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Autoimmune Polyglandular Syndrome Type 1: An Illustrative Overview

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ABSTRACT

One of the rarest autoimmune diseases is the autoimmune polyglandular syndrome type 1 which is caused by defects in the AIRE gene leading to affection of several endocrine glands. Two out of three criteria are needed for diagnosis including hypoparathyroidism, adrenal insufficiency along with other non-endocrinal symptoms such as mucocutaneous candidiasis. Management of the condition is multidisciplinary with regular long-life follow-ups. Generally, there is a paucity of illustrative articles in literature about the pathogenesis and the main signs and symptoms of autoimmune polyglandular syndrome type 1 in a simplified manner which lead to the need for such articles. This article attempts to fill that void as an illustrative overview for the purpose of education and awareness about this condition because the early the treating physician can diagnose and accordingly treat the patient, the better the prognosis of the disease becomes with less morbidity and mortality rates.

1. Introduction

Autoimmune Polyglandular syndrome Type 1 (also known as autoimmune polyendocrinopathy syndrome type 1) or APS-1 or PGA-Type I is an autosomal recessive disease caused by alterations and mutations in the AIRE (autoimmune regulator) gene which is located on chromosome 21 and presents in the thymus. (Figures 1 and 2).

Protecting the body's self-antigens from T-Cells; here comes the role of the autoimmune regulator gene therefore any mutation or disturbance in this protein's function will lead to the damage of the body's own tissues and organs which is known as (autoimmunity). It's a very rare condition, in general, occurring more frequently in Iranian Jews, Finns and Sardinians at a rate of (1:9,000), (1:14,400), and (1:25,000) respectively (Chen, et al., 2021). Very few cases were reported from the middle and the far east.

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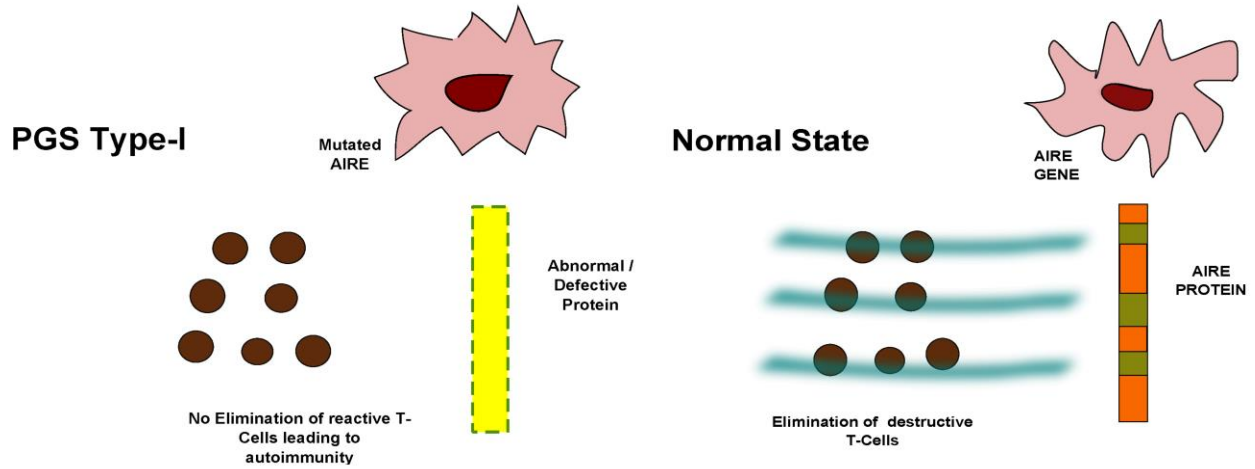

Fig. 1. AIRE Gene abnormal state versus normal state

2. Materials and Methods

Most of the published articles about the disease are case reports, surveys and reviews with no illustrative articles specifically dedicated to demonstrate the intrinsic changes (genetic mutations and biochemical defects) and extrinsic changes (visible signs and symptoms)-that make up the syndrome-in one article and here comes the purpose of this illustrative overview. Such visual explanatory article is considered a very crucial educational and guiding tool yet simplified and scientific at the same time, targeted to not only professional physicians but also to medical undergraduates and postgraduates.

Currently, in terms of diagnosing the disease, gene mutation analysis and antibodies screening are the most important tools in confirming the diagnosis of the disease once suspected with some antibodies specific to APS1. As for treatment, the current trend is adding biologic therapy and immunosuppressive agents in addition to the already established treatment modalities.

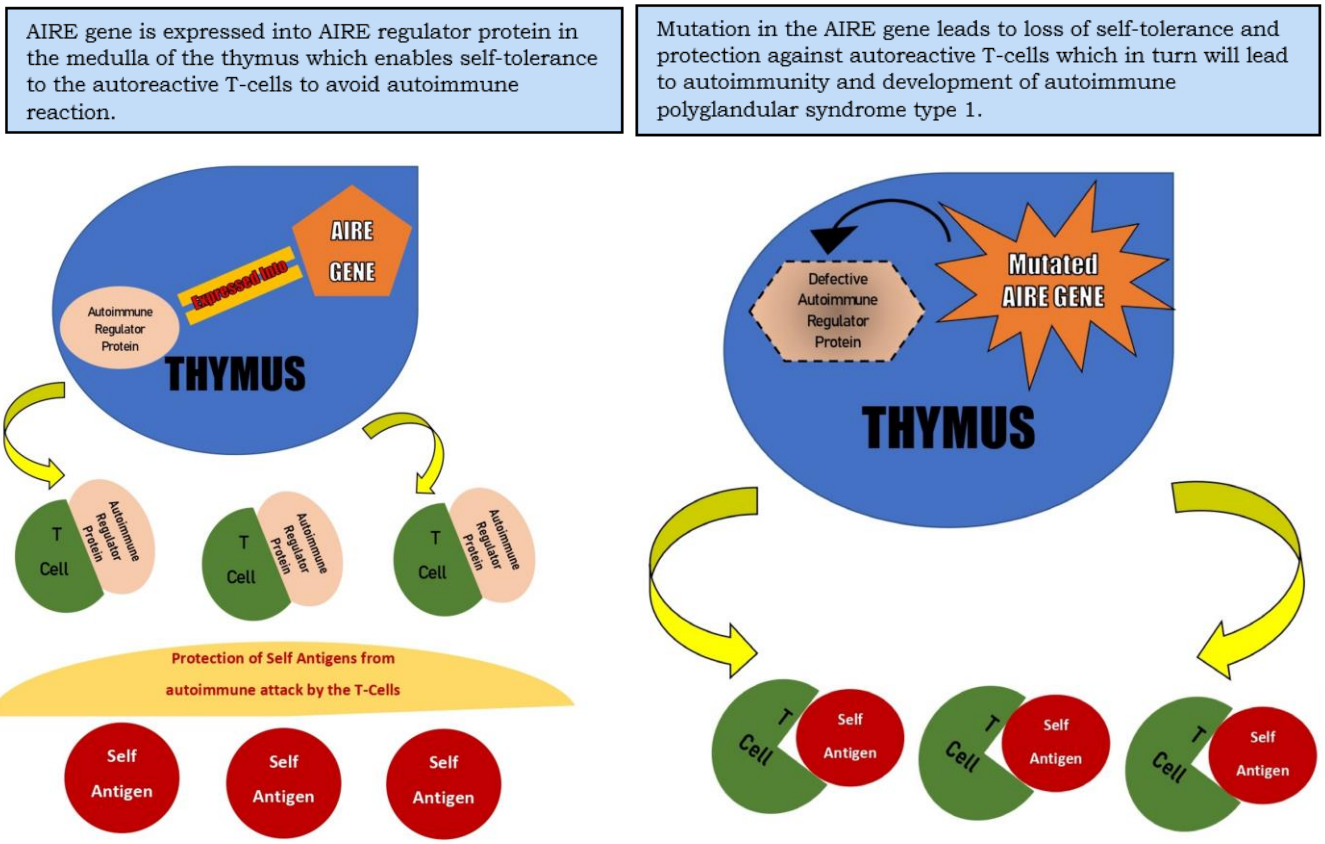

Fig. 2. Detailed illustration showing the function of the normal AIRE gene in comparison to the mutated gene

3. Results and Discussion

PGA-Type I is composed of a triad: fungal infection of skin and mucous membranes (chronic candidiasis), hypoparathyroidism and adrenal insufficiency. Two criteria are needed in order to diagnose PGA-Type1, on the contrary, only one is needed to diagnose a sibling of an already diagnosed patient (Proust-Lemoine & Wémeau, 2008).

Chronologically, the first symptom most probably to occur in majority of cases is candidiasis (before the age of 5 years), followed by hypoparathyroidism (usually before the age of 10 years), and last to occur adrenal insufficiency or Addison's disease (usually before 15 years) (Neufeld, et al., 1981; Ahonen, et al., 1990; Brun, 1982). Candidiasis mainly manifests in the skin and nails in the form of onychomycosis with hyperkeratosis and brittle nails, while it manifests in the oral mucosa in the form of oral thrush (oral Moniliasis) (Figures 3 and 4). Mucocutaneous candidiasis indicates immunodeficiency (decline in T-cell Count).

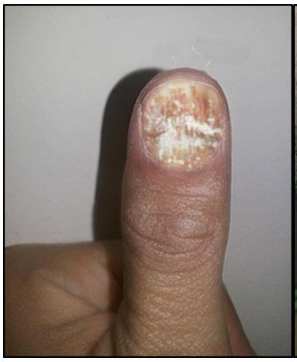

Fig. 3. Onychomycosis

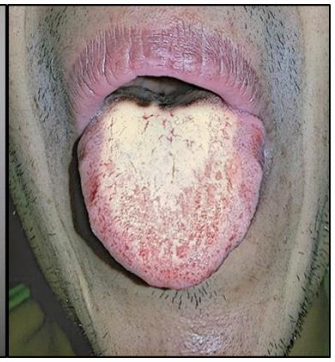

Fig. 4. Oral moniliasis/candidiasis

Since autoimmune cells attack the parathyroid gland specifically the NALP 5 protein (NACHT leucine-reich repeat protein 5) leading to hypoparathyroidism (Alimohammadi, et al., 2008). As a result of the autoimmune hypoparathyroidism, biochemical disturbances occurs in the form of chronic hypocalcaemia which in turn leads to perioral tingling and numbness, laryngospasm, tetanic spasms, Chvostek sign (contraction of facial muscles on the same side caused by gentle percussion on the facial nerve anterior to the ear and below the zygomatic arch) (Figure 5), Trousseau sign (carpopedal spasm of hand and wrist after inflating a blood pressure cuff over systolic blood pressure and leaving it for 3 minutes) (Figure 6), cataract, depression, dry skin caused by dehydration and less commonly poor dentition manifested as enamel hypoplasia. Another resulting outcome are hyperphosphatemia and hypomagnesemia.

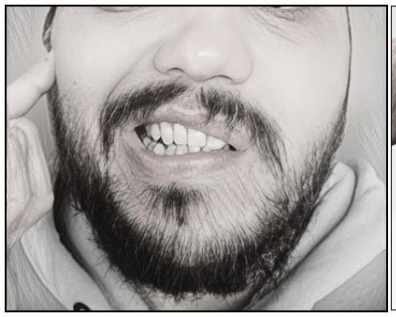

Fig. 5. Chvostek sign

Fig. 6. Trousseau sign

Hyponatremia and alopecia occur in some occasions and finally adrenal insufficiency (Addison's Disease) occurs manifested by fatigue, weakness, postural hypotension, nausea, vomiting and anorexia. Autoimmune thyroid disease, type 1 Diabetes, pernicious anaemia, stomach atrophy and vitiligo are among symptoms that are less commonly to occur (Bjørklund, et al., 2022). In addition to the manifestations and biochemical disturbances mentioned above, some defective immune functions occur as well such as deficiency of macrophage migration inhibitory factor (MIF) or inhibition of its production, these defects were present more in patients with cutaneous disorders (Betterle, et al., 1998). Hypogammaglobinaemia and selective IgA deficiency has been reported as well (Betterle, et al., 1998). Differential diagnoses include an array of syndromes and disorders such as polyglandular Autoimmune Syndrome Type II and type III, hemochromatosis, septic shock, thymoma, DiGeorge Syndrome, and WDHA Syndrome (Ahonen, et al., 1990).

Management

Investigations

-General investigations include complete blood count (CBC) (which may show lymphocytosis, neutropenia, and anaemia) in addition to vitamin B-12 levels to detect or exclude pernicious anaemia. (Garelli, et al., 2021).

-Biochemical screening in the form of serum electrolyte levels such as calcium, potassium, magnesium and phosphorus that should be measured to detect hypocalcaemia which will be associated with hypomagnesaemia and hypophosphatemia. It is very crucial to do an annual check for serum calcium and phosphate levels for patients who did not show signs of hypoparathyroidism along with anti-NALP5 assay (Husebye, et al., 2009). ACTH stimulation test (Synacthen test) is done and a low cortisol level indicates adrenal insufficiency (Figure 7).

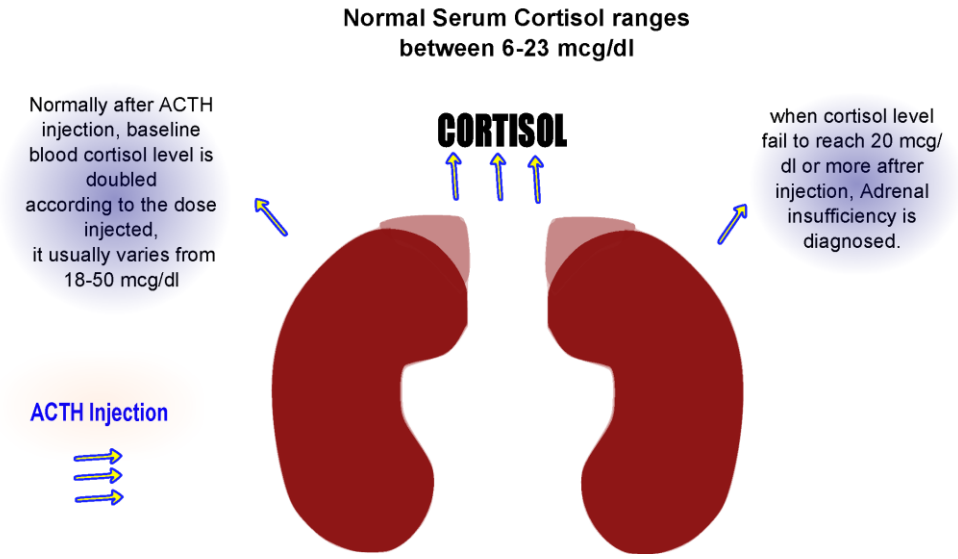

Fig. 7. ACTH stimulation test (Synacthen test)

As mentioned in the introduction, there are some antibodies that are only specified to APS1 and can aid greatly in diagnosing the condition such as autoantibodies to type 1 interferons specially interferon alpha and omega (which is of great diagnostic value since 95 % of patients with APS1 have them), autoantibodies to NALP5, which is expressed in the parathyroid and by the ovaries to a lesser extent, the potassium channel regulator KCNRG and BPI Fold Containing Family B Member 1 (BPIFB1), which both are expressed in the lung and last but not least transglutaminase-4, which is expressed only in the prostate gland (Bruserud, et al., 2016; Orlova, et al., 2017; Alimohammadi, et al., 2008; Shum, et al., 2013; Alimohammadi, et al., 2009; Landegren, et al., 2015).

On the other hand, non-specific autoantibodies include smooth muscle antibodies (SMA), antinuclear antibodies (ANA), Sjogren syndrome antibodies (SSA), 21-hydroxylase antibodies, intrinsic factor antibodies, anti-thyroid peroxidase (TPO), anti-thyroid-stimulating hormone receptor (TSHR) antibodies, anti-thyroglobulin (Tg), intrinsic factor antibodies and glutamic acid decarboxylase (GAD) (Jacobson, et al., 2021).

Liver function tests along with serologic autoantibodies targeted to the liver (autoimmune hepatitis), kidney (renal failure), and spleen (asplenia) in addition to GIT endoscopic biopsies which are done to prove the diagnosis of associated atrophic gastritis (Garelli, et al., 2021).

Hormonal screening include serum levels of TSH, T4,LH, FSH, prolactin, testosterone, estradiol and cortisol (Garelli, et al., 2021).

Treatment

Treatment of PGA-Type 1 is the treatment of each and every symptom composing this syndrome (Multidisciplinary approach).

Mucocutaneous candidiasis is treated by oral fluconazole (better because it is less hepatotoxic), itraconazole and ketoconazole along with topical antifungal creams (Azole Creams), nystatin suspension, and chlorhexidine mouth rinse.

Hypocalcaemia resulting from hypoparathyroidism is corrected by oral Vit. D and calcium. Prescence of tetany or malabsorption requires the administration of IV calcium gluconate.

In terms of corticosteroid administration to manage adrenal insufficiency, hydrocortisone and fludrocortisone have been the best options to start with due to their mineralocorticoid effect.

Biologic therapy and immunomodulator medications in the form of methotrexate, rituximab, mycophenolate mofetil, tacrolimus, sirolimus, cyclosporin A can be used with monitoring to lessen the severity of the symptoms and limit its progression (Kisand & Peterson, 2015).

Surgical Approaches

Hypoparathyroidism that leads to severe hypocalcaemia can be surgically treated by implantation of parathyroid tissues from the same patient in the forearm muscles; a procedure commonly known as (Parathyroid Auto transplantation) (Moffett & Suliburk, 2011).

Futuristic Approaches

Reversing the malfunctioning immune system through genetic alteration of the thymic epithelium with intact immune regulatory function through stem cell engineering is still a long-term objective that is being explored and has been proposed in some studies (Anderson & Su, 2016; Husebye, et al., 2018; Parent, et al., 2013).

4. Conclusions

Since there is no cure for PGA-Type I and since the disease is of an autoimmune nature, the treatment will be a lifelong process in the form of replacement therapy of

hormones, vitamins, and minerals in addition to immunomodulators and immunosuppressive drugs. Furthermore, management of accompanied co-morbidities is crucial for controlling the disease and hinders its progression. Periodic examination, regular follow-up visits, genetic counselling, patient education and phycological reassurance are the pillars of proper management of this syndrome.

Recommendations

Dietary intake of food rich in salt and blood pressure monitoring in addition to patient education and counselling are aiding factors in the management process (Yanase, et al., 2016; Nwosu, et al., 2019).

Follow-up is very important to check for serum electrolytes, endocrine functions and checking for any new emerging disorders (Wang, et al., 2021; Nwosu, et al., 2019).

Competing Interests

The authors have declared that no competing interests exist.

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