no specific psychiatric signs as visual hallucination. Early diagnosis and early management are crucial to address for a full recovery.

Keywords: Familial glucocorticoid deficiency; Melanocortin 2 receptors (MC2R) gene; Adrenal

insufficiency; Psychiatric manifestation; Visual hallucination

Introduction

Glucocorticoid Insufficiency, also known as adrenal insufficiency, is the clinical effect of inadequate glucocorticoid production or function, including mineralocorticoid and adrenal androgen deficiency. Adrenal insufficiency can lead to life-threatening conditions, including primary adrenal failure and secondary adrenal disease caused by hypothalamic-pituitary-adrenal dysfunction. It can arise from a primary adrenal disorder, secondary to adrenocorticotropic hormone deficiency, or by suppression of adrenocorticotropic hormone by exogenous glucocorticoid or opioid medications. Congenital Adrenal Hyperplasia (CAH) is a class of disorders characterized by a lack of certain enzymes in the steroidogenesis pathway, resulting in poor cortisol synthesis. Patients with CAH may have Hormone Replacement Therapy (HRT) for a variety of conditions, depending on the nature and severity of the steroid block.

Adrenal hypoplasia is a condition that represents underdevelopment or adrenal cortex hypotrophy **[1].** The complex mechanisms behind human adrenal development remain poorly explained **[2].** Adrenal hypoplasia can occur primarily as a defect in the development of the adrenal gland, in the setting of chromosomal abnormalities, or as a part of syndromes that can be inherited in an autosomal recessive or dominant manner. It can also occur secondary to defects in transcription factors involved in pituitary development or defects in Adrenocorticotropin hormone synthesis and secretion **[3].** Recently, several identified single-gene disorders can affect the hypothalamic-pituitary-adrenal (HPA) axis at different levels, and a genetic cause is found in approximately 50% of all individuals **[2].** Familial Glucocorticoid Deficiency (FGD), also known as ACTH unresponsiveness, is an autosomal recessive disorder that is characterized by a lack of glucocorticoids (glucocorticoids) when mineralocorticoids deficiency is not present. Mutations in the ACTH receptor (also known as MC2R) account for about 25% of all cases of FGD. More recently, a second gene (MRAP) has been identified and accounts for about 15–20% of all FGD cases. MRAP is a small single transmarine domain protein that plays an important role in the transport of MC2R to cell surface, also there are another gene defect as the MRAP, MCM4 and TXNRD2. The first signs of FGD usually appear during early childhood. The acute adrenal crisis may be precipitated by an ongoing illness, or recurrent hypoglycaemia (commonly accompanied by seizures). Other nonspecific symptoms may include lethargy, poor growth, pale skin and delayed developmental milestones, as well as hyperpigmentation caused by high ACTH levels. Serum electrolytes are typically normal, as aldosterone is primarily regulated by the renin-angiotensin. Plasma cortisol levels may be undetectable or low-normal when high, and do not respond exogenously to ACTH, suggesting that patients are ACTH-resistant.

Although they share symptoms with lesser hypoadrenal conditions, adrenal crises are the most severe manifestation of adrenal insufficiency. Anorexia, nausea, vomiting, exhaustion, postural dizziness, abdominal discomfort, back and limb pain, and diminished consciousness are some of these symptoms. Hyponatremia, hypoglycemia, and hyperkalemia (in primary adrenal insufficiency, such as Addison's disease and congenital adrenal hyperplasia) are examples of common biochemical disturbances (more common in children than in adults). Acute illness, however, should be classified as symptomatic adrenal insufficiency, a precursor

to adrenal crisis, or an incipient adrenal crisis instead of being physiologically distinct from an adrenal crisis in a patient who has previously been diagnosed with primary adrenal insufficiency and does not exhibit evidence of hemodynamic compromise or hypotension (or, in the case of young children, delayed capillary refill or tachycardia as alternative physical manifestations).Significant symptoms without hypotension are likely an indication of an impending adrenal crisis, which can be prevented with hydrocortisone and intravenous fluids. We will report the first case, to our knowledge, of adrenal insufficiency on low dose corticosteroid treatment who presents to the emergency department with a visual hallucination manifest.

Case Description

We present the case of a 12-year-old female who has been under regular follow-up with an endocrinologist for adrenal insufficiency, with a possible diagnosis of IMAGe syndrome. The patient has a history of bone deformity in her left leg, which worsened with age and required multiple surgical corrections. She was maintained on hydrocortisone 5 mg twice daily (equivalent to 6.5 mg/m^2/day) and fludrocortisone 0.1 mg once daily. She presented to the emergency department with confusion, frontal headache, blindness, and vomiting. She awoke in the afternoon with a severe frontal headache and sudden blindness, followed by confusion and amnesia regarding the episode. She subsequently developed visual hallucinations, manifested as inappropriate laughter, talking to herself, and pointing at non-existent objects. Alarmed, her parents brought her to the emergency department. Systemic review was otherwise unremarkable. Her past history revealed that at birth she had a normal birth weight and was discharged home in good health. However, within the first 40 days of life, she developed skin hyperpigmentation. Medical evaluation in the other hospital led to a diagnosis of congenital adrenal hypoplasia. She has had multiple episodes of hypoglycemia, with poor compliance to her medications.

Family history was significant for consanguineous parents (first cousins), both of whom are healthy. She has five siblings, two of whom are males, affected by adrenal insufficiency but without skeletal nor genitalia abnormalities. There is also a history of recurrent miscarriages in her extended family (uncle and aunt) and an affected cousin with no identified cause. The patient herself plays an active role in managing her own treatment and in assisting with the care and medications of her siblings.

On examination, the patient appeared hydrated but tachycardic (heart rate 137 bpm), with borderline low blood pressure for her height and gender. She was hypoglycemic (blood glucose 2.9 mmol/L), disoriented, and experiencing visual hallucinations, speaking and laughing inappropriately. She had generalized hyperpigmentation, normal female genitalia, and lower limb deformities with multiple surgical scars on the left side. This was her first presentation to our hospital. Given her poor supervision, uncertain medication adherence, her clinical condition, and the presence of marked hyperpigmentation, adrenal crisis was strongly suspected. After laboratory investigations (including toxicology screening to rule out ingestion as a cause of hallucinations), she was treated with stress-dose hydrocortisone. Remarkably, she showed immediate clinical improvement, regaining consciousness, normalizing vital signs, and achieving euglycemia (blood glucose 6.3 mmol/L). Laboratory results showed a markedly elevated ACTH level of 850 pg/mL, which decreased after treatment but did not

normalize. Toxicology screening was negative. Because of the absence of genital anomalies, IMAGe syndrome was considered less likely. Familial glucocorticoid deficiency was strongly suspected, and whole-exome sequencing confirmed the diagnosis, revealing a homozygous MC2R mutation: c.459dup p.(Ile154Hisfs*95), chr18:13885058.

Discussion

Familial Glucocorticoid Deficiency (FGD) is a disease of ACTH resistance in which the cells of the zona fasciculata within the adrenal cortex fail to respond appropriately to stimulation by ACTH to produce cortisol [4]. Genetic testing is essential in patients presented with familial isolated glucocorticoid deficiency (FGD)/ACTH resistance demonstrates mutations in the ACTH receptor gene melanocortin 2 receptors (MC2R), which indicates an apparent probability for causing primary adrenal insufficiency [5]. FGD is manifested by glucocorticoid deficiency alone. Therefore, the patient exhibits low cortisol and high ACTH levels [4]. Lack of glucocorticoids level consequently leads to hypoglycemia and/or failure to thrive within the neonatal or very early childhood period [4]. While in older children, the main presentation is recurrent infections or hypoglycemic seizures. If the diagnosis is undetected or managed might lead to learning difficulties, neurological symptoms, and considered as a life-threatening condition [4]. The excessive production of ACTH is often secondary to hyperpigmentation due to overstimulation of Melanocortin 1 Receptors (MC1R), which can lead to neuropsychiatric manifestations, for example, depressive symptoms, irritability, sleep disorders, apathy, cognitive impairment, delusions, and hallucinations, which can also be seen during adrenal insufficiency [4]. IMAGe syndrome is an acronym for Intrauterine Growth Restriction (IUGR), metaphyseal dysplasia, adrenal hypoplasia congenita, and genitourinary abnormalities in males, including cryptorchidism, micropenis, and hypospadias [6].

Preventing adrenal crisis is a critical clinical concern because patients with adrenal insufficiency have a potentially fatal risk of experiencing one. A retrospective analysis was conducted on the medical records of 137 patients who had been diagnosed with adrenal insufficiency in order to identify the risk factors for adrenal crisis. The explanatory variables analyzed were gender, etiology of hypoadrenalism, class of adrenocortical hormone replaced, duration of steroid replacement, age at time of survey, age at time of diagnosis of hypoadrenalism, state of other hormone deficiencies (growth hormone and sex steroids), diabetes insipidus, and mental disorder. Laboratory and physical findings were used to diagnose adrenal crisis. Out of the 137 patients, 40 (or 29%) experienced at least one adrenal crisis episode. According to the Akaike Information Criterion (AIC), mental illness and sex steroid deficiency were the next two biggest single contributors to the occurrence of an adrenal crisis, with steroid replacement therapy lasting longer than four years coming in third. In the subclass of patients with secondary adrenal insufficiency (N = 115), sex steroid deficiency was the greatest risk factor. In comparison to patients without hypogonadism or with treated hypogonadism, those with untreated hypogonadism had a significantly higher relative risk of 3.70 (95% confidential interval: 1.71-7.98). Additionally, among hypogonadism patients under 50 years old, those who received sex hormone treatment (5/51: 10%) experienced adrenal crisis less frequently than those who did not (7/11: 64%, p = 0.0004). In this case report, we present a familial glucocorticoid deficiency, MC2R homozygous mutation, who presents to our

emergency department with visual hallucination. To our knowledge, this is the first unique case report with this presentation. There is a well-known correlation between corticoid excess disorders such as Cushing's syndrome and neuropsychiatric presentations, which is the opposite of our patient who has adrenal insufficiency [7].

A multi number of scientific literatures show steroid induce of psychiatric presentation in children and adolescents [7-9]. Steroid-induced psychosis can be encountered in children with asthma, autoimmune diseases, and cancer [8]. There would be a variation of the symptoms. However, the most prominent symptoms consist of emotional lability, anxiety, distractibility, pressured speech, sensory flooding, insomnia, depression, confusion, agitation, auditory and visual hallucinations, intermittent memory impairment, body image disturbances, delusions, apathy, and hypomania [8]. The risk of severe acute psychosis was identified as the result of adrenal crisis treatment with high doses of hydrocortisone [10]. Steroid psychoses were mainly seen in the adult population, and as we discussed earlier, it is the opposite of our case presentation [7-9]. On the other hand, uncommonly, adrenal insufficiency can manifest with psychiatric manifestation [11-16]. The neuropsychiatric manifestations include depressive symptoms, irritability, fatigue, sleep disorders, apathy, cognitive impairment, confusion, delusions, and hallucinations [11,12]. Interestingly, a case report shows severe psychotic disorder as the only presentation of primary adrenal insufficiency [11]. Psychiatric manifestation is also reported in a patient with secondary adrenal insufficiency; for example, a patient on medication likes opiate [14].

Patients with conditions ranging across multiple fields, such as psychiatry, neurology, and ophthalmology, often experience hallucinations, which are characterized as the perception of an object or event (in any of the five senses) within the absence of an external stimulus. Although visual hallucinations are not pathognomonic of a primary psychiatric illness, they are frequently the cause of requests for psychiatric consultation when observed by non-psychiatrists. The causes of visual hallucinations are varied. Here, we offer a differential diagnosis of visual hallucinations and discuss potential mechanisms, with a focus on conditions that occur in the context of medical and surgical illness. The underlying etiology is usually the basis for treatment, so early identification and comprehension of the causal mechanisms are essential. A multitude of theories have been proposed to account for the origins of visual hallucinations. Asaad and Shapiro1 summed them up and divided them into three categories: psychophysiological (a disruption of brain structure), psychobiochemical (a disruption of neurotransmitters), and psychodynamic (a manifestation of the unconscious into consciousness). Due to the interaction between abnormalities in brain chemistry, prior experiences, psychodynamic meaning, and brain anatomy, visual hallucinations can arise from any one of these three processes. Although there isn't yet a single brain mechanism that can account for all kinds of visual hallucinations, there may be a final common pathway given the similarities among visual hallucinations linked to seemingly unrelated conditions. Hallucinations may happen at any age but resemble more frequently in children and adolescents, and visual hallucinations are the most common type [17,18]. Visual hallucinations can be benign but also are featured prominently in different neurological and psychiatric disorders [18]. It occurs in almost 25 % of patients diagnosed with schizophrenia [18]. It is also may occur with the use of a number of medications as antiepileptic drugs, pregabalin, and Clarithromycin [18-27].

After extensive research, we did not find any case report of an association between visual hallucinations and adrenal sufficiency.

Conclusion

Adrenal insufficiency should be suspected in a child with familial glucocorticoid deficiency who presents with no specific psychiatric signs as visual hallucination. Early diagnosis and early management are crucial to address for a full recovery.

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