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Allgrove Syndrome without Achalasia: A Rare Case Report and Brief Review of Literature

Case Report

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Abstract

Since the first description by Allgrove at al. Triple A syndrome (Allgrove syndrome) was reported rarely with an estimated prevalence of 1 in 1,000,000 individuals. It is a progressive degenerative disease comprising absent tear production (alacrima), achalasia of cardia, and adrenal insufficiency, caused by mutations in AAAS gene on chromosome 12q13. ALADIN protein is a part of nuclear pore complex with significant functional implications in many tissues. We present a 9-year 9-month old girl presenting with hypoglycemic seizures and hyperpigmentation, later found to have adrenal insufficiency. Upon investigations alacrima, and partial optic atrophy were found and Allgrove syndrome was suspected. Interestingly our case was not associated with the common presentation of achalasia, but has primary hypothyroidism which is rarely reported in association. Genetic report revealed a homozygous mutation in exon 6 of AAAS gene causing truncating protein production confirming the diagnosis. Allgrove syndrome is often diagnosed late, emphasizing the need for a high index of suspicion for alacrima and glucocorticoid insufficiency symptoms. Thorough biochemical and radiological investigations are recommended in suspected cases. Genetic testing can aid in diagnosis and provide valuable information for genetic counseling and follow-up planning. The syndrome presents with a wide range of symptoms, including achalasia, adrenal insufficiency, alacrima, and various neurological manifestations. This case highlights the importance of recognizing and managing the multisystemic features of the syndrome.

Keywords: Allgrove syndrome; AAA Syndrome; Alacrima; Achalasia; 4A Syndrome; Aladin Protein

Introduction

Glucocorticoid deficiency associated with achalasia of the cardia and absent tear production was described by Allgrove et al. It was first described in two pairs of siblings in 1978 [1].The estimated prevalence is 1 per 1,000,000 individual [2]. Lanes et al. suggested that a progressive degenerative process may be responsible for the three components of the disease and coined the term 'triple-A syndrome' (AAAS) [3]. Gazarian et al. referred this syndrome as '4A syndrome,' associating various autonomic and neurologic disturbances (ND) as components [4]. In 1996, Weber et al.[5] localized the disease gene on chromosome 12q13. The gene produces alacrima-achalasia-adrenal insufficiency neurologic disorder (ALADIN) protein, which belongs to the WD-repeat family of proteins. Clark and Weber et al. pointed out that the AAAS has variable phenotypic expression. The triple-A gene, designated AAAS, was cloned by Tullio-Pelet et al [6]. And Hands chug et al [7] in 2000.

ALADIN protein belongs to the WD-repeat family of regulatory proteins, with functions ranging from transmembrane signaling and transcription, to cell division and intracellular trafficking [7,8]. Missense, nonsense and splicing mutations in AAAS gene cause the protein to mislocalize to the cytoplasm[9]. Cells from subjects with Allgrove syndrome do not show morphologic abnormalities in the nuclei, nuclear envelope or nuclear pore complexes, suggesting that mutations in AAAS gene result in functional, rather than structural,

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abnormalities in the nuclear pore complex [10]. Frame shift, stop codon and functionally significant mutations lead to a more severe phenotype, probably occurring by a loss of function effect on the protein [11,12,13,14]. Mutations of the AAAS gene cannot be identified in all clinically diagnosed AAAS patients [7,10,13,15]. A progressive neurological syndrome with central, peripheral and autonomic nervous system impairment, often associated with mild intellectual disability, has been described [11,12,13,14].

Case

A 9-year 9-month old female child was referred from pediatric emergency for hypoglycemic seizures. The patient was apparently normal 5 years back. The parents observed darkening of the body with frequent fever, vomiting, abdominal pain, and seizures for a year.

She was diagnosed with hypothyroidism and a seizure disorder and was prescribed levothyroxine and Valproate. Valproate was discontinued after the diagnosis of Addisons disease. Hydrocortisone was added, and later she discontinued the drugs. Now she has presented with similar complaints for the past 5 days.

Careful history revealed that she had "always cried without tears", generalised blackening of skin, recurrent vomiting and seizures. She did not have the regurgitation of undigested food. Her birth history was normal without delayed milestones or speech. She was born out of non-consanguineous marriage and no similar complaints were seen in the family, including her younger sibling, who is 8 years old.

On examination she was malnourished, irritable, and had mild intellectual disability, generalised hyper pigmentation, hyperkeratosis of the palms and soles, pre-pubertal secondary sexual characters, normal blood pressure, tachycardia, and mildly exaggerated tendon jerks. Her height and weight were between the 10-25th centile for her age. No skeletal abnormalities, ambiguous genetalia, cognitive impairment, or other autonomic disturbances were observed.

Investigations showed Mild to moderate intellectual disability, low serum cortisol, high ACTH, <1 mm Schirmer test score, bilateral partial optic atrophy, and bilateral thin and streaky adrenals on CT abdomen. Barium swallow did not show achalasia.

In view of alacrima, adrenal insufficiency, and optic atrophy the clinical diagnosis of Allgrove syndrome was considered and hydrocortisone was restarted. Patient has shown significant improvement. Levothyroxine was continued. Methylcellulose eye drops were added. Clinical exome sequencing was suggested.

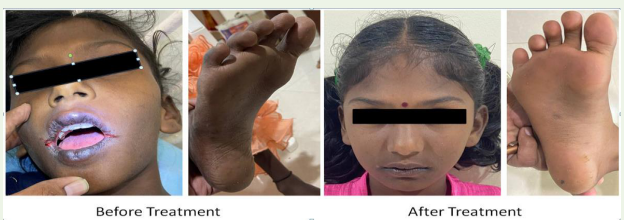

Figure 1: Hyperpigmentation of the skin and Plantar hyperkeratosis in the patient before and after the treatment.

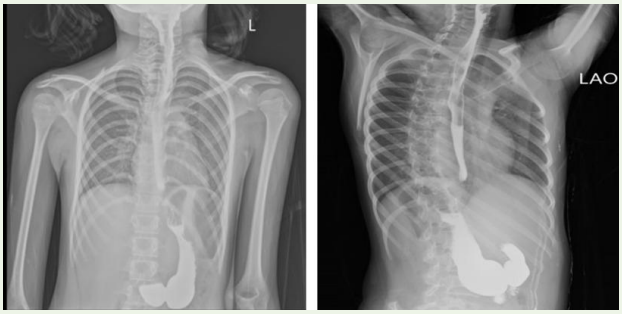

Figure 2: Barium swallow (AP, LAT) showing absence of achalasia.

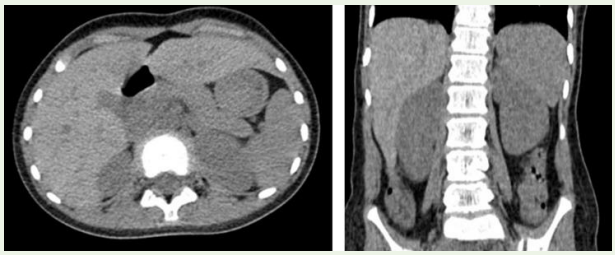

Figure 3: CT Axial & Coronal images showing streaky adrenals.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene# (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
AAAS (-) (ENST00000209873.9)	Exon 6	c.688C>T (p.Arg230Ter)	Homozygous	Triple-A syndrome (OMIM#231550)	Autosomal recessive	Pathogenic (PVS1,PS4,PM2)

Figure 4: Clinical exome sequencing of the patient.

Genetic report has shown a pathogenic variant of Allgrove syndrome which is a homozygous nonsense variant in exon 6 of AAAS gene on chromosome 12 that results in a stop codon and premature truncation of the protein at codon 230 (p.Ard230Ter). Genetic counseling was given to parents and regular follow up was advised. We have obtained written informed consent from the patient for reporting this rare case.

Discussion

The age of presentation falls within the first two decades of life (1.3 - 13.8 years) with median age being 5 years [2]. While age at presentation and diagnosis is early in familial cases, the etiological diagnosis is usually delayed until 11.4 years of age. The delay is attributed to the lack of detailed clinical characterization of the disease [16,17]. Our case was presented at the age of 6 years to an outside hospital, and the genetic diagnosis was established at the age of 10 years.

The majority of patients present with the symptoms of achalasia and adrenal insufficiency, while other presenting complaints included seizures, poor growth, hyper pigmentation of the skin, developmental delay, and autonomic disturbances [18,19]. Other associated symptoms

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Table 1: list of tests performed on the patient showing abnormal cortisol, ACTH levels and Schirmers test score

Date	Investigation	Test Value	Reference Range
22/2/19	EEG	Normal	
(Outside)	USG abdomen	4 mm calculi in gall bladder. Uterus & Endometrium are normal for age	
28/6/19	TSH	23.02 mcIU/ml	0.34 – 5.6
(Outside)	RBS	72 mg/dl	70 – 110
	Serum Creatinine	0.35 mg/dl	0.5 – 1.3
	Blood Urea	19 mg/dl	6 – 24
	LFT	Within reference range	
	S. Electrolytes	Within reference range	
	8 am Cortisol	<0.20 mcg/dl	3.7 – 19.4
	Video EEG	Normal	
22/9/22 (Outside)	CT head	No abnormality detected	
23/9/22	LFT	Within reference range	
	RFT	Within reference range	
	Serum Creatinine	0.38 mg/dl	0.5 – 1.3
	Blood Urea	25 mg/dl	6 – 29
	Hemoglobin	10.7 gm/dl	12 – 16
	Peripheral smear	Mild Normocytic normochromic anemia. Rest of the study normal.	
	Sodium	143 mEq/L	135 – 145
	Potassium	3.9 mEq/L	3.5 – 5.5
	Bicarbonate	24 mEq/L	22 - 29
	Ionized Calcium	1.25 mmol/L	1.20 – 1.40
24/9/22	TSH	4.825 mcIU/ml	0.34 – 5.6
	8 AM Cortisol	**< 0.05 mcg/dl**	**6.02 – 18.4**
	8 AM ACTH (after steroids in outside hospital)	**64.2 pg/ml**	**0 – 46**
	CT abdomen	Bilateral adrenal glands appear thin & streaky	
	Schirmers test score	**<1 mm**	**Above 5 mm**
	Barium swallow	Normal study	
2/12/22	Anti TPO Antibodies	9.20 IU/ml	< 9
	17-Hydroxyprogesterone	0.10 ng/ml	0.07-1.70
4/5/23	Clinical exome sequencing	A homozygous nonsense variant in exon 6 of the ***AAAS*** gene was detected	

included alacrima, Palmoplantar hyperkeratosis, optic atrophy, ataxia, intellectual disability, dysmorphic facies, microcephaly, sensory neural deafness, hypotonia, vitiligo, and neuromuscular dystrophy [20,21]. In our case the presenting complaint was a hypoglycemic seizure which was reported to be present in 10-36% of cases [17], even though the symptom of alacrima has been present since birth. Palmoplantar hyperkeratosis, mild intellectual disability, and hyper pigmentation of the skin are also present in our case.

Alacrima is the earliest and most consistent finding which is often overlooked by parents with prevalence reaching >90% in the affected patients[18,21]. It is present since birth or early infancy [16]. Parasympathetic dysfunction may be the cause for loss of tear production and may lead to punctiform corneal destruction [21]. It is diagnosed by Schirmer's test. Orbital MRI/CT is indicated if patient is not cooperative. T1- and T2-weighted MR images are similar to those of the extra ocular muscles and cerebral gray matter for lacrimal glands in lacrimal fossa [22]. They are often atrophic or absent on orbital CT images. Biopsy reveals neuronal degeneration and depletion of secretory granules in the acinar cells [23]. Administration of artificial tears and lubricants to relieve dryness are indicated. Alacrima may lead to corneal ulceration and keratopathy. Visual acuity assessment, ocular surface study, tonometry, and fundus examination are recommended at least yearly[21]. In our patient we diagnosed alacrima through Schirmer's test and prescribed lubricant eye drops. Partial optic atrophy present in our patient did not affect the vision. Other ophthalmic manifestations reported were kerato conjunctivitis sicca, papillary abnormalities, including sluggish pupils, hypersensitivity to dilute miotics, optic atrophy, and steroid induced lamellar cataracts in posterior subcapsule [17].

Adrenal insufficiency (AI) is seen in 80-100% of the patients. While 85% of the cases show Glucocorticoids deficiency, only 15% of cases show mineralcorticoid deficiency [23]. Glucocorticoid deficiency can be borderline with normal ACTH-stimulation test [13]. Dysfunction of the ALADIN protein has been shown to down-regulate genes encoding cytochrome P450 hydroxylases, and oxidoreductases, leading to reduced synthesis of precursors of steroid hormones [24]. Low cortisol, and DHEAS levels are seen in majority of the patients [17]. Similar to the literature, the adrenal insufficiency in our case manifested as episodic hypoglycemia-induced seizures and progressive hyper pigmentation. A 6 monthly follow up with stress dosing of steroid therapy is recommended in these patients. Normal electrolytes in our case excludes mineralocorticoid deficiency.

Achalasia cardia is seen in 75-100% of the cases and usually a first

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symptom for seeking medical attention [19]. It is rare in children, but in AAA syndrome, it presents in first decade of life. Achalasia typically presents with vomiting, swallowing difficulties, weight loss, and chronic cough, but it can also present as tooth decay[17,25]. Neuronal nitric oxide synthase deficiency due to oxidative damage to ganglionic cells and nerve fibers in lower esophagus explains the poor relaxation of the lower esophageal sphincter [26]. HRCT chest may show tracheobronchial compression, and lung parenchymal lesions[27]. Manometry is the gold standard diagnostic test. Pneumatic lower esophageal dilatations, medical treatment with calcium channel blockers, botulinum toxin, nitrates, and heller's cardiomyotomy are the main stay of treatments [21]. In contrast to many studies which has shown early achalasia with truncated protein mutations, the absence of symptoms and negative barium swallow study excluded the achalasia in our patient.

Around 30% of AAAS patients suffer from autonomic impairment along with other neurological manifestations [19]. Postural hypotension, abnormal sweating, tachycardia, and hyperreflexia are the most common neurological abnormalities [17,18]. Other autonomic dysfunction symptoms are arrhythmias, anisocoria, abnormal papillary responses, and impotence [21]. Hypernasal speech, ataxia, sensory impairment, bulbospinal amyotrophy, parkinsonian features, cranial nerve manifestations, Chiari 1 malformation, and optic atrophy are the other important neurological symptoms [2,28]. MRI/CT of head and spine are usually normal [13]. They develop slowly and presents at a later stage of life [17]. Glucocorticoid supplementation does not affect the progression of the symptoms. Muscle biopsies show neurogenic degeneration, non-specific myopathy, or mixed pathologies [21]. Our patient has already shown partial optic atrophy, hyperreflexia, and tachycardia. Due to the uncooperative patient, MRI brain was not performed. However outside CT brain was normal.

Although thyroid dysfunction is not a part of the Allgrove syndrome, TSH levels can be influenced by coexisting adrenal insufficiency. Congenital hypothyroidism [25] was reported in association with Allgrove syndrome. Interestingly our case was also diagnosed to have primary hypothyroidism during her initial presentation.

ALADIN, a 546 amino acid long protein, is ubiquitously present in cytoplasm [18]. More than 65 mutations have been reported in 16 exons of the gene. Depending upon the resultant product, the mutations were divided into truncating (T) and nontruncanting (NT) protein groups. While patients in the T group show higher prevalence of AI, the NT group shows a higher prevalence of ND. But the T group tends to have an early onset of ND, if present [2]. The mutation in our case is located in exon 6 of AAAS gene, whereas a similar mutation was previously reported in exon 7 in another database [18]. Allgrove syndrome has so far been reported through case reports. No genotypic-phenotypic correlation observed [16].

Conclusion

Despite with many case reports and reviews, Allgrove syndrome continues to be diagnosed late in the majority of patients. A high index of suspicion is needed for every symptom of alacrima and Glucocorticoids insufficiency. Thorough biochemical and radiological investigations are strongly recommended in all suspected cases. Despite sparse genotypic-phenotypic correlation, patients should be tested for genetic diagnosis, which can be useful for genetic counseling as well as follow-up planning. In view of the vast array of presentations, more research should be carried out for better understanding of the disease.

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