

CASE REPORTS

SKIN HYPERPIGMENTATION: FROM ENDOCRINE DYSFUNCTION TO PEROXISOMAL DISEASE

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Abstract

Primary adrenal insufficiency, a rare disease in pediatric population, has different etiologies that determine treatment and prognosis. Clinical manifestations can be insidious and subtle, delaying the diagnosis. Hyperpigmentation is a characteristic sign of primary adrenal insufficiency and it can be the only manifestation. X-linked adrenoleukodystrophy is a peroxisomal disorder characterized by very long chain fatty acids accumulation in different organs, namely adrenal gland, leading to adrenal insufficiency. The authors report a 10 years-old boy who presented with behavioral changes, hyperactivity, poor school performance and hyperpigmentation. He was diagnosed to have primary adrenal insufficiency secondary to X-linked adrenoleukodystrophy. His diagnosis was delayed because of the initial vague symptoms. With this case the authors aim to increase the awareness to different clinical manifestations of primary adrenal insufficiency as well as create awareness that X-linked adrenoleukodystrophy is an important etiology of adrenal insufficiency in boys.

Keywords: hyperpigmentation, peroxisomal disorder, primary adrenal insufficiency, very long chain fatty acids, x-linked adrenoleukodystrophy.

Introduction

Adrenal insufficiency, a relatively rare disease in pediatric population, is defined by the impaired synthesis and release of adrenocortical hormones. (1-3) The hypothalamic-pituitary-adrenal axis is essential in stress response. The hypothalamus produces and releases the corticotrophin releasing hormone (CRH), which induces the release of adrenocorticotrophic hormone (ACTH) by the pituitary. ACTH acts in the adrenal gland and induces the production and releasing of glucocorticoids (cortisol), mineralocorticoids (aldosterone) and androgens. (2) Adrenal insufficiency may be categorized as primary, secondary or tertiary, depending if the problem arises from adrenal, pituitary or hypothalamus tissues, respectively. (1,2) Symptoms of adrenal insufficiency are variable, depending on which hormones are deficit and also depend on the evolution of the disease. Thus, while acute adrenal insufficiency generally presents with nausea, vomiting, fatigue, abdominal pain, dehydration, hypotension, hypoglycemia, hyponatremia, hyperkalemia and metabolic acidosis, patients with chronic adrenal insufficiency usually present with chronic fatigue, anorexia, nausea, vomiting, loss of appetite, weight loss, salt-craving and skin pigmentation. (2-4) The diagnosis is frequently delayed because of its non-specific early symptoms. (1,3) This delay or no recognition could predispose to adrenal crises, which are life-threatening events. (1,3) Primary adrenal insufficiency, also known as Addison disease, results in the inability to produce adequate amounts of glucocorticoids, mineralocorticoids and androgens, despite an increased concentration of ACTH. (5) There are numerous causes of primary adrenal insufficiency,

one of them being the X-linked adrenoleukodystrophy (X-ALD).

X-ALD is a metabolic disorder characterized by impaired peroxisomal beta-oxidation that results in accumulation of very long-chain fatty acids (VLCFA) in plasma and tissues, including the white matter of the brain, spinal cord and adrenal cortex. (4,6-8) It is caused by mutations in ABCD1 gene (ATP-binding cassette, subfamily D, member 1 gene), located in X-chromosome, resulting in absence or dysfunction of adrenoleukodystrophy protein (ALDP), a peroxisomal transmembrane protein necessary to transport VLCFacyl-CoA esters from the cytosol into the peroxisome. (4,6,8) Different phenotypes are associated with this disease namely, cerebral ALD (childhood, adolescent or adult phenotype), adrenomyeloneuropathy and Addison only. (6) These disorders vary in the age of onset and severity and can change over time, although progression of X-ALD in a specific individual cannot be predicted. (6,7) X-ALD may present as adrenocortical insufficiency even decades before the onset of neurological symptoms. (6) In fact, X-ALD is a frequent cause of Addison's disease, being reported in about 35% of the cases. (6) It is therefore important to consider X-ALD in any boy presenting with Addison's disease. (6)

We report a 10 years-old boy in whom the diagnosis of Addison disease, caused by X-ALD, was delayed for about 5 years.

Case Report

A 10 years-old boy was referred to the pediatric and child psychiatry clinics because of behavioral changes, hyperactivity, poor school performance and hyperpigmentation, which have begun 5 years before. His personal history was unremarkable and no history of consanguinity was identified. Regarding his family history, there were some maternal relatives with undefined cerebral disorder. There was also a 9-years-old cousin who lost his motor skills since at 2 years of age and had now become bedridden.

The child psychiatrist diagnosed a hyperactivity attention deficit disorder and initiated treatment with methylphenidate. At the time of the pediatric evaluation the child had no new signs or symptoms. The patient was afebrile and his vital signs were within the normal range, namely his blood pressure was 90/60 mmHg (50th percentile for gender, age, and height). His weight was 26 kg (10th percentile) and his height was 125cm (<5th percentile). He had a generalized hyperpigmentation including oral mucosa, corresponding to a phototype 5. The remaining examination was normal, including the neurological exam. The evaluation of old photographs demonstrated that this child previously had a skin phototype 2, similar to his brothers. On investigations, complete blood count, renal, thyroid and liver function, iron kinetics, copper and ceruloplasmin were all within the normal range. Early morning serum cortisol and

adrenocorticotrophic hormone (ACTH) were 4.5 ug/dL (Normal 3.7 – 19.4 ug/dL) and >1000 pg/dL (Normal 9 – 52 pg/dL), respectively. Plasma renin activity (PRA) was normal and the values of luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone were compatible with Tanner stage II. The rapid ACTH stimulation test reveal a subnormal response in the cortisol levels (basal level= 3.6 ug/dL; 30 minutes and 60 minutes after ACTH stimulation = 3.5 and 3.9 ug/dL respectively) confirming the diagnosis of primary adrenal insufficiency, also known as Addison disease. Additional diagnostic exams were performed searching for the main causes of primary adrenal insufficiency at this age. Anti-adrenal antibodies were negative. Abdominal computerized axial tomography revealed no infiltrative diseases, adrenal calcifications or abnormal dimension of the adrenal gland. Plasma VLCFA levels were increased [C26:0=1.81ug/mL (Normal 0.16-0.57), C24:0/C22:0=1.54 (Normal 0.63-1.10); C26:0/C22:0=0.088 (Normal 0.004-0.022)] and the genetic tests confirmed a mutation in ABCD1 gene [c.1415_1416delAG(p.Q472fs*83)-exon5], fulfilling the diagnostic criteria for X-ALD. To define the X-ALD's phenotype, cerebral and medullary imaging study with magnetic resonance (MRI) were performed and no abnormalities were identified, characterizing this case as an Addison-only phenotype of X-ALD. He has started glucocorticoid replacement therapy with hydrocortisone 9mg/m²/day. Taking into account that X-ALD may progress to other phenotypes with neurological involvement, this child continues to follow up in endocrinology and neurology clinics, performing cerebral MRI every 6 months. Since the beginning of the treatment for adrenal insufficiency, the hyperpigmentation started to clear and he remains with no symptoms of glucocorticoid or mineralocorticoid insufficiency. Genetic studies revealed the same mutation in his mother and his older brother, although they are still asymptomatic.

Discussion

Adrenal insufficiency is rare in children and its signs and symptoms are nonspecific, making the diagnosis difficult. (2,3) Usually, symptoms in primary adrenal insufficiency are more evident because of the deficit of both glucocorticoid and mineralocorticoid. However, when the disease manifests itself slowly, symptoms are more insidious and difficult to diagnose. (2) This case report exemplifies the difficulties in making the diagnosis when symptoms are insidious and vague. In fact, 5 years passed from the onset of hyperpigmentation until the diagnosis was made. This delay in the diagnosis is common as it was demonstrated in a study in Australian children with adrenal insufficiency. In 5 of 16 children, there was a median of 2 years delay between the onset of symptoms and the final diagnosis. (9) The risk of an acute adrenal insufficiency, which is a life-threatening event, increases in undiagnosed patients. (10)

X-ALD is one of the main cause of Addison disease in boys.(6) The plasma concentration of VLCFA is elevated in nearly all males with X-ALD. However,

increased plasma VLCFA is not pathognomonic for X-ALD, since it can be influenced by hemolysis or dietary causes. Alternatively, some dietary products can result in a false negative result. (6) Because of these false positive and negative results, the diagnosis should be confirmed by analysis of the ABCD1 gene. For women with X-ALD, the diagnostic test of choice is genetic analysis of the ABCD1 gene, considering that 15% of women with X-ALD have normal plasma VLCFA levels. (6) In our patient, the diagnosis was made by both VLCFA quantification and mutation analysis.

This peroxisomal disease has different phenotypes with variable prognosis. When a diagnosis is established, it is essential to conduct further diagnostic tests to determine the degree of neurologic and endocrine involvement. (6,7) Our patient had normal brain and medullary magnetic resonance, had high levels of ACTH and low levels of cortisol excluding the cerebral form and confirming the Addison only type of X-ALD. Close follow-up of children and adolescents with X-ALD is important for early diagnosis of adrenocortical insufficiency and for identification of brain involvement. Cerebral ALD is the most devastating phenotype, resulting in progressive severe cognitive and neurologic disability. (6,7) Allogeneic hematopoietic stem cell transplantation (HCT) remains the only therapeutic intervention that can arrest the progression of cerebral demyelization in X-ALD. (6) Having no brain involvement, our patient was not a candidate for HCT, and he was treated with hydrocortisone alone. Considering the risk of the disease progression to the neurologic degenerative form, brain MRI is periodically being performed. It is recommended to have a cerebral MRI every 6 months in boys aged 3 to 12 years old. After this, as the incidence of cerebral ALD decreases, MRI should be performed yearly or earlier if neurological symptoms occur. (6)

In conclusion, hyperpigmentation is a manifestation of chronic adrenal insufficiency, particularly when it affects body surface not exposed to the sun. Because of the non-specific semiology and the risk of severe and potentially fatal episodes of acute adrenal insufficiency, a high suspicion index is essential. As X-ALD is a common cause of adrenal insufficiency in boys, this disease should always be screened in any boy presenting with this endocrine anomaly. The necessity of family screening is paramount.

Authors Contribution

All the authors contributed for conception, critical revision and submission of this article

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