Recurrent Vulvovaginitis: Diagnostic Assessment and Therapeutic Management

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Abstract. Recurrent vulvovaginitis is a common problem in clinical practice. Management is often complicated by a long history of inappropriate treatments based on tentative diagnoses after an incomplete diagnostic workup. We review the most common causes of recurrent vulvovaginitis; the appropriate steps with which to establish a diagnosis, from the medical history through to the additional tests needed; and, finally, the best therapeutic options. We will focus on infectious, irritant, allergic, and hormonal causes as the ones of most interest to the dermatologist. Given that infection is the most frequent cause of these processes and also a common reason for inopportune treatment, we will pay particular attention to infectious etiologies and their differential diagnosis.

Key words: vulvovaginal candidosis, Trichomonas, bacterial vaginosis, allergic vulvovaginitis.

Introduction

The vagina is a natural cavity that, in physiological conditions, contains a large number of commensal bacteria (around 10^9 colony forming units in each gram of secretion). These are mainly species of the genus Lactobacillus that maintain an acid pH in the vagina by producing lactic acid and hydrogen peroxide. This commensal flora can become pathogenic in certain situations in which the vaginal ecosystem is altered, such as advanced age, diabetes mellitus, the luteal phase of the menstrual cycle, sexual activity, the use of oral contraceptives, pregnancy, the presence of necrotic tissue or foreign bodies, or the use of antibiotics and feminine hygiene products.

As occurs with the oral mucosa, the vulva can be affected by dermatoses of various etiologies and the dermatologist therefore has an important role in the diagnosis and treatment of these disorders.

Vulvovaginitis is defined as an inflammation of the vulva and vagina and is associated with various symptoms such as leukorrhea, pruritus, soreness, dysuria, and dyspareunia. It is one of the most common reasons for gynecologic and dermatologic consultations, both in primary care and in specialist clinics, in which it constitutes 25% of consultations.¹

Vulvovaginitis of infectious origin, which is the most common and which may or may not be sexually transmitted, is distinguished from cases of noninfectious origin, which include disorders of allergic, irritant, traumatic, and hormonal
etologies (Table 1). In addition, we must not forget other common dermatoses that can affect the genital region, such as psoriasis, atopic dermatitis, lichen simplex chronicus, seborrheic dermatitis, and lichen sclerosus et atrophicus.

**Diagnosis**

A detailed and meticulous clinical history, establishing empathy with the patient, is essential in order to reach the diagnosis. The clinical manifestations (soreness, pruritus, pain, and dyspareunia), the presence or absence of leukorrhea and its characteristics (color, quantity, consistency, and smell), area affected (vulva, vagina, or both), time course of the symptoms (continuous or episodic), time since onset, and triggering factors (stress, menstruation, infections, antibiotics, or sexual activity) must all be taken into account. The patient should also be questioned about possible previous episodes and the diagnosis that was established, the therapies used, and the response to treatment. The type and frequency of sexual activity must be established, and whether the partner has symptoms and has received treatment. Finally, the psychological repercussions and the effect of the symptoms on the patient’s quality of life must be considered.

**Physical Examination**

Examination of the external genital area and vagina are important. Areas of erythema, edema, fissures, and ulcers must be sought during inspection of the vulva. A swab should be used to detect sensitive regions. Gynecologic inspection is performed using a speculum, collecting samples from the vaginal walls and fornix. The vaginal pH must be measured (in the secretions from the vaginal walls, not from the fornix), the amine test performed, and a smear of the vaginal exudate mixed with potassium hydroxide and examined under the microscope. Vaginal culture for fungi, bacteria, and herpesvirus is useful in doubtful cases or when the above tests are negative.

The vaginal pH varies between 4 and 5; it is slightly more acid in the premenstrual phase than in the luteal phase and is neutral during menstruation, as is also found in the prepubertal and postmenopausal stages. Table 2 lists the causes of alkalinization of the vaginal pH (Table 2).

If trophic changes or ulcers are observed, biopsies should also be taken in order to identify conditions such as lichen sclerosus et atrophicus, lichen simplex chronicus, squamous epithelial hyperplasia, and tumors.

In the following sections, we describe the most common causes of recurrent vulvovaginitis, paying particular attention to their diagnosis and treatment.

### Infectious Vulvovaginitis

The most common forms of infectious vulvovaginitis are trichomoniasis (15%-20%), candidiasis (20%-25%), and bacterial vaginosis (40%-50%). Other infectious agents that should be considered include herpes simplex, gonococcus, and chlamydia. The characteristics of the vaginal discharge have traditionally been considered to be useful in the diagnosis of a suspicion of these infections (Table 3).

### Trichomonas Vaginitis

The microorganism responsible for trichomonas vaginitis is *Trichomonas vaginalis*, which is usually acquired by sexual transmission. It is considered to be the most prevalent nonviral...
the percentage cure rate is lower.\textsuperscript{11} The use of metronidazole or povidone iodine may be used in these patients, although at the above doses is accepted during pregnancy.\textsuperscript{12}


Table 3. Characteristics of Vaginal Discharge According to the Cause

<table>
<thead>
<tr>
<th></th>
<th>Quantity</th>
<th>Color</th>
<th>Consistency</th>
<th>Smell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trichomoniasis</td>
<td>Increased</td>
<td>Greenish-yellow</td>
<td>Frothy</td>
<td>Foul odor</td>
</tr>
<tr>
<td>Vaginosis</td>
<td>Moderate</td>
<td>Grayish-white</td>
<td>Homogeneous-adherent</td>
<td>Foul odor (fishy)</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Low-moderate</td>
<td>Yellowish-white</td>
<td>Lumpy</td>
<td>No</td>
</tr>
</tbody>
</table>

sexually transmitted disease.\textsuperscript{5,6} Infection in men is asymptomatic, but in women it gives rise to a highly characteristic abundant, frothy, foul-smelling, yellow-green discharge. The symptoms include pruritus, dyspareunia, and dysuria, all of which increase during menstruation. Examination reveals erythema of the vagina and cervix, which acquires the appearance of a strawberry. The vaginal pH is above 5.

Direct examination of the discharge is performed by taking a sample from the vaginal fornix, diluting it in normal saline, and spreading it on a microscope slide. \textit{Trichomonas} (with or without flagella) are observed in 50% of cases, with abundant white cells (> 20 neutrophils/field \times 1000). In doubtful cases, culture should be performed in Diamond, Kupferberg, and Roiron media.

Screening should also be performed for other sexually transmitted diseases caused by chlamydia, mycoplasma, or gonococcus.\textsuperscript{6}

Oral treatment is performed with 2 g of metronidazole as a single dose, 500 mg every 12 hours for 7 days, or 250 mg every 8 hours for 7 days. Topical therapy with metronidazole gel, 0.75%, twice a day for 7 days is less effective.\textsuperscript{7} The most common adverse effects are a metallic taste, gastrointestinal discomfort, and interactions with alcohol. In metronidazole-resistant strains (2%-5%),\textsuperscript{8} tinidazole can be used as a single oral dose of 2 g.\textsuperscript{6,9} Cross-reactions with other nitroimidazoles are common in patients allergic to metronidazole; clotrimazole pessaries, 100 mg, once a day for 6 days, topical paromomycin 1 application per day for 14 days,\textsuperscript{10} or vaginal douches with 1% zinc sulfate or povidone iodine may be used in these patients, although the percentage cure rate is lower.\textsuperscript{11} The use of metronidazole at the above doses is accepted during pregnancy.\textsuperscript{12}

Abstention from sexual intercourse is recommended during treatment, and the partner should be treated for 1 week as the single dose is less effective in men.\textsuperscript{6}

The regimen is repeated if recurrence occurs, and if the condition still persists, metronidazole is administered orally at a dose of 2 g per day for 3 to 5 days in combination with local treatment for 15 days.\textsuperscript{12}

Bacterial Vaginosis

Bacterial vaginosis develops due to a change in the vaginal bacterial flora, leading to an overgrowth of \textit{Gardnerella vaginalis} and other anaerobic bacteria (\textit{Bacteroides} species, \textit{Prevotella} species, \textit{Peptostreptococcus} species, \textit{Mycoplasma hominis}, \textit{Atopobium vaginae})\textsuperscript{9} and a decrease in the number of lactobacilli. Although it is not itself considered to be a sexually transmitted disease, it can be associated with diseases such as gonorrhea and chlamydia.

The disease is often asymptomatic and in many patients the diagnosis is made during a routine examination or cytology. The Amsel criteria continue to be used for diagnosis, and 3 of the 4 criteria must be satisfied:

1. Increased amounts of thin, homogeneous, grayish-white, adherent vaginal discharge with a characteristic, fishy smell
2. Vaginal pH higher than 4.5
3. A smell of amines before or after the addition of potassium hydroxide
4. Presence of clue cells, which are vaginal epithelial cells covered by bacteria, giving them a granular appearance. There should be at least 20% of these cells in the smear, as well as few lactobacilli.

Culture is not useful. In recent years, commercial methods have been developed that detect the pH and \textit{Gardnerella vaginalis} enzymes or DNA,\textsuperscript{6,12} such as FemExam pH and Amines TestCard, FemExam PIP Activity TestCard, which detects an enzyme of the bacterium, and Affirm VP III Microbial Identification Test, which is a DNA probe for the identification of \textit{Gardnerella}, \textit{Candida}, and \textit{Trichomonas} species.

Therapy is recommended in symptomatic women, recurrent disease, and bacterial vaginosis during pregnancy. Treatment of the partner is not indicated unless symptomatic.\textsuperscript{12}

The recommended treatment is oral metronidazole, 500 mg, every 12 hours for 7 days; metronidazole gel, 0.75%, once a day for 5 days; or clindamycin cream, 2%, once a day (preferably at night) for 7 days.\textsuperscript{12,13} Alternatives include the use of oral clindamycin, 300 mg, every 12 hours for 7 days or clindamycin pessaries, 100 mg, once a day (preferably at night) for 3 days.\textsuperscript{12,13} During pregnancy, patients may be administered oral metronidazole, 250 mg, every 8 hours for 7 days\textsuperscript{12,13} or oral clindamycin, 300 mg, every 12 hours for 7 days.\textsuperscript{6,14,15}

Recurrent bacterial vaginosis is defined as 3 or more episodes per year,\textsuperscript{14} and it develops in 15%-30% of patients.\textsuperscript{6}
It has been related to the use of intrauterine devices and the vaginal diaphragm, whereas condoms appear to be useful in prevention. These patients require regimens of 10 to 14 days with the above treatments.

The use of intravaginal metronidazole gel, 0.75%, twice a week for 4 to 6 months or oral clindamycin, 150 mg, twice a day for several months is accepted for the prevention of recurrence. Lactate gel has also been used to maintain the pH during the first 3 days after menstruation, and is continued for 6 months in association with metronidazole or tinidazole.

Candidal Vulvovaginitis

Candidal vulvovaginitis is a common infection among young women and is associated with a certain morbidity and considerable health costs; it accounts for 30% of all cases of vulvovaginitis. Candida albicans can be found as part of the commensal flora in up to 25% of healthy women. Seventy-five percent of all women will have an episode of candidal vulvovaginitis and, of these, half will have a second episode. The majority of authors do not consider this to be a sexually transmitted disease.

In recent years, this condition has been categorized into complicated forms, which are increasing in incidence, and uncomplicated forms (Table 4).

Recurrent candidal vulvovaginitis is defined as 4 or more symptomatic infections per year or 3 episodes not related to the administration of antibiotics occurring within a year. Recurrent disease occurs in 5% of women, and in the majority of cases recurrence occurs within 3 months of the initial infection. Between 10% and 33% of recurrent candidal vulvovaginitis is due to species other than C. albicans, such as Candida glabrata (the most common), Candida tropicalis, Candida krusei, Candida parapsilosis, and Saccharomyces cerevisiae.

A number of theories have been proposed to explain the etiology of recurrent disease, based on the intestinal reservoir of Candida species, though this has not been demonstrated in subsequent studies, and sexual transmission, as 20% of sexual partners have colonization of the mouth, genitalia, and fingers by the same species. The most widely accepted theory at the present time is that recurrent candidal vulvovaginitis is due more to persistence of the pathogen in the vagina than to reinfection; this is supported by the isolation of microorganisms with an identical karyotype in recurrences.

Recurrent disease usually presents with a lesser degree of vulvovaginal inflammation, and is more commonly characterized by local discomfort that increases in the days prior to menstruation. The most common symptoms are pruritus (50%), abundant vaginal discharge (24%), and dysuria (33%). Burning and stinging sensations have also been reported. However, these symptoms are nonspecific and other etiologies should always be considered.

The following aspects must be taken into account in women who present recurrent candidal vulvovaginitis:

1. The presence of triggering or associated factors such as poorly controlled diabetes mellitus, high-sugar diets, the recent use of broad spectrum antibiotics, and steroid treatment.
2. The association with sexual activity, particularly with certain sexual practices such as oral and anal sex.
3. The relationship with states of hyperestrogenism, such as pregnancy, particularly in the third trimester, and the use of oral contraceptives with a high estrogen content.
4. The presence of other dermatologic disorders that can cause itching or soreness and need to be excluded, such as irritant or allergic dermatitis (including those related to the use of topical antifungal agents) and lichen sclerosus et atrophicus.
5. The association between atopic dermatitis and these recurrent infections.
6. The possible implication of immunosuppression, such as that associated with human immunodeficiency virus infection and immunosuppressant treatments, and changes in the vaginal microenvironment leading to differences in local immunity.
7. The possible association between recurrent candidal vulvovaginitis and other infections (trichomoniasis, vaginosis).
8. Deficiencies of trace elements and minerals such as magnesium, zinc, and calcium; however, there does

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Uncomplicated</th>
<th>Complicated</th>
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<tbody>
<tr>
<td>Frequency</td>
<td>Sporadic, infrequent</td>
<td>Recurrent (more than 4 episodes per year)</td>
</tr>
<tr>
<td>Host</td>
<td>Healthy</td>
<td>Diabetes, immunosuppression, pregnancy</td>
</tr>
<tr>
<td>Species</td>
<td>Candida albicans</td>
<td>Species other than C. albicans</td>
</tr>
<tr>
<td>Intensity</td>
<td>Mild, moderate</td>
<td>Severe</td>
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Vulvovaginal Candidiasis
Comparison of Diagnostic Methods for Vulvovaginal Candidiasis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
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<tbody>
<tr>
<td>Direct examination</td>
<td>40-60</td>
<td>&gt; 96</td>
</tr>
<tr>
<td>Culture</td>
<td>70-80</td>
<td>&gt; 99</td>
</tr>
<tr>
<td>Latex agglutination</td>
<td>71-81</td>
<td>96-98</td>
</tr>
<tr>
<td>DNA probe</td>
<td>85-90</td>
<td>&gt; 99</td>
</tr>
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not appear to be any association between recurrent disease and iron deficiency.20
9. Infections due to species other than *C albicans* that are usually resistant to standard azole therapy.30,39
10. Candidal vulvovaginitis occurs principally in women of childbearing age and is rare in young girls and postmenopausal women. In this latter group, hysterectomy appears to favor recurrent episodes of vaginal candidiasis.49
11. Genetic factors, such as the non-secretor blood group, and certain genetic polymorphisms of the yeasts; these factors facilitate the adhesion of yeasts to the epithelial wall, favoring colonization and infection.35

The different factors that contribute to the onset of recurrent candidal vulvovaginitis are listed in Figure 1. Diagnosis begins with clinical suspicion and a compatible physical examination. On direct examination, *C albicans* and *C tropicalis* show the typical pseudohyphae and mycelia; other species such as *C glabrata*, *C parapsilosis*, *C krusei*, and *S cerevisiae* only show blastospores and cannot therefore be identified on direct examination.17,39 When direct examination is negative but the clinical suspicion persists, culture should be performed on Sabouraud agar or in Nickerson medium and we should use one of the commercially available standardized systems, such as API20Caux, for their identification.20,39 Other methods that are useful for research but of little use in clinical practice are latex agglutination and techniques based on the polymerase chain reaction. The different diagnostic methods for vulvovaginal candidiasis are compared in Table 5.

It must be realized that culture is not totally reliable, as up to 25% of healthy, asymptomatic women are colonized by *Candida* species and will have positive cultures. Clinical data, direct examination, and culture must therefore be considered together in order to reach the diagnosis.50

There are a number of therapeutic options. The treatment of choice is with a single dose of fluconazole, 150 mg, or intravaginal clotrimazole, 100 mg, daily for 7 days.35 Oral and topical treatments with azoles for 1 to 14 days (Table 6) are also useful and there are no significant differences between them.51,52 The adverse effects of oral therapy that have been reported include gastrointestinal discomfort, headache, tiredness, and skin rashes, but they are rare and well tolerated.51 Fluconazole and itraconazole can cause arrhythmias when associated with cisapride or H1-antihistamines such as astemizole.17 Topical azoles belong to risk category C and since they have not been associated with any increase in the risk of congenital defects they may be used for 7 days during pregnancy.12,38 The efficacy of oral and topical treatments is similar,38 and the decision regarding which to use will depend on the doctor’s experience and patient’s preferences.

Fluconazole, 150 mg (2 doses separated by 3 days), is used in recurrent candidal vulvovaginitis.12,38 Maintenance treatment should be continued for 6 to 12 months with clotrimazole pessaries, 500 mg per week; fluconazole, 100-150 mg per week; itraconazole, 400 mg per month; itraconazole, 100 mg per day; or oral ketoconazole, 100 mg per day.12,35,51 The same regimen is used in patients with human immunodeficiency virus infection who develop vulvovaginal candidiasis.3,2,54

There is no evidence that treatment of sexual partners contributes to resolution of the condition.51,55,56 Treatment of the partner is therefore only recommended in symptomatic cases.12

Although 90% of patients do not suffer recurrences during maintenance treatment,3 symptoms do recur in 30%-40% of patients after withdrawal of the treatment. The maintenance regimen can be repeated in these cases.

Infections due to yeasts other than *C albicans* often involve azole-resistant species, particularly *C krusei*. Cross-resistance to topical and oral azoles has also been detected.57 In these...
cases, daily intravaginal treatment with boric acid pessaries is recommended at a dose of 600 mg/d for 2 to 4 weeks. Maintenance treatment in recurrent candidal vulvovaginitis is given with 1 or 2 doses per week, although there is a danger of teratogenicity. If there is no response, other alternatives include topical flucytosine (as a 17% hydrophilic cream, not marketed in Spain) applied intravaginally once a day for 1 week and topical amphotericin. Applications of 1% gentian violet solution have also been used in these cases, once a week for 4 to 6 weeks in combination with topical nystatin or boric acid. The new azoles voriconazole, rilopirox, and eberconazole are effective against C. krusei and C. glabrata.30

The treatment algorithm for candidal vulvovaginitis is shown in Figure 2.

Cure is defined as 2 negative cultures separated by 1 week, performed at least 1 week after finishing antifungal therapy.59

In recent years, much has been said about the protective effect of the lactobacilli, and this continues to be a subject of discussion. It appears that these bacilli contain bactericidal compounds and, due to their adherence to vaginal epithelial cells, they also displace other microorganisms. It is currently accepted that, in view of the very low number of adverse effects, Lactobacillus acidophilus, Lactobacillus rhamnosus, and Lactobacillus fermentum may be used both orally and vaginally as prophylactic agents in recurrent candidal vulvovaginitis.60

The development of therapeutic vaccines for recurrent candidal vulvovaginitis is under investigation.60

### Bacterial Vaginitis

Bacterial vaginitis is caused by Streptococcus agalactiae, group B, α-hemolytic Streptococcus species, or Staphylococcus aureus. The first of these is a commensal organism that, under certain conditions, such as the presence of a foreign body or atrophic vaginitis, can give rise to symptoms. Clinically, it is characterized by local inflammation, pain, dyspareunia, and a yellow discharge. Examination reveals vulval and vaginal erythema, which may be associated with desquamation and fissures in the skinfolds. Direct examination of the exudate reveals abundant white cells, immature epithelial cells, and the causative microorganisms in the form of chains. Culture confirms the diagnosis. Treatment consists of the elimination or control of the precipitating condition and antibiotic treatment with oral penicillin, 500 mg, every 12 hours or clindamycin cream applied at night for 10 days.17

### Cytolytic Vaginosis

The etiology of cytolytic vaginosis is not fully understood. Some believe it to be due to an increase in the concentration of lactobacilli that causes lysis of the vaginal epithelial cells, while others believe it to be due to an increased proliferation of the vaginal epithelium. Clinically it is characterized by local pruritus and vaginal erythema, which may be associated with desquamation and fissures in the skinfolds. Direct examination of the exudate reveals abundant white cells, immature epithelial cells, and the causative microorganisms in the form of chains. Culture confirms the diagnosis. Treatment consists of the elimination or control of the precipitating condition and antibiotic treatment with oral penicillin, 500 mg, every 12 hours or clindamycin cream applied at night for 10 days.17
inflammatory signs. The diagnosis is confirmed by direct examination, which reveals abundant lactobacilli and fragmented epithelial cells with nuclear remnants, and a negative culture for bacteria and fungi. Treatment consists of alkalinization of the vagina by means of twice weekly douches with 30 to 60 g of sodium bicarbonate in a liter of water until the symptoms resolve.17

Vaginal Lactobacillosis

Vaginal lactobacillosis has been related to an increase in the number of lactobacilli and to antifungal therapies.62 Direct examination shows an increase in the number and size of the lactobacilli, which have a characteristic form called leptothrix. Cultures are negative. Oral treatment is given with doxycycline at a dose of 100 mg every 12 hours or amoxicillin-clavulanic acid, 500 mg, every 12 hours, administered for 15 days in both cases.17

Allergic and Irritant Vulvovaginitis

Allergic and irritant vulvovaginitis are rare causes of recurrent vaginal dermatitis. However, the absence of keratinization and the natural moistness of the vulval mucosa favor the penetration of irritant and allergenic agents.63,64 The most commonly implicated factors are inhaled allergens and mites; semen; latex present in condoms, gloves, or diaphragms; C. albicans;64 parasites (Enterobius vermicularis); spermicides (nonoxynol-9); topical medication (antibiotics, antifungal agents, and local anesthetics); nail varnish; and feminine hygiene products. The most common symptoms are pruritus, a burning sensation, dyspareunia, and an odorless, whitish discharge. Predisposing factors include frequent sexual intercourse, atopic diathesis, and excessive hygiene, among others.63,65

The diagnosis is based on clinical suspicion and tests such as the skin prick test for suspected antigens, measurement of the total and specific immunoglobulin E, and patch tests that include the standard series, topical corticosteroids, topical azoles, caine mix, dyes, preservatives, and vehicles.63,65

The basis of management is to avoid the triggering allergen or irritant agents involved. Oral treatments, such as antihistamines and cromoglycate, and topical treatments with corticosteroids, pimecrolimus, and tacrolimus are used for symptomatic relief. Improvements have also been reported with desensitization therapies.

Atrophic Vaginitis

Atrophic vaginitis is due to a fall in the level of estrogens that leads to a thinning of the vaginal walls and a loss of...
glycogen, producing changes in the vaginal pH and alterations of the flora. Symptoms vary from mild and well tolerated to disabling, with irritation, pruritus, and dyspareunia. Diagnosis is based on a thin, clear discharge, a high pH, and the presence of basal epithelial cells on microscopic examination, with negative cultures for bacteria and fungi. Treatment involves topical application of estrogens and lubricants.

Conclusions

When evaluating the results of the diagnostic tests and treatments for the management of these patients, we should take the following into account:

1. Recurrent vulvovaginitis is relatively common and constitutes a challenge for the patient and for health professionals. It is therefore essential to establish the correct diagnosis, and this should involve primary care doctors, gynecologists, and dermatologists.
2. The diagnosis is not reached in up to 30% of patients with vulvovaginal symptoms.
3. Many women with chronic vulval and vaginal symptoms perform self-medication with topical agents (antibiotics, antifungal agents, corticosteroids, and combinations) and systemic treatments that may mask or exacerbate the symptoms, making diagnosis difficult.
4. A number of causes that could explain the symptoms may coexist in some patients, and each cause must be treated.
5. Finally, in cases that are refractory to treatment, the diagnosis should be reconsidered.

Conflicts of Interest

The authors declare no conflicts of interest.

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