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Fibrosing Frontal Alopecia: A comprehensive study to understand its etiology

Alopecia Frontal Fibrosante: Um estudo integral para compreender sua etiologia

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ABSTRACT

Objective: To analyze the most recent data on the etiology, mechanisms, clinical signs, diagnostic methods, and therapeutic approaches for Frontal Fibrosing Alopecia (FFA). Methods: Systematic review organized based on five sentences: formulation of the guiding question and from the acronym PICO, search for articles and studies in the online database, selection and review of studies, critical evaluation of the material of the selected articles and interpretation of the results. Literature Review: Frontal Fibrosing Alopecia is a form of acquired primary cicatricial alopecia clinically characterized by a recession of the frontotemporal line, often accompanied by eyebrow alopecia. Its pathophysiology involves immunological, genetic, hormonal, photoexposure mechanisms, use of cosmetics, environmental factors, trauma and stress. The diagnosis is made clinically, through physical examinations and trichoscopy, and can be complemented with biopsy and optical coherence tomography. Conclusion: Because it is a relatively new pathology, more research is still needed to better understand the disease and establish more effective treatments.

Keywords: Frontal Fibrosing Alopecia, Pathophysiology, Diagnosis.

INTRODUCTION

Frontal Fibrosing Alopecia (FFA) is an increasingly prevalent form of acquired primary cicatricial alopecia, first described by Kossard in 1994, whose incidence has increased in recent years. The first six cases documented in Brazil in 2004 showed the typical characteristic of hair loss in the frontal line after menopause and also hair loss in the eyebrows. Over the years, reports of cases in both sexes, both men and women, that occurred before menopause, have emerged, which has started the first discussions about this pathological condition. (BRENNER FM and OLDONI C, 2019)

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Recently, the inclusion of facial, axillary and limb involvement has altered the scope of the problem, suggesting a possible systemic involvement of the hair. In addition, although frontal fibrosing alopecia has a distinctive clinical pattern, its histological analysis reveals similarities with lichen planus pilaris (PPL), leading to the current belief that it is a clinical variant of this condition. (BRENNER FM and OLDONI C, 2019)

Several drugs have been evaluated in observational studies, however, the most promising results to date have been associated with the use of anti-androgens, corticosteroids administered directly to the lesions, and antimalarials. (GASPAR NK, 2016)

Finally, it should be noted that older individuals, who are the most affected by AFA, tend to have a tendency to reduce their self-esteem, as well as feelings of anxiety and depression. Upon receiving the diagnosis of this alopecia condition, not only are they more likely to suffer from mental problems, but they may also feel more helpless in controlling the disease, since it progresses slowly and continuously, without a clearly defined treatment to this day. Therefore, it is crucial to consider the importance of understanding this condition and developing an effective therapeutic approach. (SACEDA-CORRALO D, et al., 2018)

METHODOLOGY

It refers to a systematic review organized based on five sentences: formulation of the guiding question and from the acronym PICO, search for articles and studies in the online database, selection and review of studies, critical evaluation of the material of the selected articles and interpretation of the results of the integrative review.

The acronym PICO is manifested as follows: The letter P (patient) refers to the patient with Frontal Fibrosing Alopecia; the letter I (intervention) designates the study of the pathophysiology of the disease; the letter C (comparison) consists of the evaluation of the various types of studies; and, the letter O (outcomes) refers to the pathophysiology to be explored to determine an effective treatment. So, the research question is: "What is the integral view on the etiology of Frontal Fibrosing Alopecia?".

The descriptors were: "Alopecia"; "Fibrosis"; "Causality", according to the Health Sciences Descriptors (DeCS). To search for the articles, the LILACS databases, CAPES Portal and the Virtual Health Library (VHL) were explored. The search expression used was "Alopecia AND fibrosis AND causality".

Regarding the inclusion criteria, we have: free studies found in the databases that were related to the theme defined for this review, according to the research question. Thus, the

criterion for excluding the articles was the divergence of the theme with the guiding question elaborated, being paid and repeated articles among the databases of the theme with the research question developed.

In short, regarding the number of articles found: in CAPES 01, in LILACS 3 and in VHL 45, concluding with 48 publications. Then, after filtering based on the reading of the titles and abstract, 10 publications were benefited to discuss this article.

DEFINITION AND CLINICAL MANIFESTATIONS

Frontal Fibrosing Alopecia is a type of cicatricial alopecia, with progressive and permanent loss of hair follicles, which affects the anterior border of the scalp and eyebrows and progresses continuously to the occipital region less frequently to other areas of the body. The disease has a slow and progressive evolution. (GASPAR NK, 2016)

Initially, patients present with recession of the frontotemporal hairline, which is physiologically 5.5 cm away from the glabella in women. Over time, it evolved with lateral and posterior retraction. In addition, they may present lesions in the hair follicles, such as erythema, micropapules and hyperkeratosis and other symptoms, as well as itching, burning, atrophy of the skin, more evident frontal veins and difference in color in the integument, since the scalp margin has no photodamage. (GASPAR NK, 2016; KUSANO LDC and BRENNER FAM, 2019 ; MELO DF, et al., 2019)

A study published in 2019 showed that predictors of disease severity are age at onset of involvement, lower educational level, disease duration, and body mass index. In addition, a severity prediction scale has been developed in Spain, which can be used to differentiate patient harm. The developers concluded that a tricoscopic evaluation can improve the specificity and sensitivity of the evaluation. (MORENO-ARRONES O, et al., 2019; SACEDA-CORRALO D, et al., 2017)

Due to the gradual nature of the disease, in some situations, late detection of the disease and subsequent delay in the application of treatment can have adverse impacts on patient progression and outlook. (MELO DF, et al., 2019)

EPIDEMIOLOGICAL ASPECTS

According to a retrospective observational study applied to 38 female patients diagnosed with Frontal Fibrosing Alopecia in a Brazilian state, the mean time between the onset of the

disease and the correct medical diagnosis was 3 years. (KUSANO LDC and BRENNER FAM, 2019)

Regarding the climacteric, at the initial moment, 10 patients (26.31%) were in the premenopausal phase, while 28 patients (73.68%) had already gone through menopause. In addition, 16 patients (42.1%) had received hormone replacement therapy before the diagnosis of FAF. The mean age of disease onset was 44 years for the premenopausal group and 59 years and 7 months for the postmenopausal group. (KUSANO LDC and BRENNER FAM, 2019)

Regarding the use of cosmetics and previous procedures, the vast majority, i.e., 86.84% of the patients, mentioned that they used to frequently use chemical treatments, such as dyes or straightening, on their hair. In addition, 39.47% of the patients reported that they used sunscreen regularly, and 21.05% of them applied sunscreen at least once a month. In addition, a total of six patients, equivalent to 15.78%, mentioned that they had undergone facial plastic surgery at the same time that AFF manifested itself. (KUSANO LDC and BRENNER FAM, 2019)

At the genetic level, ten patients, corresponding to 26.31% of the group, mentioned that their mothers had a history of alopecia. In addition, 16 patients, i.e., 42.1%, reported that their parents also had this history. There was also a case where one patient mentioned that his daughter had Frontal Fibrosing Alopecia, while another patient mentioned that his daughter suffered from cutaneous lichen planus. (KUSANO LDC and BRENNER FAM, 2019)

Of the clinical manifestations of this group, each patient analyzed exhibited a hairline recession in the frontotemporal region. In addition, three of them also had diffuse hair loss, without the formation of scars, and one patient had a recession in the hairline in the occipital region. The majority of patients, equivalent to 89.47%, also showed eyebrow involvement, which is in line with information previously described in the literature. (KUSANO LDC and BRENNER FAM, 2019)

Regarding treatment, the vast majority of patients, representing 89.47% of the group, received topical treatment, which included the use of topical steroids and minoxidil. In addition, 86.84% of the patients received systemic treatment, 27 of whom were treated with antimalarials (hydroxochloroquine), 17 with 5α-reductase inhibitors (finasteride), and only four with methotrexate, cyclosporine, and mycophenolate mofetil. Within that group, 20 patients reported that the condition stabilized, while six had a worsening of the disease, and nine experienced hair growth. (KUSANO LDC and BRENNER FAM, 2019)

FISIOPATOGENIA

It is known that understanding the pathophysiological mechanism of Frontal Fibrosing Alopecia is essential to indicate more effective treatments, since it is still considered a disorder with poor therapy. Currently, researchers have addressed the main ways in which the disease develops, namely: Immunological, genetic, hormonal, photoexposure, use of cosmetics, environmental, trauma and psycho-emotional stress. (PHOTIOU L, et al., 2019)

In an inflammatory scenario characterized by the activation of Th1 cells, a subtype of CD4 T lymphocytes, followed by the collapse of the immune protection system of the hair follicle, we observed the permanent destruction of the follicle's epithelial stem cells. In addition, the lack of adequate signaling of the gamma peroxisome proliferator-activated receptor (PPAR-γ) results in the inhibition of fat metabolism and the formation of peroxisomes, leading to the accumulation of pro-inflammatory fats. As a consequence, this promotes the infiltration of inflammatory cells and the deterioration of the hair follicle. Lastly, an additional immune-mediated response involves the transition of follicular epithelial protuberances from the epithelial to the mesenchymal state, resulting in the loss of their polarity and a shift to a connective tissue-like phenotype reminiscent of the wound healing process. These complex events represent the most substantial level of evidence to date. (PHOTIOU L, et al., 2019)

The genetic influence still needs more clues, however, reports of family history of AFF were documented in 17.7% of affected individuals, indicating a possible autosomal dominant inheritance with incomplete penetrance. Epigenetic modifications are thought to play a role in regulating gene expression or suppression, thereby influencing the onset of AFF and its clinical phenotypes. Increasingly, evidence is emerging to support the idea that environmental factors and lifestyle can impact epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA expression. (PHOTIOU L, et al., 2019)

The hormonal relationships with the pathogenesis of AFF are based on physiology, that after menopause, there is a significant decrease in estrogen levels in the body, while androgen hormone levels tend to increase. Although AFF is most commonly seen postmenopausal, there are increasing case reports in women before menopause and even in men, as mentioned earlier, which raises questions about the role of low estrogen levels in this context. A study conducted in the United States with 168 patients affected by AFF/LPP (i.e., Lichen Planus Pilaris), focused on the analysis of hormonal and endocrine imbalances, found that 32.1% of individuals with AFF had androgen deficiency. Dehydroepiandrosterone (DHEA), which plays a key role in the production of androgens and estrogen, has been observed to influence PPAR-γ function and has

been shown to possess strong antifibrotic effects. Therefore, the decrease in DHEA and androgens may contribute to the creation of a pro-fibrotic environment in AFF. This discovery promises to be revolutionary in relation to the treatment of this type of alopecia, as the regulation of PPAR-γ may be more effective than some agents currently used. (GASPAR NK, 2016; PHOTIOU L, et al., 2019)

It is believed that sun exposure may be a possible environmental trigger of AFF. A smaller-scale survey conducted in Brazil found that 87% of patients with AFF reported being sensitive to sunlight, while only 13% of people in the control group had this sensitivity. In addition, patients with AFF mentioned using sunscreen more often, associating this habit with their greater sensitivity to sunlight. There has been much discussion about whether this type of cosmetic could increase photosensitivity or even cause an inflammatory reaction in some patients. However, the authors of the studies noted that the use of sunscreen cannot fully explain certain aspects of AFP, such as why many people in the general population who use sunscreen do not develop AFP, why many patients with AFF do not make regular use of sunscreen, or the occurrence of the disease in areas such as the occipital region and in places more exposed to the sun, where the use of sunscreen is not so relevant. (PHOTIOU L, et al., 2019)

To date, no definitive relationship has been established between the use of ultraviolet filters in hair products, the use of facial cosmetics, the use of chemicals in the hair (such as progressives, relaxations), considerations of trauma and psycho-emotional stress, and AFF, although it has been the subject of speculation. In addition, there is no convincing evidence linking environmental toxins, such as smoking, alcohol consumption, and occupational exposures to organic solvents, to the development of alopecia. Therefore, the need for additional research to identify the possible environmental triggers of the disease is evident. (MELO DF, et al., 2019; PHOTIOU L, et al., 2019)

DIAGNOSIS

The diagnosis of Frontal Fibrosing Alopecia depends on an appropriate clinical evaluation, which can be complemented with some tests. Early and accurate recognition is of paramount importance, as this allows the implementation of treatments that can reduce symptoms, disease progression, scarring and the impact on patients' quality of life. (MELO DF, et al., 2019)

Clinically, most of these patients are asymptomatic, although some symptoms such as pruritus, pain and burning can be observed in the affected sites. In addition, on physical

examination, erythema with perifollicular desquamation in the peripheral part of the alopecia areaabsence of vellus hairs, which are thin, light-colored hairs on the scalp line, reduction in the number of follicular ostia, more evident frontal veins, solitary and isolated hairs on the original hairline, the sign of pseudophinga is observed when there is a retention of hair along the frontal region, With an appearance similar to a fringe, identification of hypopigmented areas, drooping of the eyebrow and eyelashes bilaterally, facial papules and association with lichen planus pigmentosum may be suggestive of the disease. (MELO DF, et al., 2019)

Regarding complementary exams, trichoscopy is important to help identify signs of the disease, such as Vellus, in addition to delimiting the area to be performed for biopsy. This is preferably done in areas where there are perifollicular concentric scales. The characteristic biopsy result of AFF has the presence of a lymphocytic infiltrate involving the bulge and infundibulum, apoptotic cells in the outer rod sheath, and concentric fibrosis around the follicle with a decrease in the number of follicles, replaced by fibrous tissue. (GASPAR NK, 2016)

Another strategy that has been used to better identify skin architecture and vascularization is OCT (optical coherence tomography), which was developed by ophthalmology, but has been used in dermatology as a non-invasive imaging method. In it, the findings include absent follicular vellus openings, decreased and irregular terminal follicular openings, disorganized arrangement of the interfollicular tissue, increased perifollicular vascularization, and increased epidermal thickness. This means can be used both for diagnosis and follow-up of cases. (VAZQUEZ-HERRERA NE, et al., 2018)

TREATMENT

The more recent the diagnosis of the disease, the more effective the treatment to try to stabilize it, since there is still no cure. Intralesional corticosteroids may be an option for this stabilization of the hair implant. Hydroxychloroquine has also been shown to be effective in leading to a reduction in signs and symptoms in some cases, over an estimated 12-month period. In addition, some classes of drugs such as systemic anti-inflammatory drugs, tetracyclines, cyclosporine are also options to be used, with antiandrogens having the best results in controlling the progression of the disease. These intralesional corticosteroids associated with antiandrogens are routinely used in the treatment of erythema or follicular hyperkeratosis. (GASPAR NK, 2016)

The ideal treatment of AFF has not yet been established, although there are some proposals such as hydroxychloroquine and chloroquine, finasteride and dutasteride, hormone

replacement, mycophenolate mofetil, topical corticosteroid preparations, doxycycline, systemic prednisolone, intralesional triamcinolone acetonide, topical calcineurin inhibitor (tacrolimus), and topical minoxidil. Some reviews suggest methotrexate as the best treatment. The evidence remains unclear, making it difficult to determine whether the slowing of progression is a response to medications or a natural stabilization of the disease. (CRANWELL W and SINCLAIR R, 2017)

It is also worth mentioning that, in cases where there is remission of the disease, hair transplantation can be considered an option, since its duration is long and helps to bring back the individual's self-esteem. However, there is a possibility of reactivation of the inflammatory process at the root of the follicle. Performing the transplant with artificial fibers can be an alternative that does not cause inflammation of the hair follicle. (CRANWELL W and SINCLAIR R, 2017)

CONCLUSION

In view of the above, it is known that fibrosing alopecia is a disease that has been increasingly prevalent, systemically involving the hair. The disease permanently affects the hair follicles, evolving with lateral and anteroposterior retraction, and of a slow and progressive nature. It may be asymptomatic, but some patients report symptoms such as pruritus. With this study, it is concluded that the pathophysiology is broad, but the most accepted theory is currently immune-mediated. Lack of PPAR-gamma receptor signaling and reduction of DHEA causes inflammation and damage, resulting in a fibrosing phenotype. Although it is a disease that has been described for some years, it still faces some challenges, especially with regard to treatment and diagnosis, since patients' self-esteem is directly affected and the therapy is not yet established or definitive. In addition, not all physicians have the theoretical capacity to identify the disease, since there are some differential diagnoses to be considered, and they often end up being ignored.

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