Actas Dermosifiliogr. 2010;**101(10)**:820–826

ACTAS
Dermo-Sifiliográficas

Full English text available at
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PRACTICAL DERMATOLOGY

Clinical Guidelines for the Diagnosis and Treatment of Dermatitis Herpetiformis

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Manuscript received March 24, 2010; accepted for publication June 10, 2010

KEYWORDS
Celiac disease;
Dapsone;
Dermatitis herpetiformis;
Duhring disease;
Gluten

Abstract
Dermatitis herpetiformis is an autoimmune blistering disease that appears as a cutaneous manifestation of gluten intolerance. It is one of a group of disorders that have gluten sensitivity in common, including celiac disease and gluten ataxia. Patients with dermatitis herpetiformis present with a pruritic papulovesicular rash on extensor surfaces and on the buttocks. Immunological studies demonstrate the presence of specific immunoglobulin (Ig) A antiendomysial and antitransglutaminase antibodies. The finding of granular deposits of IgA along the dermal-epidermal junction is pathognomonic of dermatitis herpetiformis. Treatment of dermatitis herpetiformis is based on a life-long, strict gluten-free diet, which improves all clinical aspects of gluten sensitivity, and dapsone, a drug that is only effective for the skin manifestations.

PALABRAS CLAVE
Celiaquía;
Dapsona;
Dermatitis herpetiforme;
Enfermedad de Duhring;
Gluten

Guía clínica de diagnóstico y tratamiento de la dermatitis herpetiforme

Resumen
La dermatitis herpetiforme es una enfermedad ampollosa autoinmune que aparece como expresión cutánea de la intolerancia al gluten. Forma parte de un abanico de patologías que tienen en común la sensibilidad a este componente, entre las cuales se encuentra la celiaquía y la ataxia por gluten. Los pacientes con dermatitis herpetiforme presentan una erupción papulovesicular pruriginosa de predominio en superficies de extensión y nalgas. El estudio inmunológico demuestra la presencia de anticuerpos específicos IgA antiendomisio y antitransglutaminasa. El hallazgo de depósitos granulares de IgA en la

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0001-7310/$ - see front matter

unión dermoepidérmica es patognomónico de la dermatitis herpetiforme. El tratamiento se basa en dos pilares: mantener indefinidamente una dieta estricta libre de este componente (la cual mejora todas las formas clínicas de la sensibilidad al gluten) y la dapsona, fármaco que es eficaz solo para las manifestaciones cutáneas.

Dermatitis herpetiformis (DH) is a chronic autoimmune disease that presents with a pruritic papulovesicular eruption mostly involving the extensor surfaces. Histologically, it is characterized by neutrophilic microabscesses in the dermal papillae. The disease is associated with gluten-sensitive enteropathy (GSE)[1] and remits with the introduction of a gluten-free diet.

Immunogenetics

Both DH and celiac disease, another form of GSE, are strongly associated with haplotypes HLA-DQ2 and HLA-DQ8; indeed, approximately 90% of patients with these diseases are DQ2$^+$ and the majority of the remaining 10% are DQ8$^+$.[2-4] Specifically, both diseases manifest the class II HLA alleles DQA1*0501 and DQB1*0201, which are present on chromosome 6.[5-7] While these alleles are not very specific, they have an extremely high negative predictive value in the diagnosis of DH. In other words, if they are not detected, a diagnosis of DH can be practically ruled out.

The presence of associated alleles such as HLA-DR3, HLA-B8, and HLA-A1 would explain the relatively high incidence of other autoimmune diseases such as thyroid disorders, systemic lupus erythematosus, and type 1 diabetes mellitus in patients with GSE.[8,9]

A recently described animal model for DH based on transgenic NOD HLA DQ8$^+$ mice[10] has opened very promising avenues for the study of the pathophysiologic mechanisms of DH.

Epidemiology

DH can appear at any age,[9] but onset is most frequent in the third decade.[11] It is very rare in children under 3 years of age.[12] Unlike celiac disease, DH is slightly more common in men than in women.[13] It has been calculated that approximately 5% of patients with celiac disease will develop DH in their lifetime.[13]

Digestive Disorders

While all patients with DH are sensitive to gluten, the vast majority do not develop digestive symptoms.[14] In a recent series of almost 300 patients with DH, only 13% had digestive symptoms,[9] namely diarrhea, abdominal pain, or growth failure in the case of children. In the remaining 87%, GSE was diagnosed only after an intestinal biopsy. Histopathologic alterations have been detected in the intestinal biopsy in between 60% and 75% of patients with DH.[9,15,16] No prospective studies showing the true prevalence of GSE in patients with DH have yet been published.

Cutaneous Manifestations

The skin eruption in DH is intensely pruritic and typically affects the extensor surfaces and the buttocks (Figure 1). The elbows are the most common region affected. The lesions consist of erythematous papules, small vesicles, excoriations, and scarring that is often hyperpigmented. It can be difficult to make an accurate diagnosis as intact vesicles may be difficult to find and blisters are very rare. There are several atypical forms of presentation that are worth noting, namely purpuric palmar lesions in children and oral and genital mucosal involvement in adults.[13]

Histopathology and Immunofluorescence Findings

Skin biopsy shows neutrophilic microabscesses in the dermal papillary tips (Figure 2), variable degrees of inflammatory infiltrate in the superficial dermis, and, on occasions, subepidermal vesicles. These findings, however, are nonspecific and can also be found in other autoimmune blistering diseases.

The detection by direct immunofluorescence assay (DFA) of granular deposits of immunoglobulin (Ig) A (with or without complement factor C3) at the dermal-epidermal junction of healthy perilesional skin (Figure 3, Table 1) is pathognomic for DH.[17,18] These deposits are often—and sometimes exclusively—found in the tips of the dermal papillae. The test has a sensitivity of between 90% and 95%.[9]

One should reconsider a tentative diagnosis of DH if the DFA is negative. In such a case, a second sample of healthy perilesional skin should be biopsied and it should be checked that the patient is not already on a gluten-free diet. If the patient is already on such a diet, has no visible rash, and has a negative DFA, it may be necessary to conduct an oral gluten challenge; if the patient has DH, suggestive lesions should develop within a few days. If the DFA is still negative, it is essential to check whether or not an error might have occurred during the assay.[11]

Autoantigens and Immunology Studies

Tissue transglutaminase (tTG)[19,20] and epidermal transglutaminase (eTG)[21] are two recently discovered endomysial autoantigens that are specific to celiac disease and DH, respectively. According to data available, anti-tGT antibodies have a specificity of over 90% and a sensitivity of between 50% and 95%[11] (Table 1).

Smooth muscle antiendomysial autoantibodies are highly specific for GSE (celiac or DH),[22-24] with a specificity of

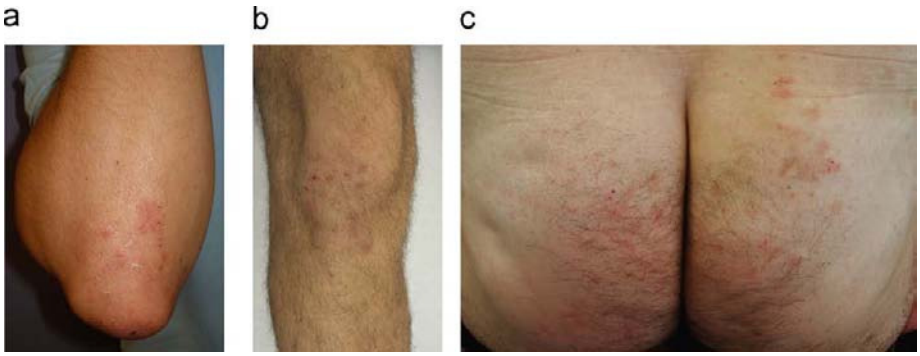

Figure 1 Excoriated erythematous papules on elbows (A), knees (B), and buttocks (C).

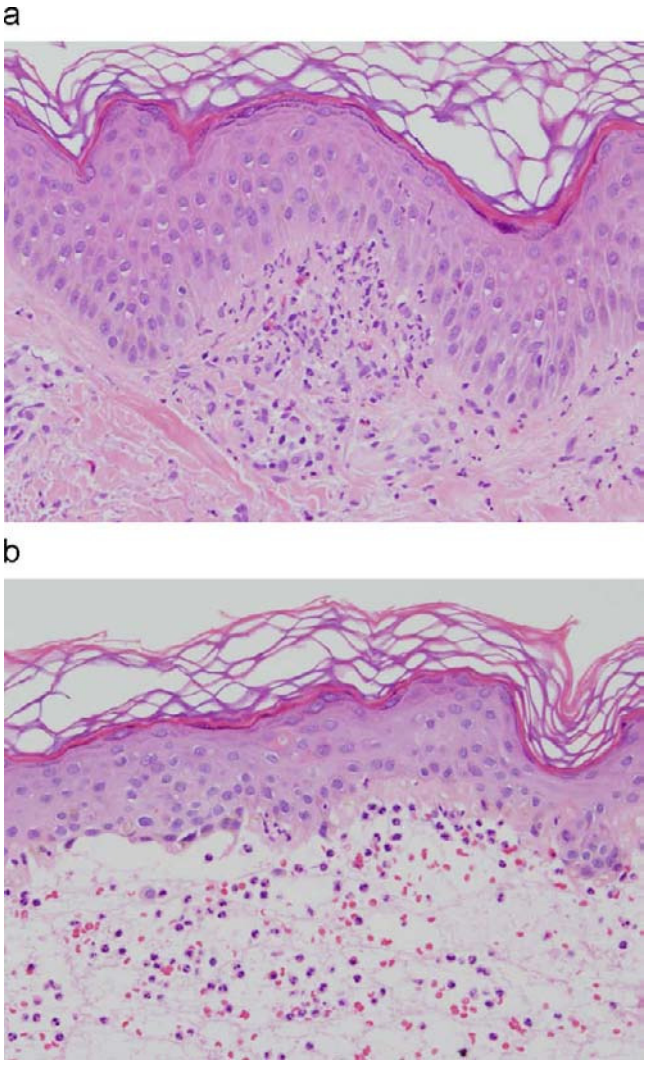

Figure 2 a, Neutrophilic microabscesses in dermal papillae. b, Site of dermal-epidermal separation with multiple polymorphonuclear cells in the lumen (hematoxylin-eosin; original magnification, ×200).

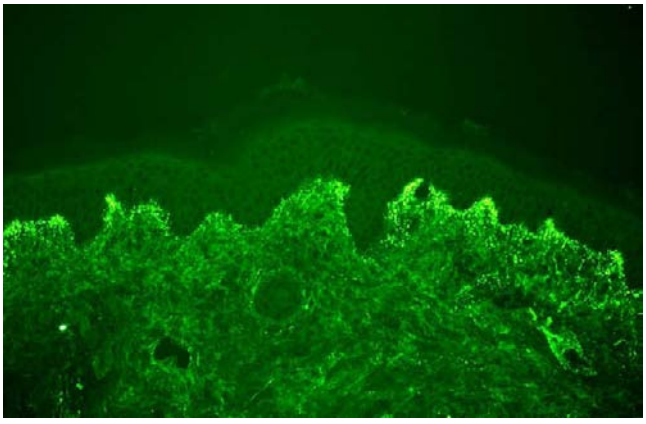

Figure 3 Granular immunoglobulin A deposit at dermal-epidermal union detected by direct immunofluorescence assay (fluorescein isothiocyanate; original magnification, ×200).

Table 1 Diagnostic Tests in Dermatitis Herpetiforme (DH)

1. Skin biopsy
   - Histopathology study (lesional skin): neutrophilic microabscesses in dermal papillary tips, subepidermal separation
   - Direct immunofluorescence study (healthy perilesional skin): granular immunoglobulin (Ig) A deposits in the basement membrane → diagnostic of DH
2. Immunology study
   - IgA antiendomysial antibodies
   - IgA antitransglutaminase antibodies
3. Class II HLA typing (optional)
   - DQ2
   - DQ8
4. Digestive system study (optional)
   - Malabsorption markers (iron, B12, folic acid)
   - Duodenal biopsy

almost 100% and a sensitivity ranging between 50% and 100%, depending on the series.[9,11,20,22,23]

All the above autoantibodies are immunoglobulin (Ig) A1 subclass antibodies (antiendomysial IgA, anti-tTG IgA, and anti-eTG IgA) and their levels drop drastically in patients on a gluten-free diet. They are thus of great value not only for diagnostic purposes but also for monitoring adherence to diet in these patients.[19,21,23,25]

One recent development in this area is a test to detect antibodies that recognize deamidated gliadin peptides.[26,27] Although it is not yet used in routine practice, it could soon become the serologic test of choice in patients with DH or celiac disease.

Tests for reticulin and gliadin antibodies can also be performed, although systematic determination is not currently recommended. IgA class reticulin antibodies are highly specific[22] and are found in 1 in 4 patients with DH[23] as well as in patients with celiac disease; the levels of these antibodies also drop—and eventually disappear—when a gluten-free diet is prescribed.[23] Both IgG class reticulin antibodies and IgA or IgG class gliadin antibodies are nonspecific and are often found in patients with other autoimmune blistering diseases or even in healthy individuals.[22,23]

A total IgA test should be requested for patients in whom there is a strong clinical suspicion of disease but who have negative IgA class autoantibodies as they might have selective IgA deficiency. In such cases, a serologic diagnosis of gluten sensitivity can be made by measuring IgG antitransglutaminase antibodies.[28,29]

Association with Lymphomas and Other Autoimmune Disorders

The association between DH and the development of lymphomas is a controversial subject. Unlike the situation in patients with celiac disease, where the association between enteropathy and hematologic malignancies (particularly T-cell intestinal lymphomas) has been well established[30], the incidence of lymphomas—of any type—in patients with DH is lower than 2% according to findings published to date.[9,31-34] A recent epidemiologic study of 846 patients with DH did not reveal higher mortality or increased risk of fractures, lymphomas, or gastrointestinal malignancies in these patients compared to the general population.[35] One possible explanation, although it has not yet been fully confirmed, is that patients with DH have a lower level of gastrointestinal inflammation than those with celiac disease. Nevertheless, based on results from studies of patients with celiac disease,[36] it is scientifically plausible that a gluten-free diet would also exert a protective effect against the development of lymphomas in DH[31] as the diet has a healing effect on inflammatory processes in the intestine.

DH and celiac disease are frequently associated with diverse autoimmune disorders, noteworthily, thyroiditis, diabetes mellitus, and pernicious anemia.[11] Approximately 20% of patients with GSE have antithyroid antibodies and antiparietal cell antibodies, hence the recommendation to measure these autoantibodies in addition to antinuclear antibodies, blood glucose, and thyroid function in patients with DH (Figure 4).

Differential Diagnosis

The differential diagnosis should essentially include scabies, atopic eczema, contact eczema, and other autoimmune blistering diseases such as linear IgA dermatosis and bullous pemphigoid.

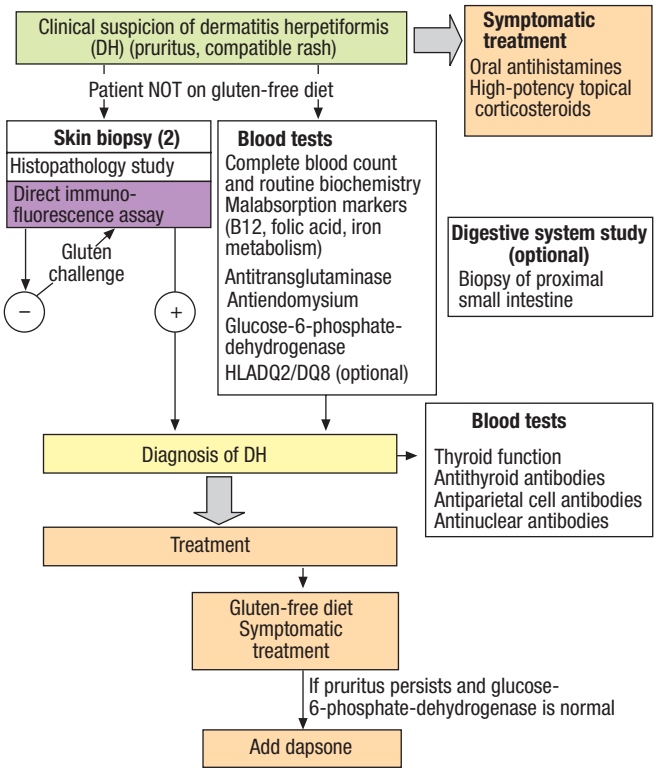

Figure 4 Diagnosis-Treatment Algorithm

In general, a diagnosis of DH can be made with relative ease and certainty based on histopathology and DFA findings.

Treatment

DH is treated by a gluten-free diet and dapsone.

A gluten-free diet is the treatment of choice and absolutely essential in all patients with DH. It is effective against skin manifestations—and digestive symptoms if these exist—although improvements may not be seen until 1 to 2 years after the elimination of gluten from the patient's diet.[11]

Wheat, barley, and rye must be eliminated completely, but rice, corn, and oats are allowed.[37] The diet must be maintained for life as the vast majority of patients with DH experience a resurgence of symptoms when they reintroduce gluten into their diet. Only 10% to 20% of patients develop immune tolerance and are capable of following a normal diet after years of a strict gluten-free diet; this is particularly true in cases of childhood onset and in patients who have been treated with dapsone.[14,38,39]

Strict long-term adherence to a gluten-free diet has the following benefits: a sensation of general well-being (of being healthy), a reduced need for medication, a reduced risk of intestinal lymphomas, and resolution of the skin rash and signs and symptoms of enteropathy/malabsorption.[38]

Dapsone (Dapsone Fatol 50 mg tablets authorized for use as a foreign drug as they are not available in Spain or dapsone 50 mg prepared as a compounded drug product in a no. 90 capsule) is an efficient means of resolving the skin manifestations of DH in just a few days. This drug is used until gluten avoidance alone is successful in resolving the rash.[11] Dapsone is not active against possible intestinal involvement and it has not been proven to reduce the risk of lymphoma. It does not have a healing effect on DH and skin manifestations return as soon as the drug is withdrawn. The dose in adults should be low (50 mg/d) initially and gradually increased to 200 mg a day depending on the patient's needs and tolerance. The recommended dose for children is 1 to 2 mg/kg/d. Before treatment is started, the following tests should be performed: glucose-6-phosphate-dehydrogenase, reticulocyte count, complete blood count, and a routine biochemistry (including kidney and liver profiles).[40] The last 3 tests should be performed regularly during treatment, ideally every week or 2 weeks for the first month, every month for the next 2 months, and every 3 to 6 months thereafter.[40]

The adverse hematologic effects associated with dapsone (hemolysis and methemoglobinemia) are dose-dependent and are generally well-tolerated (ie, it is not always necessary to withdraw the drug)(Table 2).[40,41]

Methemoglobinemia levels should be tested if suspicious clinical symptoms are detected (dizziness, dyspnea, fatigue, or headache).[40] Methemoglobinemia levels under 20% rarely cause symptoms and do not require attention. Nevertheless, certain patients with low levels may develop severe clinical manifestations; this is particularly true for patients with diseases that affect oxygen delivery to the tissues.[41] Dapsone should be withdrawn when methemoglobinemia levels exceed 20%; when they are higher than 30%, treatment with methylene blue should be considered.[40]

Table 2 Dapsone: Contraindications, Clinically Significant Interactions, and Adverse Effects

Contraindications
Allergy to sulfonamides and para-aminobenzoic acid
Acute porphyrias
Anemia or severe cardiopulmonary disorders
Glucose-6-phosphate dehydrogenase deficiency
Drug Interactions
Probenecid
Trimethoprim
Dose-dependent toxicity
Hemolysis
Methemoglobinemia
Idiosyncratic toxicity
Digestive intolerance
Hypersensitivity reactions (urticaria, drug rash with eosinophilia and systemic symptoms [DRESS] syndrome)
Agranulocytosis
Hepatitis
Neuropathy (peripheral, optic)
Psychosis/anxiety/depression/lethargy
Nephropathy/nephrotic syndrome
Reduced fertility
Stevens-Johnson syndrome/toxic epidermal necrolysis
Photosensitivity
Hypothyroidism

Hemolysis is common in patients on dapsone and dose reductions may be required in certain cases. Determination of hemolysis markers (bilirubin, lactate dehydrogenase, and haptoglobin) is indicated in clinically compatible cases and/or when there is a significant reduction in hemoglobin levels. Dapsone should be completely withdrawn in patients who develop severe hemolytic anemia with clinical repercussions.

Several authors recommend using dapsone in association with vitamin E (800 U/d)[42] or oral cimetidine (1.2-1.6 g/d)[43] to minimize the risk of hemolytic anemia and methemoglobinemia, respectively. Dividing the daily dose of dapsone into 2 separate doses reduces peak blood concentrations, and therefore, possibly, hematologic toxicity.[40]

Rarer adverse effects include hypersensitivity reactions (1 in 100 patients), agranulocytosis ($<0.5\times10^9$ neutrophils/L), hepatitis, peripheral neuropathy, psychosis, nephrotic syndrome, and reduced fertility (Table 2).[40]

Hypersensitivity reactions are the most common nonhematologic complication. Onset generally occurs after 3 to 6 weeks of treatment and is generally characterized by pruritus, fever, and dermatitis. In such cases, drug withdrawal should be immediate and practically all patients require prolonged treatment with systemic corticosteroids given the long half-life of dapsone.[40]

Agranulocytosis is estimated to affect between 1 in 400 and 1 in 10 000 patients treated with dapsone[40]; it generally appears in the first 12 weeks of treatment and resolves within a week after the medication is withdrawn. Patients who develop agranulocytosis can develop severe, potentially life-threatening, infectious complications.[41] Fever is generally the first detectable symptom. Accordingly, patients should be informed of this possibility and instructed to seek urgent medical attention should they develop fever.

The administration of dapsone is contraindicated in patients with hypersensitivity to dapsone and related drugs (sulfonamides, para-aminobenzoic acid) or in patients with acute porphyrias, severe anemia, or glucose-6-phosphate dehydrogenase deficiency (Table 2).

No clinically significant interactions between dapsone and other drugs have been described (see summary of product characteristics). The concomitant use of probenecid or trimethoprim can raise dapsone plasma levels and thus increase the risk of hematologic toxicity[40] (Table 2).

Dapsone is categorized as a class C drug by the United States Food and Drug Administration and as such is not recommended for the treatment of DH in pregnant or breastfeeding women.[40] Its use is allowed in children at the aforementioned doses.[40]

Dapsone should always be used as a complementary treatment to a gluten-free diet and should be withdrawn as soon as the diet alone is effective in resolving the skin manifestations (normally after 1 to 2 years). It is also indicated in patients who choose not to follow a strict gluten-free diet and whose symptoms need to be controlled.

Finally, the prescription of oral antihistamines and very potent topical corticosteroids (clobetasol propionate) are of relative value in treating symptoms. Systemic corticosteroids are not indicated in DH.

Long-Term Follow-up

Patients with DH should be monitored annually once their symptoms and any related organ damage have been controlled (and once dapsone has been withdrawn). The annual workup should include:

- Medical history
- Physical examination
- Blood tests (glucose, thyroid function, complete blood count, routine biochemistry, iron, folic acid, vitamin B12, antithyroid antibodies, antiparietal cell antibodies, antinuclear antibodies, anti-tGT antibodies, and antiendomysial antibodies)

Economic and Psychosocial Impact and Patient Associations and Websites

Patients with DH need to constantly monitor their diet and carefully analyze all the ingredients of any food they are going to eat. This, logically, can result in considerable psychological stress, time, and financial effort, and support from a dietician in this respect is essential.

DH can also have a considerable social impact as many social activities revolve around food. Patients thus need to be informed and mentally prepared to deal with the social limitations imposed by their disease so that they can face the corresponding challenges and adjust as best as possible to living with DH from the outset.

Finally, there are numerous associations and websites in Spanish (eg, www.celiacos.org and www.celiacscatalunya.org/cas/index.php) for patients with celiac disease and/or DH that provide helpful information for patients and carers such as suitable brands of food, recipes, shops and restaurants, activities, information for school canteens, sources of financial support, etc.). These associations play a key role in improving adherence to diet among patients and it is therefore highly recommendable that physicians inform their patients of the existence of these support networks at the time of diagnosis.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

This review was performed with grants from the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III - FEDER (PI-06/1548, awarded to Josep E. Herrero) and the IMIM (Ayudas de Intensificación, IMIM-Hospital del Mar).

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