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RESEARCH ARTICLE

APECED SYNDROME (FAMILY OBSERVATION)

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Abstract

Introduction: APECED (Autoimmune Polyendocrinopathy Candidiasis Ectodermal Dystrophy) is an autosomal recessive disease characterized by the association of autoimmune endocrine involvement, mucocutaneous candidiasis and ectodermal tissue involvement.

Observation: We report the case of 2 brothers from a 2nd degree consanguineous marriage with a history of 2 deaths in the siblings for whom the diagnosis of APECED syndrome was retained on clinical and biological criteria (genetic study in progress).The eldest had candidous onychomycosis of the hands and feet, generalized mucocutaneous candidiasis, profound hypocalcemia with tetany crisis, autoimmune hepatitis, Biermer's anemia and ADDISON's disease. Meanwhile the youngest had onychomycosis, vitiligo, atrophy of the tongue, alopecia and adrenalinsufficiency.

Discussion: Autoimmune polyglandular syndrome type 1 (APS-1) is classically characterized by at least two of the three components of Whitaker's triad: chronic mucocutaneous candidiasis (CMC), hypoparathyroidism, and chronic adrenal insufficiency. If a sibling is affected, only one component of the triad is necessary to make the diagnosis.

Conclusion: This syndrome requires a multidisciplinary approach, without forgetting the importance of genetic counseling for this autosomal recessive disease.

Introduction:-

Autoimmune polyglandular syndrome type 1 (APS-1), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rarebut serious disease whit autosomal recessive transmission, linked to mutations in the AIRE gene, involved in central and peripheral immune tolerance mechanisms. [1] Its diagnosis is classically based on the association of 2 of the following 3 major criteria: chronic cutaneous-mucosal candidiasis, hypoparathyroidism and adrenal insufficiency with autoimmune origin. If one of the siblings is affected, only one of the 3 criteria is sufficient for the diagnosis. [2]

We report the case of 2 brothers, followed at the pediatric department of the Hassan II University Hospital of Fez, for APECED syndrome. Through these 2 observations we will discuss the different clinical, paraclinical and therapeutic aspects of this syndrome.

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Observation1:-

The older brother is a 14-year-old child from a 2nd degree consanguineous marriage with a history of 2 sibling deaths, who consulted at the age of 8 years for tetany attacks, generalized mucocutaneous candidiasis (Image 1) with onychomycosis of the hands and feet (image 2,3). The biological workup revealed severe hypocalcemia with a total calcium level below 50 mg/l with a PTH: 6 pg/ml, confirming hypoparathyroidism, and allowing the diagnosis of APECED syndrome on 2 of the 3 majorcriteria.

The workup for other autoimmune diseases did not allow to retain adrenal insufficiency since baseline and post-synacthenic cortisol levels were normal, but the patient presented collapsed levels of vitamin B12, with positive anti-intrinsic factor antibodies, in favor of Biermer's disease, and hepatic cytolysis was also observed, in favor of autoimmune hepatitis, later confirmed by the positivity of the anti-LKM1 antibodies.
The patient received vitamin-calcium treatment for his hypoparathyroidism and vitamin B12 supplementation for his Biermer disease. The autoimmune hepatitis was treated with immunosuppressants associated with an antifungal treatment, in order to avoid the exacerbation of CMC.

The evolution was markedafter 1 year, by a bilateral cataract, a grade I nephrocalcinosis caused by the vitamin-calcium treatment prescribed at high dose. After 2 years of evolution, the patient presented vomiting, asthenia and melanoderma (image 4), the assessment allowed the diagnosis of Addisson's disease, treated with hydrocortisone.

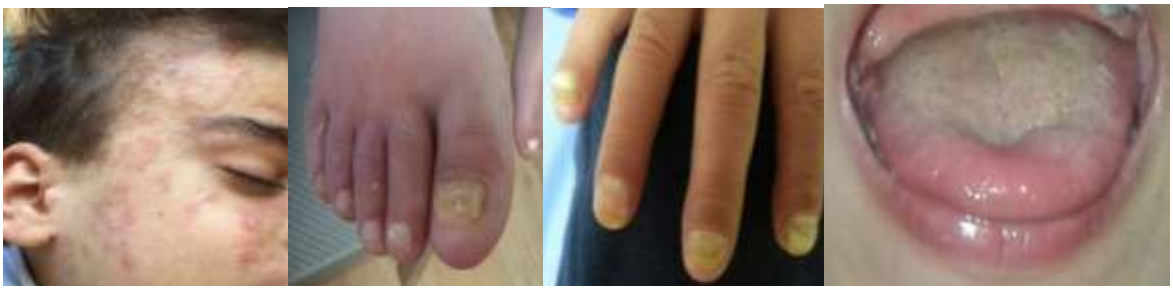


Image 1 Image 2 Image 3 Image 4

Observation 2:

The youngest child is a 9-year-old boy who consulted at the age of 4 years for dermatological lesions, wich are onychomycosis (image 5), vitiligo (image 7, 8, 9, 10), alopecia (image 6, 7) and tongue atrophy (Images 8). Given the context of APECED syndrome in the family, an autoimmune and endocrine workup was performed, objectifying: Primary adrenal insufficiency, cytolysis with hepatic cholestasis. In addition, the phospho-calcium balance was normal, the rest of the autoimmune workup in search of celiac disease, Biermer's disease, autoimmune thyroiditis was normal. A duodenal biopsy showed a non-specific chronic duodenitis.

The patient was put under hydrocortisone replacement therapy, with therapeutic education about the risks of acute decompensation. The systemic antifungal treatment was prescribed for 3 months, but replaced by a local treatment because of the worsening of his hepatic balance and finally a topic treatment by Tacrolimus was administered for his vitiligo lesions.

The evolution was marked by the occurrence of a cholestatic jaundice, in 2022, the exploration made it possible to find a homogeneous hepatosplenomegaly by the ultrasound with a positive viral hepatitis A serology.

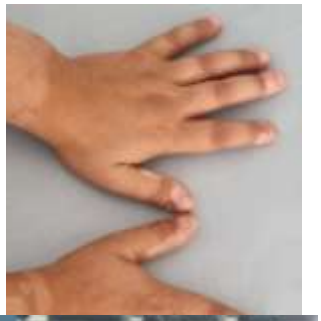
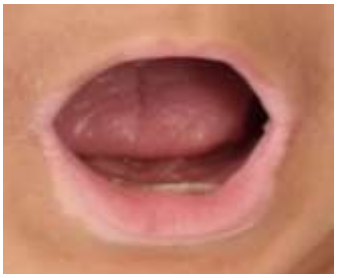
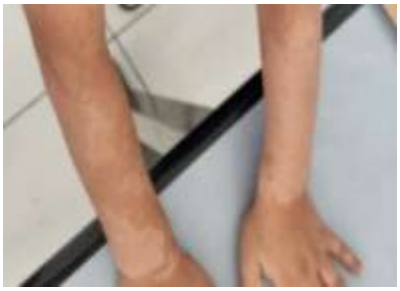


Image 5 Image 6Image 7





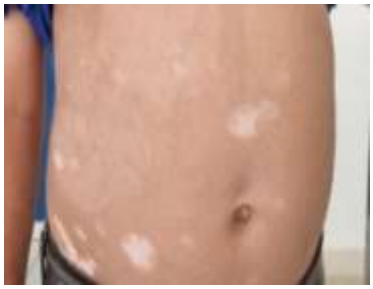


Image 8 Image 9 Image 10

Discussion:-

APS-1is a rareautosomal recessive genetic disease linked to a mutation in the AIRE gene. It's prevalence in France is estimated at one in 500,000 individuals, but it is more frequent in certain populations such as Finland, Sardinia and Iranian Jews.

APS-1is classically characterized by at least two of the three components of Whitaker's triad: chronic mucocutaneous candidiasis, hypoparathyroidism and chronic adrenal insufficiency (Our first patient presented all three criteria of this triad, the last major criterion, namely adrenal insufficiency, appeared only after 2 years of evolution). If a sibling is affected, only one component of the triad is necessary to make the diagnosis (For the 2nd patient, the appearance of dermatological manifestations was sufficient to orient us towards the APECED1 syndrome).

CMC is the most frequent and earliest manifestation of the disease. In our case, CMC appeared at the age of 08 years for the 1st patient. Candidiasis can be chronic or sequential and its severity varies from one individual to another. It often affects the mouth, leading to a moderate (ulcerations, erythema, painful cheilitis of the labial

commissures), hyperplastic (white patches of mycosis and hyperkeratosis), or atrophicform (leukoplasia or nodular areas). Onychomycosis is also frequent, as for our 2 patients, but skin involvement is less represented (10 to 17% of cases). Esophageal candidiasis is present in 5 to 22% of European series. It may be complicated by retrosternal pain, dysphagia and stenosis. At the intestinal level, it promotes abdominal pain, gas and diarrhea. CMC is sometimes complicated by candidemia, especially if immunosuppressive treatment is started.

SCC have been described at sites of chronic fungal infection in the mouth or esophagus in young APECED patients. This supports the potential carcinogenic effect of Candida albicans infection, and the need to screen and treat this infection.

Autoimmune hypoparathyroidism is the most frequent endocrine manifestation of APECED syndrome, its prevalence varies between 63 and 96%, it occurs early in childhood and rarely remains isolated. In our case, the older brother initially consulted us for a tetany attack which revealed hypoparathyroidism at the age of 8 years.

Autoimmune adrenal insufficiency is the second most common and earliest endocrine manifestation. Autoantibodies are 21-hydroxylase, 17-hydroxylase, and SCC (side chain cleavage). Their presence may precede the symptoms and, if these antibodies are present, it is necessary to monitor adrenal function twice a year. The main complication of chronic adrenal insufficiency is acute decompensation which occurs in case of stress or intercurrent events, but also in case of malabsorption. Our 1st patient presented an adrenal insufficiency revealed by an acute decompensation, 2 years after the diagnosis of APECED syndrome and aggravated by his candidiasis. While the 2nd patient presented a fruste IS revealed by the dosage of the cortisol level.

The ectodermal disorders associated with APECED syndrome include skin diseases such as vitiligo and alopecia, keratoconjunctivitis, dental enamel hypoplasia, nail dystrophy and tympanic membrane calcifications. Our 2nd patient presented with vitiligo and alopecia which motivated his consultation at the age of 4 years.

Other autoimmune diseases are associated with APECED syndrome, endocrine (hypergonadotropic hypogonadism, thyroiditis, hypophysitis and type 1 diabetes), or non-endocrine (atrophic gastritis, Biermer anemia, exocrine pancreatic insufficiency, celiac disease, autoimmune hepatitis or interstitial lung disease...). Our 1st patient presented a Biermer anemia with autoimmune hepatitis, while the 2nd patient presented a cytolysis with hepatic cholestasis and a non-specific duodenitis.
Our 2 patients, have two deceased brothers. APS-1 is a serious disease leading to premature death if all components of the disease are not detected and treated. Some conditions are severe and life-threatening, such as SCC, fulminant hepatitis, candidemia or malabsorption and acute adrenal insufficiency.

The association of these different autoimmune diseases can be explained by the mutation of the AIRE gene. The transcription factor AIRE allows the expression of autoantigens in the thymus, the T lymphocytes whose affinity is too high towards these autoantigens are eliminated and do not migrate to the periphery, this is the negative selection of autoreactive T lymphocytes and regulatory T lymphocytes. The mutation of the AIRE gene will therefore be characterized by a central tolerance defect and a functional deficit of regulatory T cells.

The management of APECED syndrome involves the management of the various diseases
Treatment of CMC is aimed at preventing azole antifungal resistance and squamous cell cancer. Oral candidiasis requires good dental hygiene and the use of topical polyene antifungals as mouthwashes for 4-6 weeks. Subsequent prophylaxis involves one week of treatment every three weeks. Any lesion that persists after two weeks of well-managed treatment should be biopsied. The use of high-dose fluconazole (200 to 300 mg once daily for 1 week) should be restricted to severe candidiasis resistant to topical treatments. Onychomycosis is difficult to eradicate; systemic treatments are often required for six weeks. Intravenous antifungals are reserved for candidiasis.
The treatment of endocrine deficiencies is not different from that of other etiologies, except that poorly controlled candidiasis or malabsorption may require an increase in dose, or recourse to injectable treatment with hemisuccinate or recombinant PTH.

Autoimmune liver disease may require immunosuppressive therapy. Because of the risk of systemic candidiasis and neoplastic disease under immunosuppressive therapy, it seems reasonable to initiate prophylactic antifungal therapy. Intravenous immunoglobulin has also been shown to be effective in the treatment of autoimmune hepatitis in combination with immunosuppressive drugs.

In our case, vitamin-calcium supplementation in our first patient induced subcutaneous calcium deposits and nephrocalcinosis, necessitating treatment adjustments. Mineralocorticoid substitution was not available for our 2 patients. Moreover, the hepatic involvement made the prescription of antimycotics difficult. Finally, genetic counseling is important to establish because of the autosomal recessive monogenic character of this syndrome.

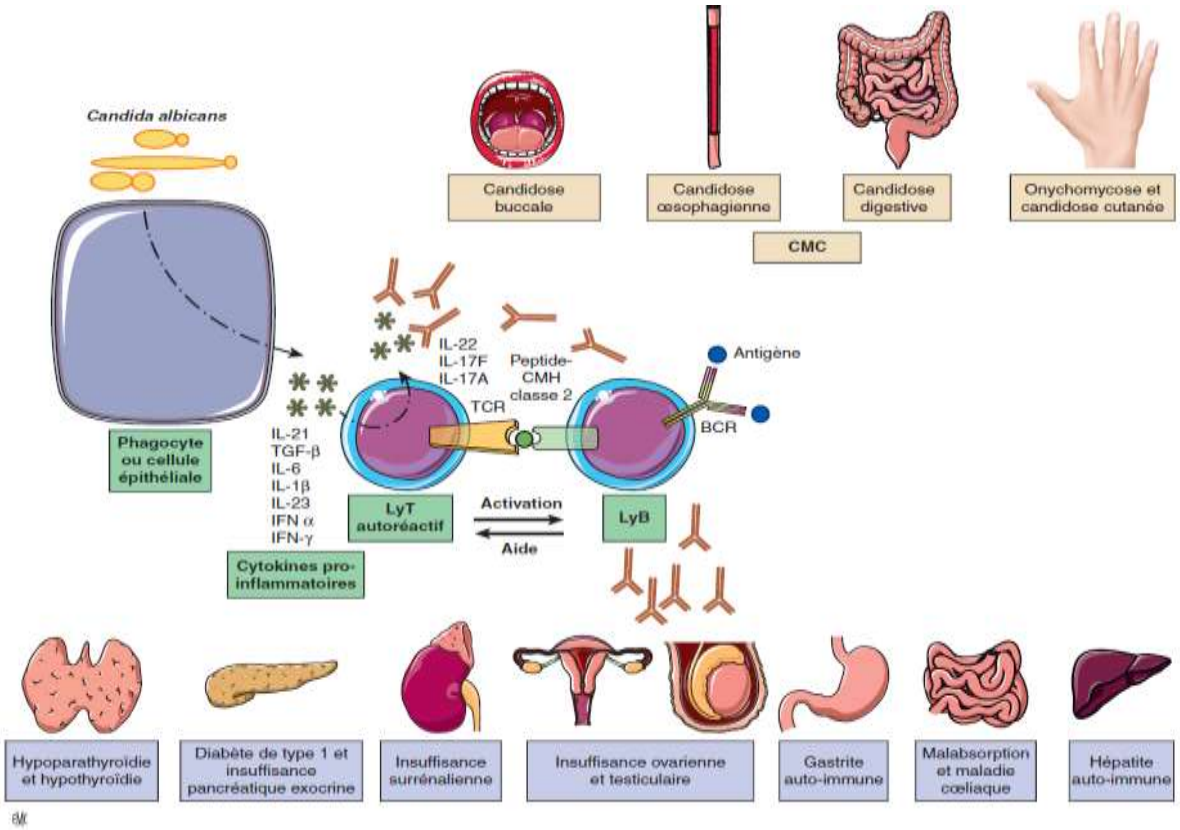


Image 11:- Physiopathology of APECED syndrom [2].

Conclusion:-

The APECED syndrome is an exceptional disease both in terms of its frequency and its pathophysiological mechanisms. Its treatment consists of substituting endocrine deficiencies and controlling the consequences of the immune deficiency, and the patient must be monitored regularly to detect the appearance of other pathological elements of the syndrome.

This syndrome requires a multidisciplinary approach: pediatricians, endocrinologists, gastrohepatologists, dermatologists and geneticists...

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