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A Brief Overview of Triple A Syndrome

Jamaal Khan
Nova Southeastern University, jk1658@mynsu.nova.edu

Triple A Syndrome

What you need to know

By: Jamaal Khan

What is Triple A Syndrome?

A brief overview

Having even a single congenital disease is terrible, but having three at the same time, it's dreadful. That is the unfortunate reality of those who have had the misfortune to be diagnosed with Triple A syndrome. Triple A syndrome is a rarely fatal, inherited group of diseases that are comprised of alacrima, Addison disease, and achalasia. These three diseases are almost always present in individuals, however they may only have two.

Alacrima is when there is an abnormality in the production of tears leading to either a reduced or complete halt in their production. Addison disease is characterized by the adrenal gland's producing an insufficient amount of cortisol and aldosterone, hence why it is often referred to as adrenal insufficiency. Lastly, achalasia can be defined as the body having an abnormal immune response to the nerves in the esophagus, causing them to be damaged, leading to difficulty in swallowing food and water (Vega-Lopez, 2018).

Triple A syndrome is an autosomal recessive disorder caused by any mutation in the AAAS gene (Figure 1), that is involved in the transportation of molecules to and from the cytoplasm and nucleus (Pogliaghi ,2020). Currently there is no one treatment for AAA syndrome, however they do treat the individual disorders by themselves.

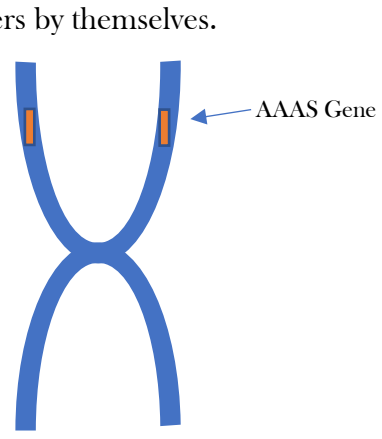

Figure 1 (above): shows chromose 12q13 that houses the AAAS gene.

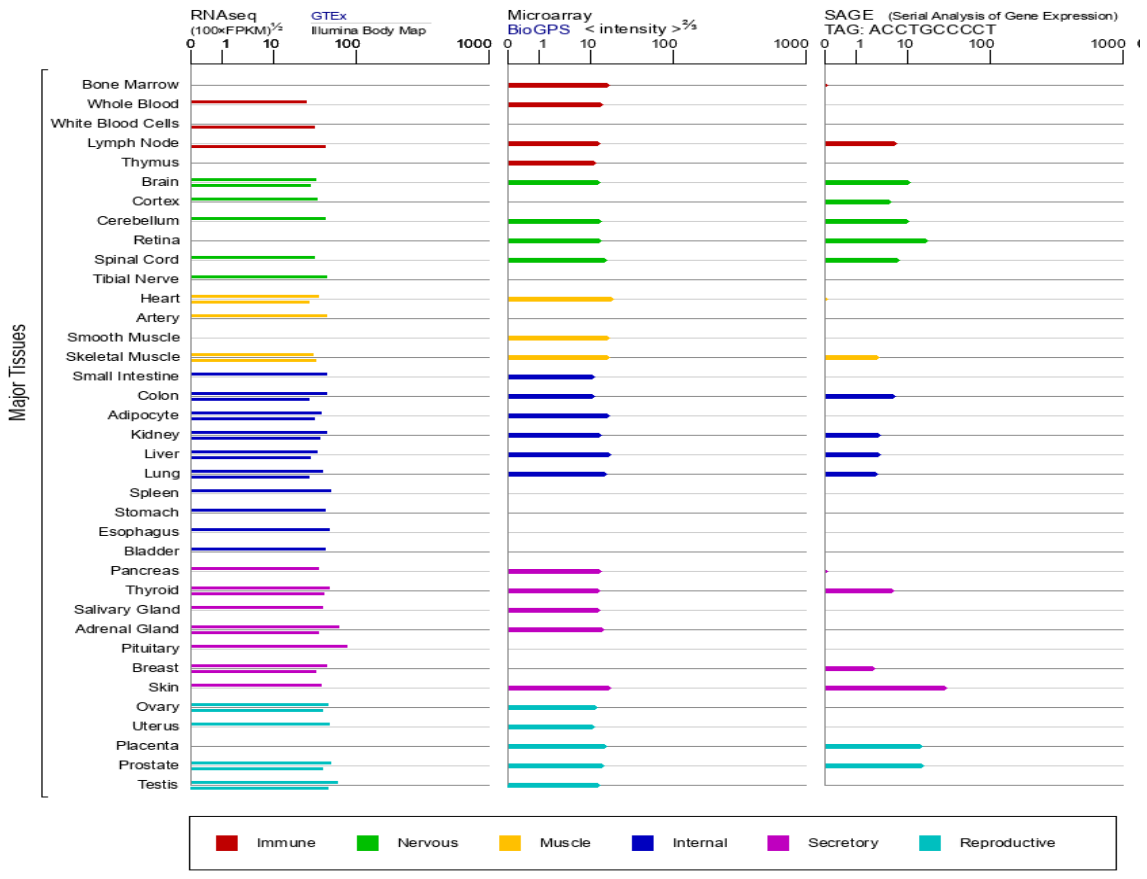

Figure 2 (above): shows three different tests done to show gene expression of the ALADIN protein in various tissues througout the body (Gene card, 2022).

Triple A syndrome's cause

A deeper look into what causes AAA syndrome

Triple A syndrome is caused by mutations in the AAAS gene located on chromosome 12q13. No single mutation has been shown to cause triple A syndrome as there has been a multitude of missense, point, and nonsense mutations found within the 16-exon gene that can lead to AAA syndrome (Li, 2015).

The AAAS gene's main function is to code for a WD-repeat family regulatory protein that is known as ALADIN. It plays a vital role in the nucleocytoplasmic transport of molecules since it is part of the nuclear pore complex, signal transduction, and DNA repair. However, the AAAS gene's protein product AlADIN isn't only localized in one area of the body. It is found all throughout and serves a multitude of different functions. The figure above shows relative ALADIN protein expression through various parts of the body.

How exactly does the mutation in the AAAS gene cause AAA syndrome is yet to be determined, however there has been a recent breakthrough showing that ALADIN is involved in oxidative stress response which can have an effect in steroidogenesis in the adrenal cortex (Vega-Lopez, 2018).

Currently, there have been new research suggesting renaming this disease 4A syndrome as patient have been known to suffer from autonomic disturbances too (NORD, 2022). But this disease is so rare and not much is currently known about it that it makes it hard to understand the inner workings of it.

Below are the diseases that comprise Triple A syndrome and the current treatments for them as there isn't a treatment to cure all at the same time.

Alacrima

Alacrima is the insufficient production of tears (figure 3), that can lead to discomfort in the eyes. Typically, artificial tears are prescribed or in more extreme cases, gels and ointments may be prescribed (DeAngelis, 2021).

Addison Disease

Addison disease is the lack of hormone production (cortisol and/or aldosterone) in the adrenal cortex. The recommended treatment for this is to be given medication for hormone replacement therapy (Mayo clinic, 2020)

Achalasia

Achalasia is categorized as nerve damage in the esophagus that leads to difficulty in swallowing. The treatment for this includes a Laparoscopic Heller Myotomy where a small incision is made on the lower esophageal sphincter to allow for food/water to pass (Mayo clinic, 2022.)

Alacrima:

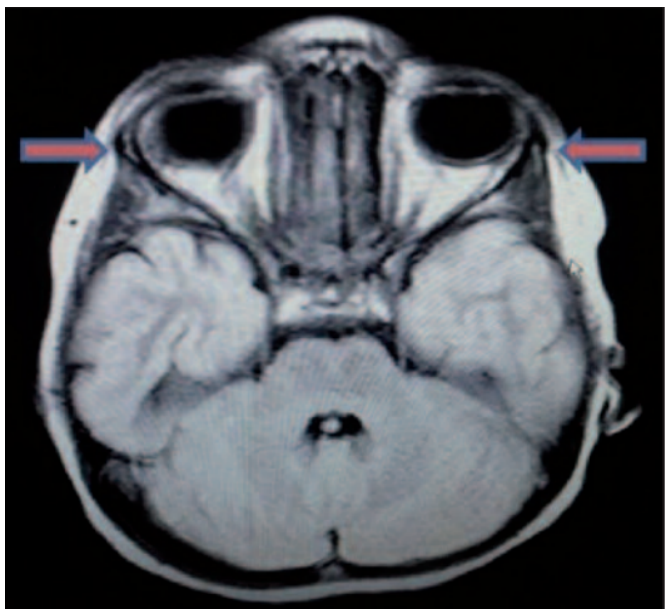

Figure 3 (above): MRI image that shows hypoplastic lacrimal glands (Eldem, 2016).

Addison Disease:

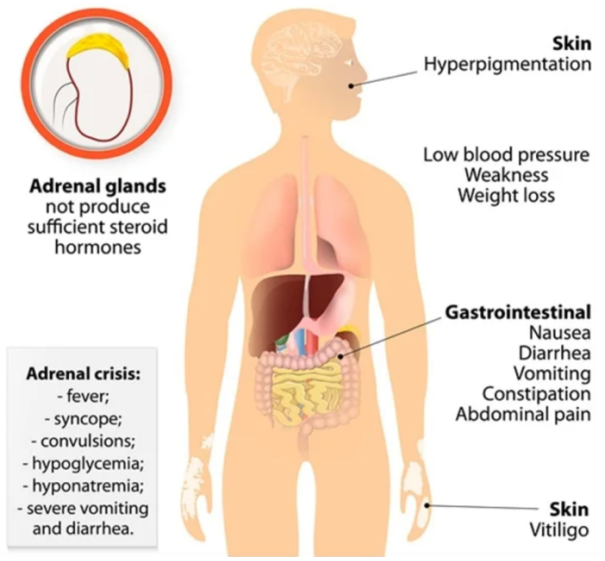

Figure 4 (above): Infographic that shows potential symptoms that may arise with Addison's disease (Mandal, 2018).

Achalasia:

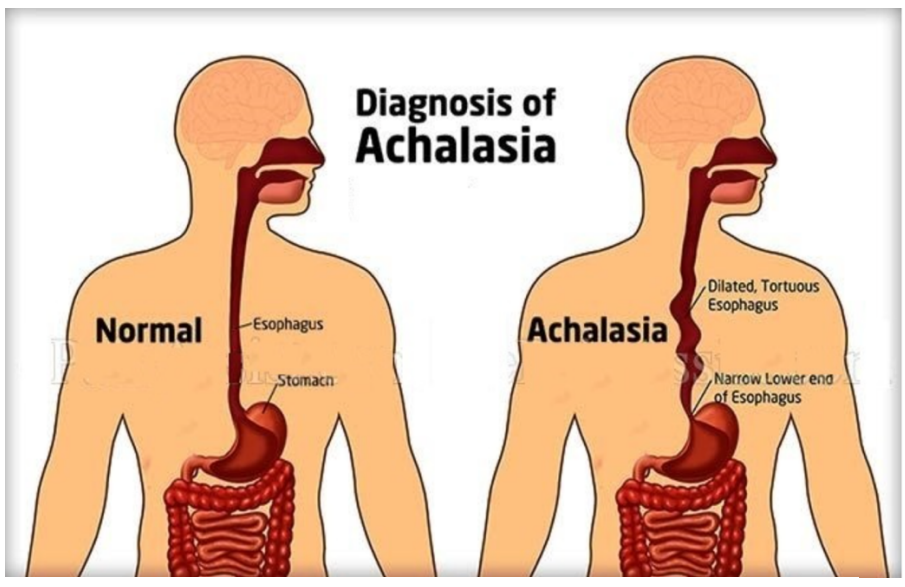

Figure 5 (above): shows a diagram depicting the esophagus of someone diagnosed with achalasia (Monitor, 2019).

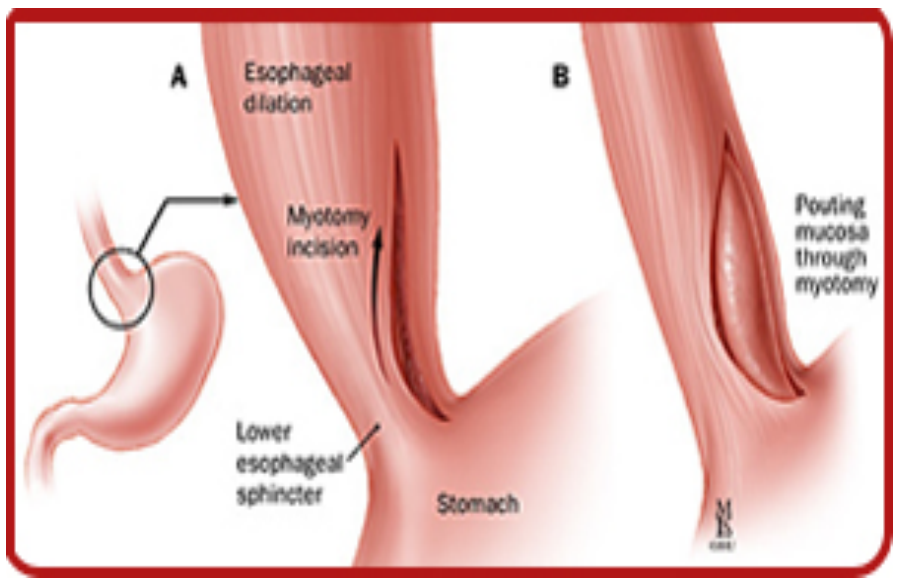

Figure 6 (above): Laparoscopic Heller Myotomy for achalasia (Lee Bariatric, 2022).

References:

Database, G. C. H. G. (n.d.). AAAS. GeneCards is a searchable, integrative database that provides comprehensive, user-friendly information on all annotated and predicted human genes. Retrieved September 24, 2022, from https://www.genecards.org/cgibin/carddisp.pl?gene=AAAS#proteins

DeAngelis, D. D. (2022, March 11). Alacrima. Background, Pathophysiology, Epidemiology. Retrieved September 24, 2022, from https://emedicine.medscape.com/article/1210539-overview

Eldem, I., Kocaay, P., Şıklar, Z., Kuloğlu, Z., Baş, Z., Uçakhan, Ö., & Berberoğlu, M. (2016). Alacrima-Achalasia: Look for Adrenal Insufficiency: Case Report. Turkiye Klinikleri Journal of Pediatrics, 25, 119-12

Lee, B. Laparoscopic Heller myotomy. Laparoscopic Heller Myotomy. (n.d.). Retrieved September 24, 2022, from https://www.texashealth.org/thpg/lee-bariatrics/Conditions-and-Services/Laparoscopic-Heller-Myotomy

Li, W., Gong, C., Qi, Z., Wu, D. I., & Cao, B. (2015). Identification of AAAS gene mutation in Allgrove syndrome: A report of three cases. Experimental and therapeutic medicine, 10(4), 1277–1282. https://doi.org/10.3892/etm.2015.2677

Mandal, D. A. (2018, November 27). What is Addison's disease? News. Retrieved September 11, 2022, from https://www.news-medical.net/health/What-is-Addisons-Disease.aspx

Mayo Clinic. (2020, November 24). Addison's disease. Mayo Clinic. Retrieved September 24, 2022, from https://www.mayoclinic.org/diseases-conditions/addisons-disease/symptoms-causes/syc-20350293

Mayo Clinic. (2022, March 5). Achalasia. Mayo Clinic. Retrieved September 24, 2022, from https://www.mayoclinic.org/diseases-conditions/achalasia/symptoms-causes/syc-20352850

Monitor, K. (2019, February 20). Have you heard about achalasia? here's what you need to know about itKashmir. The Kashmir Monitor. Retrieved September 11, 2022, from https://www.thekashmirmonitor.net/have-you-heard-about-achalasia-heres-what-you-need-to-know-about-it/

Pogliaghi, G., Cangiano, B., Duminuco, P., Vezzoli, V., & Bonomi, M. (2020). Triple-A syndrome (TAS): An in-depth overview on genetic and phenotype heterogeneity. Protein & Peptide Letters, 27(12),1192–1203. https://doi.org/10.2174/0929866527666200613215449