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***Case Report***

# TRIPLE A SYNDROME – A CASE REPORT

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## ABSTRACT
Triple A syndrome is a rare autosomal recessive disorder characterized by triad of Adrenocortico- Tropic Hormone (ACTH) insensitivity, achalasia cardia and alacrima. We are reporting a case of 20 years old female who presented with dysphagia and dryness of eyes to general medicine outpatient department. Further investigations like complete haemogram, hormonal assay, serology for autoantibodies, barium swallow, abdomen ultra-sonogram, upper GI endoscopy and CECT thorax were done and diagnosed as Triple A syndrome.

***Keywords:*** *Triple A Syndrome, Allgrove's Syndrome, Achalasia Cardia, Alacrimation, ACTH Insensitivity, Autonomous Neuropathy, Modified Heller Cardiomyotomy*

## INTRODUCTION
***Why it is called as AAA Syndrome?***
Triple A (Achalasia-Addisonianism-Alacrima) syndrome or Allgrove's syndrome is a rare autosomal recessive condition characterized by Adrenocortico- Tropic Hormone (ACTH) insensitivity, achalasia andalacrima. In 1978, this syndrome was first described by Allgrove and his colleagues in two unrelated pairs of siblings (Allgrove *et al.,* 1978). Three of these individuals also had defective tear production, leading the authors to confine that the combination of achalasia, adrenal deficiency, and alacrima represented an inherited familial disorder (Kasar *et al.,* 2007). Exact prevalence of this syndrome is unknown. Later it was named as "4A" syndrome as it has some autonomic nervous disturbances along with original Allgrove's triad (Gazarian *et al.,* 1997).
*When does it Manifest?*
Usually, this syndrome manifests with dysphagia during first decade of life. In early childhood, alacrima and achalasia are the indicative signs. In childhood & adolescence, it manifest with features of achalasia and adrenal insufficiency. Achalasia predominantly neurological with autonomous and polyneuropathic involvement present in adulthood (Chu *et al.,* 1996; Pedreira *et al.,* 2004). Specific autonomic disturbances described in this syndrome include poor heart rate variability, abnormal pupillary reflexes, and orthostatic hypotension. We can make the provisional diagnosis as Allgrove's syndrome who presenting with combination achalasia and alacrima and make the final diagnosis with further specific investigation for adrenal insufficiency and achalasia. Patient was responding well after modified Heller's myotomy surgery and steroid therapy.

## CASES
A 20 years old female was 2$^{nd}$child born to 2$^{nd}$ degree consanguineously married couple presented with dysphagia for both solid and liquid foods for past 2 years which was insidious in onset and progressive in nature. She also presented with nasal twang of voice. She gave history of one episode of fever preceding this illness, recurrent respiratory tract infection and regurgitation while taking food and also history of weight loss about 10 kg in past 2 months. She attained menarche at 14 years of age and had irregular menstrual cycle. Her younger brother had similar complaints of difficulty in swallowing, hyperpigmentation patches, absence tears and he underwent 'Heller's Myotomy' for achalasia cardia and his post operative period was uneventful and he was under treatment. Patient also gave the history of absence of tears while crying since childhood.
On general examination, patient was conscious, co-operative and well oriented. Patient presented with long thin face with a long philtrum, down-turned mouth and narrow upper lip. Patient was cachectic,

pallor, gingival hypertrophy, hypo pigmented patches over lips and hyper pigmented patches over the extremities were present (Figure 1& 2). Minimal axillary and pubic hair were present. No cyanosis, clubbing, icterus, lymphaedenopathy and edema.

**Figure 1 & 2: Patient Looks Thin Built and with Distinct Facial Appearance with Hypo Pigmented Patches over Lips**

Vital signs with regular pulse of rate 78/min, BP of 100/60mmHg in supine position, BP in standing position 90/60mmHg, respiratory rate of 18/min. Her Head circumference was 51 cms (normal-56 cms). Central nervous system examination showed normal higher mental function, lower cranial nerve (IX,X,XII) involvement. Generalized muscle wasting over both hands (small muscles), normal superficial reflex, power of grade 4/5, exaggerated deep tendon reflex, bilateral equivocal plantar response, normal sensory and cerebellar function. Examination of per abdomen, cardiovascular and respiratory system were unremarkable. Required investigations were done and reports were tabulated (Table 1).

Barium swallow suggestive of filling defect in the middle 1/3$^{rd}$ and lower end of esophagus (Figure 3 & 4).

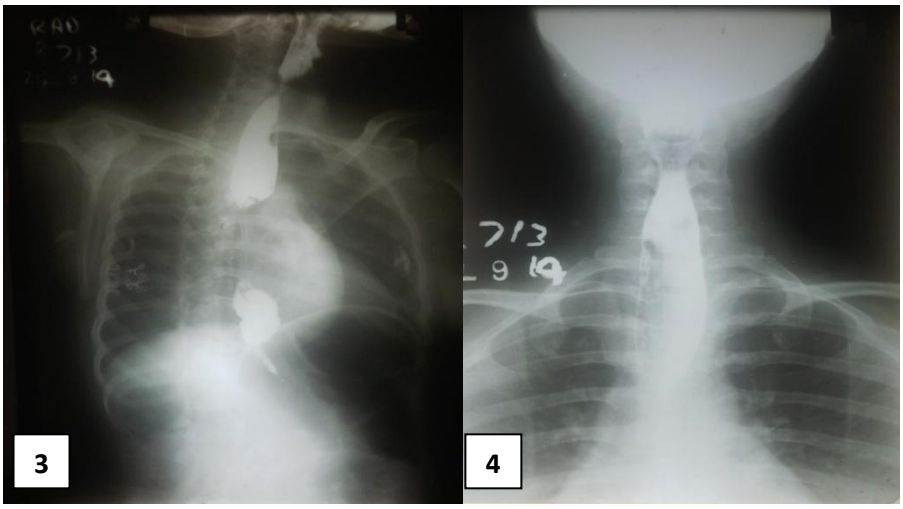

**Figure 3 & 4: Shows Filling Defect in Middle 1/3 rd and Lower End of Esophagus**

**Table 1: List of Investigations with Reports**

| Investigations | Results |
|---|---|
| CBC – **HB** | **8.1gm%** |
| **WBC** | **12,300cells/cu.mm** |
| DC- Neutrophils | 64.3% |
| Lymphocytes | 27.2% |
| Eosinophil | 5.8% |
| Monocytes | 2.1% |
| Basophils | 0.4%, |
| **Peripheral smear** | **Microcytic hypochromic anemia** |
| **ESR** | **62mm/hr** |
| Reticulocyte count | 03% |
| Bleeding time | 3 mins 00 sec |
| Clotting time | 5 mins 30 secs |
| RBS | 75.0 mg/dl |
| Urea | 18.0 mg/dl |
| Creatinine | 0.7 mg/dl |
| Urine analysis | Normal |
| TFT: Free T3 | 2.05 pg/ml |
| Free T4 | 1.10 ng/dl |
| TSH | 1.17 µIU/ml |
| Sr.calcium | 8.2mg/dl |
| Serum electrolytes | $Na^+$ 143.7 mEq/L |
| Day 1 | $K^+$ 5 mEq/L |
| | $Cl^-$ 100.9 mEq/L |
| Day 2 | $Na^+$ 140.6 mEq/L |
| | $K^+$ 4.82 mEq/L |
| | $Cl^-$ 105.3 mEq/L |
| Human Growth Hormone | 0.3ng/ml( 0-5ng/ml) |
| DHEA-Sulphate (DHEAS) | 8.86µg/dl(12-535µg/dl) |
| Hormone test: | LH- 4.74 mIU/ml (Luteal phase -0.6-19.0mIU/ml ) |
| | FSH- 10 mIU/ml (Luteal phase: 2-10 mIU/ml ) |
| | Prolactin: 14.10 ng/ml ( adult: 1.9-25 ng/ml ) |
| ECG | within normal limits |
| **USG abdomen** | **shows B/L polycystic varies**. |
| **MRI BRAIN** | **shows bilateral hypo plastic lacrimal glands** |
| **CECT** | **diffusely thick walled and dilated esophagus.** |
| ANA BLOT:ANA | <0.50(Negative) |
| SS-A | NEGATIVE |
| Sm | |
| nRNP/Sm | |
| AMA- M2 | |
| PCNA | |
| PM-Scl | |
| Rib.P-Protein | |
| dsDNA | |
| Histone | |
| Ro-52 | |

| | |
|---|---|
| **COSYNTROPIN TEST** | |
| In fasting sample | |
| Serum Cortisol (5-25 µg/dl) | 6.99 µg/dl |
| Plasma ACTH : (6-76 pg/mL) | 948.0pg/mL |
| After Injection | |
| Serum Cortisol : | 7.28 µg/dl |
| Plasma ACTH : | 901.0pg/ml |
| | **Indicates Primary adrenal insufficiency** |
| Nucleosomes(NUC) | Negative |
| Schirmer's test (5mints) | **<3mm suggestive of severe dry eye** |

Upper GI endoscopy showed stricture in OG junction (Figure 5 – 9) and biopsy was taken from the OG junction. Biopsy from stricture OG junction showed no evidence of malignancy in the tissue. Histopathology examination showed presence of stratified squamous epithelium with hyperplasia.

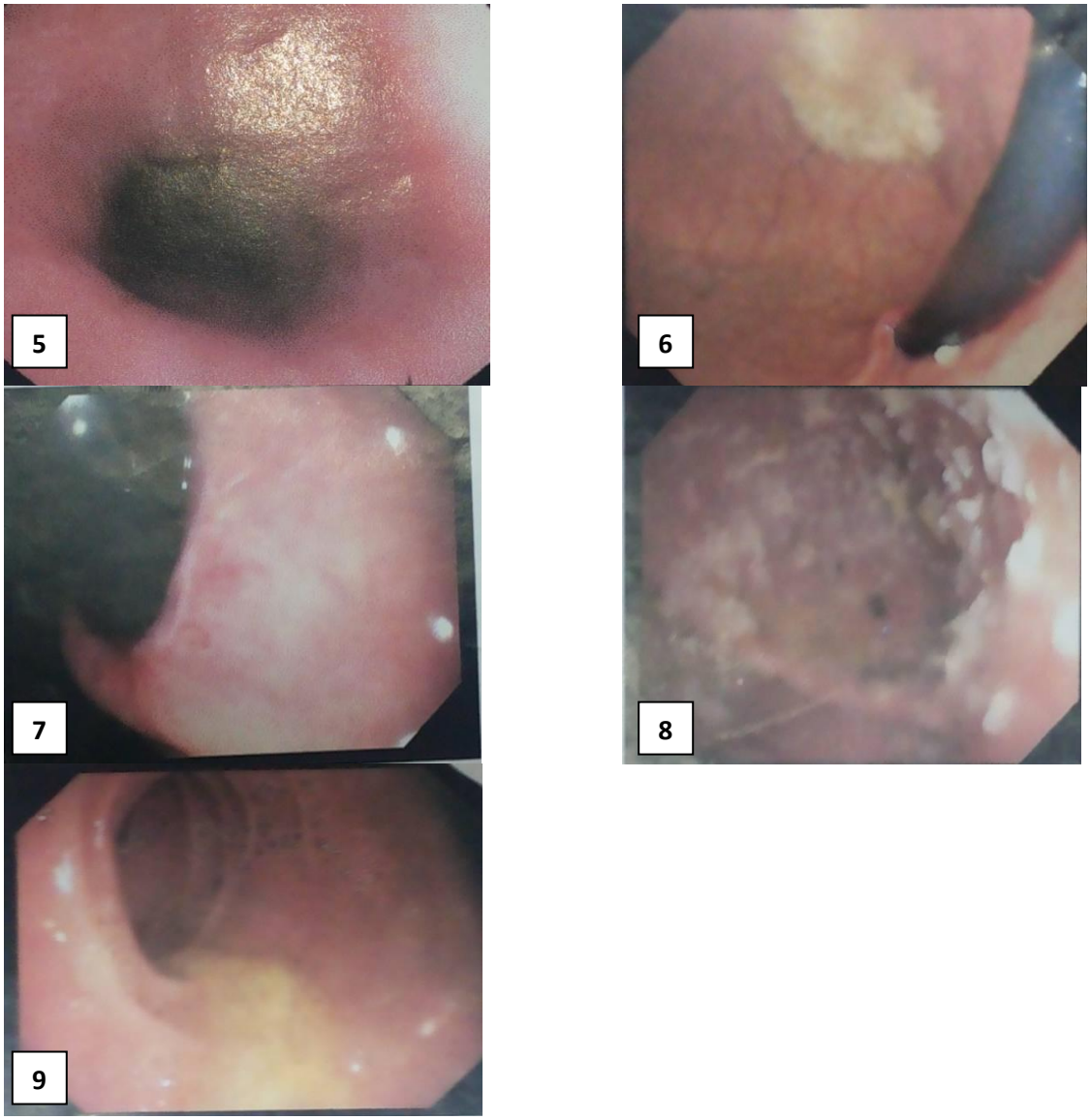


**Figure 5-9: Upper GI Endoscopy Shows Stricture in OG Junction**

***Case Report***

Gastrograffin study showed no evidence of contrast leak at OG junction and no evidence of contrast entry into stomach. Manometer revealed that median basal lower esophagealsphincter pressure was high with no normal peristalsis noted with 5ml wet swallows indicates Achalasia Cardia Type II.

Nerve conduction study showed prolonged latency in left median nerve, decreased amplitude in left & right ulnar nerve with normal conduction study. Ophthalmology opinion was obtained for dry eyes and described keratinized conjunctiva, absent tear film meniscus, Schirmer's test (5mints) showed <3mm suggestive of severe dry eye with reactive pupil and normal fundus. She was treated with regular application of topical lubricants with punctal occlusion and advised to use artificial tears.

Dermatology opinion was obtained for hypo and hyper pigmented patches and described as pigmentary disturbance due to adrenal insufficiency. ENT opinion was obtained and was normal with normal pure tone audiometry. Dental opinion was obtained for stained teeth and denture replacement was done.Patientwas referred to surgical gastroenterologist in MMC in which there she underwent laparoscopic modified Heller's cardiomyotomy. Her post operative period was uneventful. She started oral sips after gastrograffin study and now she was tolerating all kinds of foods and she is on medication for adrenal insufficiency (Tab. Fludrocortisone 10mg 1-0-1 and Tab. Hydrocortisone 10mg 1-0-0).

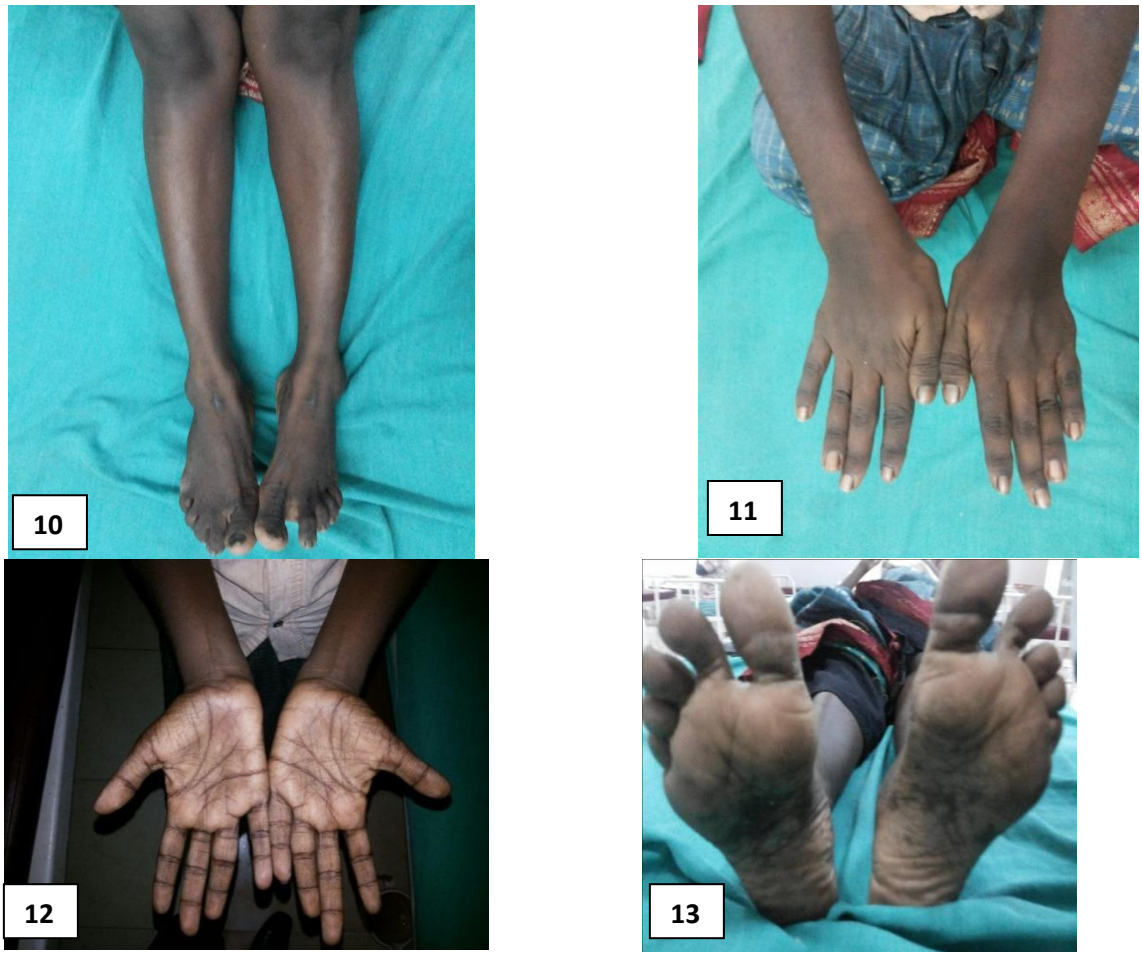


**Figure (10- 13): Extremities Show Hyperpigmentation**

**DISCUSSION**

Allgrove syndrome is considered as an autosomal recessive disorder with variable presentation (Allgrove *et al.,* 1978; Grant *et al.,* 1993). Incidence is unknown and only scattered family and case reports are noted in the literature. The actual incidence is difficult to determine because of the variable presentation,

including unexplained sudden childhood death due to adrenal crisis and mild disease that is not apparent until adulthood. No evidence suggests that gender affects the frequency. Age at onset of symptoms varies. Alacrima is typically present from early infancy. Symptoms of achalasia cardiamay appears as young as 6 months or late as early adulthood, glucocorticoid deficiency is not apparent at birth but develops during the first 2 decades of life.

Recent Studies have shown that this syndrome is due to mutation in the AAAS gene on chromosome 12q13, which encodes ALADIN (Alacrima Achalasia Adrenal Insufficiency Neurologic disorder) protein which is a part of the nuclear pore complex, resulting in an impaired protein function. Also, other changes in the AAAS gene include a missense mutation c.618delC, p.R155H, and p.Ser207fs (Weber *et al.*, 1996; Krull *et al.*, 2010). In Huebner *et al.*, (2000) mapped the syndrome to a 6 cM interval on human chromosome 12q13 near the type II keratin gene cluster.

A distinct facial appearance associated with Allgrove syndrome consists of a long thin face with a long philtrum, narrow upper lip, and a down-turned mouth. These features are not seen in unaffected siblings.

Clinically this syndrome presents with achalasia, alacrima and features of adrenal insufficiency and some autonomic nervous disturbances, vomiting, dysphagia, regurgitation, recurrent chest infection, and failure to thrive are symptoms of achalasia. Alacrima was considered the most early and consistent feature that leads to conjunctival keratopathy and corneal melting. Many studies revealed that dysphagia and achalasia were the presenting feature of this syndrome even though alacrima is the most constant feature (Milenkovic *et al.*, 2010). Weight loss, malaise, weakness, anorexia, nausea vomiting, diarrhea or constipation, pigmentation, are the common symptoms due to. Postural hypotension and hypoglycemia due to adrenal insufficiency which may cause sudden death (Makari *et al.*, 1988; Lanes *et al.*, 1980). There may also be signs of autonomic dysfunction with AAA, such as pupillary abnormalities, an abnormal reaction to intradermal histamine, abnormal sweating, orthostatic hypotension, and disturbances of the heart rate (Brooks *et al.*, 2005).

In this study, our case presented with micro cephalic with normal mentation, features of severely dry eyes due to alacrima confirmed by schirmertest, MRI brain shows bilateral hypo plastic lacrimal gland. Dysphagia was further investigated with barium swallow and OGDs copy with manometry confirmed achalasiacardia. Patient presented with features of adrenal insufficiency like anorexic cachexia, postural hypotension, pigmentation of oral mucosa, extremities, palmarcrease, sole and confirmed with Cosyntropintest. Our case did not show prominent clinical autonomic dysfunction.

Patient was managed surgically with modified Hellers cardiomyotomy for achalasia.

Alacrima was treated with topical lubricant with punctual occlusion and artificial tears. Patient was under oral glucocorticoid and mineralocorticoid replacement therapy for primary adrenal insufficiency. Patient was responding well to the treatment and she was symptomatically better.

***Conclusion***

Allgrove's syndrome may be an under diagnosed multi-system disorder in which achalasia and alacrima are the most valuable clinical signs to reach the diagnosis. Although, our cases do not show prominent clinical autonomic dysfunction, they were diagnosed as Allgrove syndrome due to a combination of alacrima, achalasia and adrenal insufficiency. We can make differential diagnosis as triple A syndrome with combination of dysphagia and absence of tear. Final diagnosis can be confirmed by upper GI endoscopy with esophageal manometry, Schirmer’s test and Cosyntropin test for achalasia, alacrima and adrenal insufficiency respectively. Diagnose earlier to avoid sudden death due to hypoglycemia and postural hypotension due to adrenocortical insufficiency, and shock due to autonomic neuropathy and adrenocortical insufficiency. Since triple A syndrome is autosomal recessive disorder, genetic counseling is considered to reduce the incidence. We can increase their life span near normal by effective management when we diagnosed earlier.

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