Editorial

Alpha fodrin and primary Sjögren’s syndrome diagnosis, experience of a Rheumatology center in Bogotá, Colombia

Alfa fodrina y diagnóstico de síndrome de Sjögren primario, experiencia de un centro de reumatología en Bogotá, Colombia

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Sjögren’s syndrome (SS) is a frequent systemic autoimmune disease, characterized by the clinical presence of a dry syndrome, mainly oral (xerostomia) and ocular (xerofthalmia), due to a reduction or absence of glandular secretions, as a result of a glandular autoimmune inflammation associated with certain extra-glandular manifestations. This condition which some authors define as Autoimmune Epithelitis, presents isolated (called primary SS-pSS) or associated with other autoimmune diseases, mainly rheumatoid arthritis, and if this the case, it is called secondary SS. Although keratoconjunctivitis sicca and xerostomia are the most prevalent manifestations, SS presents as a multisystem condition, with a broad range of clinical manifestations. The spectrum of the disease ranges from a form of organ-specific autoimmune involvement (called autoimmune exocrinopathy) to a more generalized process that involves the musculoskeletal system, the respiratory tract, the gastrointestinal tract, and the renal, neurological, vascular and hematologic systems, inter alia.

The autoimmune component, resulting mainly from biological abnormalities associated with the activation of B-lymphocytes, is an essential marker of the pathology and includes the rheumatoid factor (RF) positivity, hypergammoglobinemia, the presence of anti-Ro antibodies (anti-Sicca Syndrome A-SSA), and anti-La (SSB), normal distribution of mature B lymphocytes in the peripheral blood, in addition to an increased risk of Non-Hodgkin Lymphoma in 5% of the patients.

The clinical polymorphism of the pathology is responsible for approximately a 6-year delay in the diagnosis, after the onset of symptoms. The most commonly used classification criteria in epidemiological studies have been defined by the American-European Community Study Group (AECG) in 2002. However, a better understanding of the disease, in addition to the desire to make an early diagnosis and improve the inclusion of patients in clinical trials, has led the scientific societies to generate two additional groups of criteria, published by the American College of Rheumatology in 2012, and by a Consensus between the same American group and the European League Against Rheumatism (EULAR), published in 2016. The 2012 criteria included 4 antibodies for the classification of patients: the anti-Ro and anti-La antibodies; however, a patient may be classified with SS, in the absence of these antibodies, but in the presence of a positive RF and a positive ANA (with a title above 1:320). Under the 2016 criteria, the final classification comprises the sum of 5 items: presence of anti-Ro antibodies and sialadenitis with a Focus Score ≥ 1 focus/4 mm², each one with a score of 3; an Ocular Staining Score (OSS) ≥ 5 (or a van Bijsterveld stain ≥ 4), a Schirmer test...
of less than 5 mm/5 min and a non-stimulated salivary flow of less than 0.1 ml/min; each receiving a score of 1. Hence, if someone presents with symptoms or signs suggestive of SS, and the sum of the scores totals ≥ 4, is considered to have SS (with a sensitivity and specificity of 96% and 95%, respectively). These criteria are intended to facilitate the inclusion of patients with more homogeneous diseases, that facilitate the development of clinical trials.8

However, because the anti-Ro (sensitivity 60–80%) and the anti-La (sensitivity 10–40%) may not be present in all patients with SS, different autoantibodies have been described that may help in the classification or diagnosis of the pathology, including some of them with a potential role in the pathophysiology of the disease. Some of these antibodies are anti-alpha fodrin; anti-muscarinic receptor type 3 – anti-MR3 (with potential pathophysiological implications in the reduction of glandular secretion and in intestinal motility)9; anti-carbonic anhydrase II (associated with pulmonary and renal involvement, and involved in the pathophysiology of renal tubular acidosis), anti-hnRNP1, anti-NR2 A/B, anti-IF16 antibodies and cyclic anti-citrullinated peptide antibodies, inter alia,10 all with varying performance in accordance with the population evaluated.

The paper “Alpha fodrin and diagnosis of the primary Sjögren syndrome, experience of a Rheumatology center in Bogotá, Colombia” written by Dr. Carlos Arteaga et al. is published in this issue of our Journal. The article evaluates the diagnostic performance of the anti-fodrin antibodies IgA and IgG in our population, using ELISA. As mentioned in the article, fodrin is a protein of 240 KD that is part of cytoskeleton and bound to actin. It is made up by heterodimers of one α and one β subunit. In 1997, Haneji et al., in an important publication in Science, described how they were able to purify from the glandular tissue of a murine model of SS, a protein of 120 KD, capable of generating T lymphocytes proliferation and production of IL-2 and IFN-γ in that model. This purified protein was identified as alpha-fodrin.11 Additionally, the authors showed that the serum of patients with SS reacted with a high specificity (96%) against this antigen, while the serum of patients with other pathologies such as systemic lupus and rheumatoid arthritis, did not react.

These initial findings were extremely promising, suggesting that anti-alpha fodrin antibodies could be most helpful in the diagnosis of SS. However, it must be highlighted that this pioneer study was conducted in a Japanese population and its replication in different series failed to produce the same results.

In fact, a meta-analysis published in 2003, evaluated the various studies conducted to this date, including 23 papers from different geographies (studies from Japan, Germany, China, Turkey, inter alia), in which the sensitivity of the anti-alpha fodrin tests was low, both for IgG and IgA, whilst the specificity was high for diagnosing SS.12 Specifically, the grouped sensitivity for the IgG isotype was 38%, whilst for IgA was 41.9%. In contrast, the specificity was 83.1% and 82.3%, respectively. Therefore, the authors concluded that the overall performance of this test was moderate.12

These results were obtained through various methodologies for detection, including immunoblot, radioimmunoassay, or the ELISA test.12–14 However, some authors suggest that immunoblot may be a more specific method, as compared against other methodologies.15

Due to the geographical differences in the results, the study published in this issue is indeed relevant because it reveals the behavior of the IgA and IgG anti-alpha fodrin tests in the Colombian population.

Just as in a number of previous studies, and using the ELISA methodology, the authors identified a low sensitivity and a high specificity for both tests. The sensitivities for iso-types IgA and IgG only achieved 18% and 5%, respectively, while the specificities were 92% and 96%. Additionally, the test doesn’t seem to deliver – at least in our population – a higher performance in patients that are negative to the conventional antibodies, anti-Ro and anti-La. There are various reasons to explain these results, including the selection criteria used in this and in other studies (AECG 2002 vs. ACR 2012 or ACR/EULAR 2016), the genetic background of the population (Japanese and Asian in general vs. Caucasian and Latin Americans), the methodology used (immunoblot vs. ELISA), among other options.

However, due to the high specificity found in this and in other studies, this test could be helpful in selected cases for diagnostic purposes, particularly in the setting of patients with other negative auto-antibodies, or in difficult clinical settings, as has been reported in cases of patients with neurological involvement of unclear etiology, where the manifestation of anti-alpha fodrin antibodies suggests the presence of SS vs. other autoimmune diseases such as multiple sclerosis.16

In view of the importance of the alpha-fodrin antigen in the pathophysiology of the disease, it is essential for future development that any further studies in our population and in other groups, involve diverse types of analytical methodologies or antigen modifications that result in improved sensitivity for detection, so that the use of these antibodies becomes a routine practice in the assessment, diagnosis, and classification of patients with primary and secondary SS.

Conflict of interest

The author has no conflict of interest to disclose.

References


