



RARE CAUSE OF HYPERPIGMENTATION - ALLGROVE SYNDROME

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<p>Article Info <i>Received 15/01/2016</i> <i>Revised 27/01/2016</i> <i>Accepted 22/02/2016</i></p> <p>Key words: adrenal crisis.</p>	<p>ABSTRACT We report a case of 21 year old man who presented at the hospital with adrenal crisis that was triggered by acute gastroenteritis with history of achalasia and alacrima for past 9 years.</p>
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INTRODUCTION

Allgrove or Triple A syndrome first described in 1978 by Allgrove and his colleagues [1], is a rare autosomal recessive disorder, characterized by alacrima, achalasia, adrenal insufficiency resulting from adrenocorticotrophic hormone resistance. It is a rare cause of Adrenal dysfunction seen sporadically in families. Alacrima or hypolacrima is probably the earliest and most consistent sign which can aid the diagnosis, which can be easily over looked by the family and physician [4,5]. Achalasia cardia occur in about 75% of patients and may precede adrenal insufficiency by few years [4-6]. While adrenal insufficiency begins after dysphagia and develop gradually over the first decade, it can manifest as late as the third decade of life [4-8]. The AAAS gene is coded on chromosome 12q13. Mutation in the AAAS gene results in insufficiency in the protein function known as aladin or adrcalalin[2].

Case Report:-

A 21-year-old man presented to our hospital with tachycardia, sweating, exhaustion, fainting and loose stools. He had a past medical history of achalasia diagnosed nine years ago. On examination, his blood pressure was 80/50 mmHg, pulse was 110 beats per minute

and body temperature was 35°C. He had generalized hyper-pigmentation which was more pronounced at knuckles and his skin was dry, particularly in hands and soles. There was no dysmorphic features. There was hyperpigmentation on the buccal mucosa also. He gave history of watery diarrhea. There was no history of pulmonary tuberculosis in the family. On examination, he was poorly built and nourished. He had bluish black pigmentation of tongue, oral mucosa, teeth, sclera. There was also pigmentation of ear lobes, extremities, knuckles and skin creases and secondary sexual characters were absent. Testicular size was reduced.

The basic laboratory findings were as follows: haemoglobin 9.7 mg/dL (normal range [NR] 12–16 mg/dL); fasting plasma glucose 51 mg/dL; blood urine nitrogen 51 mg/dL (NR 8–20 mg/dL); creatine 3.1 mg/dL (NR 0.4–1.0 mg/dL); sodium 132 mmol/L (NR 136–144 mmol/L); potassium 4.9 mmol/L (NR 3.6–5.1 mmol/L); cortisol 4.52 µg/dL (NR 6.2–19.4 µg/dL); C-reactive protein 213 mg/L (NR 0–8 mg/L).

No bacterial growth in the blood culture was detected at admission. The patient was assessed to have adrenal crisis, and glucocorticoid treatment was administered. For supportive care, erythrocyte suspensions



were transfused. His esophagus was found to be full of solid food during endoscopic examination. An esophagography was performed three days after he was fed liquid food, and revealed narrowing in the cardio-esophageal junction. Balloon dilatation was performed to relieve the obstruction. The dose of glucocorticoid was slowly tapered and then discontinued. ACTH stimulation test was performed three days after the discontinuation. Cortisol values at baseline, 30th, 60th, 90th and 120th minutes were as follows: 2.33 $\mu\text{g/dL}$, 2.14 $\mu\text{g/dL}$, 1.97 $\mu\text{g/dL}$ and 2.54 $\mu\text{g/dL}$. The diagnosis of adrenal insufficiency was confirmed after the ACTH stimulation test, and prednisolone 5 mg/day was given for maintenance. The patient's past medical history revealed

that he had not have tears when crying since childhood. Alacrima was detected after he was referred to the Department of Ophthalmology. He was diagnosed with AS in view of the existing clinical and laboratory findings. Electromyography (EMG) and brain magnetic resonance (MR) imaging, which were performed to rule out neurological involvement, were found to be normal. The patient was started on steroid replacement therapy with oral hydrocortisone 15mg / m² /d in two divided doses with poor compliance especially in summer time. There were no more attacks of hypoglycemia but there was hyper-pigmentation of the skin in time of poor compliance. On observing clinical improvement, he was discharged.

Figure 1. Hyperpigmentation of Hands.



Figure 2. Hyperpigmentation of Feet.



Figure 3 Hyperpigmentation of Lips.



DISCUSSION

Our patient had features of Allgrove syndrome or triple A syndrome, which is an inherited familial disorders in which there is adrenal unresponsiveness to ACTH. Incidence is unknown but it is an extremely rare syndrome with an autosomal recessive inheritance. The primary cause of mortality is unrecognized adrenal crisis. It affects all races and can have a variable presentation. Age at onset of symptoms is variable. The glucocorticoid deficiency is not apparent at birth but develops over the first two decades of life. Alacrima generally is present from early infancy, while symptoms of achalasia may appear in individuals as young as six months or as late as early adulthood. Most cases present with classic symptoms of primary adrenal insufficiency, including hypoglycemic

seizures and shock. Less frequently a child may be evaluated initially for recurrent vomiting, dysphagia and failure to thrive and for ocular symptoms. Patients may show neurological features like mental retardation, autonomic neuropathy, ataxia, muscle weakness, and peripheral neuropathy.

Dermatologic abnormalities such as palmoplantar hyperkeratosis as well as short stature, microcephaly and osteoporosis may occur. Genome linkage scans map the syndrome to a 6 cm interval on human chromosome 12q 13 near the type II keratin gene cluster. Pathogenic mutations have been identified in the ACTH receptor gene in families with isolated familial ACTH unresponsiveness. Whether the ACTH receptor represents the locus of the defect for the triple A syndrome is not known.

The achalasia - alacrima (AA) syndrome has been defined as a distinct clinical entity. It is most likely a variant of the triple A syndrome as shown by haplotype analysis.² Autonomic neuropathy may be associated when it is called the 4A syndrome¹ (adrenal insufficiency, achalasia of the cardia, alacrima and autonomic abnormalities). Autonomic disturbances may include abnormal pupillary reflexes, poor heart rate variability, and orthostatic hypotension. There is considerable intra and interfamilial variability of severity implying a variable expression of an impaired pleiotropically acting gene.

Globally, the pathology may be due to a progressive loss of cholinergic function throughout the body. Alternatively there may be a dysfunction of melanocortin receptor signalling, as melanocortin receptors are known to regulate adrenal function and skin exocrine gland function. The mineralocorticoid function is usually normal although deficiency of mineralocorticoid can occur. The glucocorticoid deficiency is probably due to degeneration of an initially normal zona fasciculata, there being no evidence to support a biologically inactive hormone or an autoimmune process.

Our patient presented with history of absent tear secretion while crying since nine years. He had no

symptoms attributable to hypoglycemia, and mineralocorticoid deficiency was ruled out since the blood pressure and serum electrolytes were normal. Our patient had no ophthalmologic manifestations of deficient lacrimation, which was diagnosed only on the Schirmer test.

CONCLUSION

We report this case to highlight that adrenal insufficiency may appear at a later stage in AS and there is a need to evaluate the adrenal functions of young patients with alacrimia and achalasia.

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CONFLICT OF INTEREST: NIL

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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