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Primary Gougerot-Sjögren's Syndrome Revealed by an Ischemic Stroke in a Premenopausal Woman: A Case Report with Review of the Literature

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Abstract **Case Report**

Gougerot-Sjögren's syndrome (GSS) is a systemic autoimmune disease whose target is the epithelium of the exocrine glands and in particular the salivary glands. As a result, the condition is referred to as autoimmune epithelitis. GSS is manifested by a symptomatic triad of dryness, pain and fatigue and may be complicated by systemic complications in 30-50% of patients. Neurological involvement is found in 10-60% of primary Gougerot-Sjögren's syndromes, with highly polymorphic presentations, which may involve both the peripheral and central nervous systems. Involvement of the central nervous system is very rare, affecting less than 5% of patients, and may result in clinical pictures similar to multiple sclerosis. The aim of our study is to illustrate, through a clinical case, the interest of evoking Primary Gougerot-Sjögren's Syndrome in the face of an attack on the central nervous system, in this case an ischemic stroke. The methodology was the study of the clinical file of a patient consulted in the rheumatology department of the CHU Aristide LeDantec in Dakar, Senegal in 2020.

Keywords: Primary Gougerot-Sjögren's syndrome; ischemic stroke; Senegal.

I. INTRODUCTION

Gougerot-Sjögren's syndrome is a systemic autoimmune disease characterised by a combination of manifestations affecting certain glands, particularly the lacrimal and salivary glands, with a reduction in tear and saliva secretion, resulting in a dry syndrome, and systemic manifestations that can affect various organs. The dry syndrome often leads to significant functional discomfort, but it is the visceral damage that makes this disease serious [1, 2, 3]. Gougerot-Sjögren's syndrome is a rare disease affecting just under one in 10,000 adults [4]. Women are affected 10 times more than men, and the disease most often begins in the mid-50s. However, it can occur much earlier in life, between the ages of 20 and 30 [5]. These younger forms are often more severe. GSS occurs in individuals with a genetic predisposition to autoimmunity, marked by the high prevalence of HLA B8 and DR3 haplotypes, and there is a high frequency of autoimmune diseases in relatives of GSS patients (20-30%) [6]. Gougerot-Sjögren's syndrome is associated with two types of clinical manifestations : the first is the consequence of the involvement of the exocrine glands, particularly the salivary and lacrimal glands, whose secretions decrease, which is responsible for the dry syndrome [7, 8, 9, 10]. Extraglandular manifestations characterise the systemic forms of Gougerot-Sjögren's syndrome. There is no parallel between the severity of the dry syndrome and the existence or severity of systemic manifestations [7, 8, 9, 10]. The diagnosis is based on the ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria published in 2016, which are often used as diagnostic criteria in practice [11]. Involvement of the central nervous system is very rare, affecting less than 5% of patients, and can lead to clinical pictures similar to multiple sclerosis [12]. The aim of our study is to illustrate, through a clinical case, the interest of evoking Primary Gougerot-Sjögren's Syndrome in the face of an attack on the central nervous system, in this case an ischemic stroke. The methodology was the study of the clinical file of a patient consulted in the rheumatology department of the CHU Aristide LeDantec in Dakar, Senegal in 2020.

II. OBSERVATION OF THE PATIENT

Patient of 1976 (44 years old), Senegalese, of black race, the history of the disease goes back to April 2016 marked by the spontaneous and insidious onset of joint pain at the end of the night, followed by stiffness, located mainly in the metatarsophalangeal, metacarpophalangeal and proximal interphalangeal joints of both feet and both hands. This pain is fixed and addictive with extension to both shoulders and both

knees. On examination, dry eyes with a sensation of foreign bodies in the eyes, absence of tears after irritation or emotion, decreased visual acuity, eye pain, dry mouth and episodes of constipation were noted. Her main history in January 2020 was of right hemicranial headaches associated with a bifocal ischaemic stroke in the right semi-oval centre and right temporal lobe and a second episode of bifocal ischaemic stroke in the right deep sylvian and anterior cerebral regions on MRI followed since then in the neurology department. She is not menopausal. Her usual treatment includes anticoagulation and corticotherapy with Prednisone 1 mg/kg/d. The general examination noted a physical asthenia. The rheumatological examination revealed a chronic, peripheral, symmetrical, bilateral, polysynovial, non-deforming, non-ankylosing polyarthritis involving the small joints and right cervical-brachial and dorsal spinal pain. The neurological examination revealed a left hemiparesis. The biology examination showed an inflammatory syndrome with a blood pressure of 30 mm at the first hour, a CRP of 7.8 mg/l and a slight normocytic normochromic anaemia. Immunology showed a positive latex test and anti-Ro/SSA autoantibodies at 2.9. Anti-citrullinated peptide antibodies, antinuclear antibodies, antiphospholipid antibodies, neutrophil cytoplasmic antibodies and HLA B27 antigen were negative. The following functional tests are normal: ECG, Holter ECG, cardiac ultrasound and transesophageal ultrasound. The biopsy of the accessory salivary glands showed a diffuse interstitial inflammatory infiltrate of lymphocytes and some plasma cells, with clusters of over 50 cells. There were at least 2 lymphocytic foci per 4 mm2 of glandular parenchyma, this histological aspect is in favour of a chronic sialadenitis of Chisholm and Masson grade IV. The SGS was evoked and retained in view of the epidemiological arguments, in particular the age of our patient, who was 44 years old and female; in view of the clinical arguments, in particular the dry oculo-buccal and digestive syndrome, and the chronic peripheral acromegalic polyarthritis, which was bilateral and symmetric; paraclinical arguments, notably the non-specific biological inflammatory syndrome, the positive latex test, anti-Ro/SSA autoantibodies at 2.9; and the biopsy of the accessory salivary glands with a chronic sialadenitis of Chisholm and Masson grade IV. The diagnosis of SGS was evoked and retained mainly thanks to the 2002 criteria of the American-European Consensus Group (AECG) with a score of 4/6 (Subjective ocular dryness (1); Subjective oral dryness (1); Histological signs of sialadenitis on the BGSA superior to grade III of the Chisholm classification (1) and the presence of Anti-Ro/SSA autoantibodies (1)). In conclusion, the diagnosis of SGSP revealed by an ischemic stroke was retained in this patient. The treatment initiated in our patient was corticosteroid therapy (Cortancyl® 10 mg per day), hydroxychloroquine 400 mg per day, methotrexate 15 mg per week, folic acid (Acfol® 15 mg per week), calcium-vitamin D3 (Fixical D3® 500 mg per day) and Esomeprazole (Inexium® 20 mg per day). The evolution was marked by a clear improvement of joint pain, dry syndrome and physical asthenia, without any new episode of ischemic stroke.

III. REVIEW OF THE LITERATURE

Epidemiological point of view

Primary GSS is a rare disease, but remains the most common connective tissue disease after rheumatoid arthritis which affects 1% of the population. Its prevalence ranges from 0.3% to 3% (European criteria). The possible influence of ethnicity on the frequency and presentation of primary GSS is not known [13].

The incidence of ischaemic stroke in young women varies between studies. Risk factors such as migraine with aura, pregnancy, postpartum or ovarian hyperstimulation syndrome are frequently found. Some etiologies are more frequent in women, such as antiphospholipid syndrome, Sneddon's syndrome, Takayashu disease and lupus [14].

Neurological involvement in pSSS is observed in 20-25% of cases [15, 16], and is largely dominated by peripheral neurological manifestations, which are reported in 10-30% of cases, followed by central manifestations in the second rank, their frequency is highly variable, according to Alexander et al. central manifestations can occur in more than 20% of pSSS cases [17], in a recent study by Garcia-Carrasco involving 400 patients, the frequency of these manifestations is 1%.

A study was done in 2007 in the department of Seine-Saint-Denis in France, where the prevalence of the disease is estimated at 102 to 153 per million adults (0.01 to 0.02%). The study suggests that subjects of North African origin are at higher risk of GSSp than subjects from sub-Saharan Africa with a distinct disease profile (young age, hypergammaglobulinemia, and positive anti-SSA) [18].

The central neurological manifestations are extremely varied and none are characteristic. According to Alexander et al [19], central neurological manifestations may occur in more than 20% of cases, yet their pathogenesis remains unknown. Vasculitis is the most commonly suggested mechanism, but an autoimmune process has also been proposed. In almost 60% of cases, they are associated with peripheral neuropathy [15, 20, 21, 22].

Focal encephalic manifestations are the most frequently observed CNS manifestations [13, 23]. The onset may be acute, such as a stroke [24], or progressive [25]. They can also develop in a recurrent manner, mimicking a multiple sclerosis picture [19].

Diagnosis

In GSS, a series of tests are carried out, which can be divided into specific and non-specific tests for the disease.

- Non-specific work-up: the haematological manifestations associated with GSS were noted as early as its description in 1933 by H. Sjögren. Since then, there have been only a limited number of studies in which primary and secondary GSS were associated. The blood count may reveal an anaemia in 25-30% of patients [26] that is inflammatory, normochromic or hypochromic in appearance; it may also be autoimmune or haemolytic. Leukopenia of less than 4000 leukocytes/mm3 with lymphopenia and/or neutropenia is observed in 30-50% of patients without significant pathological consequences. Hypereosinophilia is frequently observed and is seen in almost one in three patients [26].

Finally, thrombocytopenia is rarely described. A few cases of thrombocytopenic purpura have been reported. The inflammatory syndrome is marked by an increase in the sedimentation rate, sometimes above 100 in the first hour, this increase is related to the presence of polyclonal hyper-γ-globulinemia which is seen in 70% of patients on average [26]. On protein electrophoresis, there is an increase in α2-globulins and γ-globulins in 65% of cases. Hyper-γ-globulinaemia can sometimes reach very high levels; when the gamma globulin level is low or decreased during the course of the disease, it should raise concerns about the development of a lymphocytic malignant syndrome. Hyper-γ-globulinaemia is evidence of B-cell hyperactivity. Cryoglobulinemia is found in about 20% of cases, 2 out of 3 times it is type 3, mixed polyclonal, 1 out of 3 times type 2 with a monoclonal component [26].

- Specific tests: Anti-SSA/Ro and anti-SSB/La antibodies are part of the extractable nuclear antigens (ENA). Anti-nuclear autoantibodies are the most frequently encountered in medical practice. They are the diagnostic markers of GSS [27]. Anti-SSA and anti-SSB antibodies are polypeptides attached to small ribonucleoprotein acids (RNA) called YRNA. Two types of. The physiological role of these proteins is not clearly determined but they are probably involved in the regulation of RNA polymerase III activity and the transit of YRNA from the nucleus to the cytoplasm. The pathogenic role of anti-SSA antibodies seems to be demonstrated in the context of congenital atrioventricular block. The reference method for the detection of anti-SSA and anti-SSB antibodies was the Ouchterlony immunodiffusion method. However, this method lacks sensitivity. Currently, an ELISA test is most often used for screening. The frequency of these antibodies varies according to the methods used: on average 60-95% of primary and 40% of secondary SGS for anti-SSA, and 40% for anti-SSB [27]. The two antibodies co-exist in about 50% of patients with GSS and characterise the severe forms of the disease, particularly with regard to extraglandular manifestations : Raynaud's phenomenon, cutaneous or visceral vasculitis [28].

Numerous methods have been developed to demonstrate dry mouth syndrome, such as the sugar test (placed under the tongue, it should dissolve in 3 to 4 minutes) and the measurement of oral pH (the mouth is acidic (PH≤ 6). Other more effective tests include.

a. Sialometry [29]

b. Sialochemistry [29]

c. Salivary gland imaging (Parotid Sialography, Salivary Gland Scintigraphy, Parotid Ultrasound, Sialo-MRI) [27, 30, 31].

d. Salivary gland biopsy : This is the most important additional examination. The vast majority of biopsies are taken from the mucosal part of the lower lip to obtain 5-10 accessory salivary glands. A parotid biopsy is only performed in exceptional cases and its diagnostic validity is not superior to a biopsy at the usual site. If glandular swelling persists, and especially if it is asymmetric, a biopsy of the gland should be considered. Histological analysis allows quantification of the lymphocytic infiltrate, typically organised in rounded clusters of at least 50 cells (focus=focus). In the Chisholm classification, a Chisholm and Mason stage 3 corresponds to a focal score of 1, while stage 4 corresponds to a focal score > 1. Stage 3 has a sensitivity of 87.3% and a specificity of 90.3%. Stage 4 is only slightly more specific (96%) and less sensitive (68.4%) while stage 2 lacks specificity. Stage 1 (less than one focus per 4 mm 2) or stage 0 (no focus) has no diagnostic value. A sheet-like infiltrate suggests lymphoma. Sometimes, the gland is invaded by fibrosis with little infiltrate, either a very advanced post-infiltrative stage of a primary SGS, or secondary SGS of fibrosing disease, or age-related sialadenitis according to Daniel [32].

e. The neurological examination is brain MRI: studies show a high frequency of abnormalities related to brain MRI in neuro-Sjögren's disease. These are mainly T2 hypersignals involving the periventricular and subcortical white matter [33] or juxtacortical white matter involving more rarely the basal ganglia or cortex [13, 34]. These MRI abnormalities are often described as very similar to those seen in MS. Contrast enhancement after gadolinium injection is rare. There does not always seem to be an anatomical correlation between these brain lesions and neurological manifestations.

Since 1965, 12 classifications have been proposed for the diagnosis of Sjögren's syndrome. The current criteria are based on the presence of objective and subjective criteria of a dry eye and/or mouth syndrome, and the mandatory presence of a lymphocytic infiltrate on the BGSA, and/or the presence of nuclear autoantibodies of SS (sicca syndrome) A or B specificity. The current classification

was revised in 2002 by the AECG. It has since been widely used in clinical and routine practice [35].

The diagnosis of primary GSS is made when four out of six items are present, with the mandatory presence of item 5 (histology) or item 6 (immunology), and the presence of three of the four objective items (items 3, 4, 5 and 6).

Therapeutic aspect

The basic treatment of the central manifestations of GSS differs according to the clinical picture, but all the series dealing with the treatment of central disorders propose the same therapeutic scheme. This consists of a bolus treatment with methylprednisolone at a dose of 1g/day for 3 days, followed by prednisone at a dose of 1mg/kg/day for 2 months, then a gradual decrease in dose to a dose of 10mg/day, combined with 6 monthly boluses of cyclophosphamide at a dose of 600mg/m2/cure. Azathioprine has sometimes been prescribed as a back-up. An observational series on a case of transverse myelitis in primary GSS published by I. Ben Ghorbal [36] reported a favourable evolution with disappearance of the muscle deficit and sensory disorders after 6 months. A Moroccan series [37] reported improvement in Devic's neuromyelitis optica, using the same treatment regimen with azathioprine at a dose of 3mg/kg/day after cyclophosphamide boluses. The study conducted in Morocco in 2007 reported that the patient studied was given a bolus of corticosteroid at a dose of 1g/d for 5 days, followed by oral prednisone 1mg/kg/dr between sessions, in combination with monthly cyclophosphamide at a dose of 600mg/m2 of body surface area [38]. In a French series of cerebellar syndrome revealing Gougerot Sjögren's syndrome [39], corticosteroid therapy was initiated with a bolus of solumedrol followed by oral therapy at a dose of 1mg/kg/day in combination with cyclophosphamide (6 boluses of 500mg/m2). Data on the duration of maintenance treatment are also lacking in the literature and we cannot therefore draw any conclusions.

Evolution

The evolution of the facial paralysis, whether peripheral or central, was marked by the absence of recurrence [40]; while an exacerbation of the paresthesias of the 4 limbs and the stability of the lesions on MRI with a 2-year follow-up were noted.

While the evolution of sensory neuropathies associated with GSS [41] was unfavourable and without notable success under corticosteroids or immunosuppressants, treatment with rituximab has an important influence on the evolution of sensory forms. Cases of dramatic but transient improvement have been reported with polyvalent Ig [42].

The role of cryoglobulinemia has been little studied in the literature [43 ; 44]. In the series by Melgreen et al. [4'], 25% of patients with neuropathy had cryoglobulinemia, and the inverse relationship between serum gamma globulin levels and the presence of neurological damage, particularly peripheral damage, in some studies suggests the involvement of cryoglobulinemia, even though it has not been systematically investigated [46].

The evolution of acute transverse myelitis was favourable with the disappearance of the muscle deficit and sensory disorders. The follow-up was 6 months.

Therefore, the combination of high-dose corticosteroids and IV cyclophosphamide seems to be the most effective.

Partial motor recovery without new visual episodes at 3 years follow-up was marked in the evolution of Devic's syndrome.

The evolution of NORB [47] was favourable under bolus methylprednisolone and oral corticosteroids with partial recovery of visual acuity from 2/10 in both eyes to 5/10 at 18 months.

The combination of corticosteroid therapy and cyclophosphamide boluses, cited in the treatment of cerebellar syndrome, was effective with a clear improvement in the cerebellar syndrome but progressive and incomplete in the dysarthria. The study conducted in 2007 on a single case reported a favourable evolution under bolus prednisolone in association with cyclophosphamide [48].

CONCLUSION

Gougerot Sjögren's syndrome is an autoimmune disease characterised by lymphocytic infiltration of glandular and extraglandular parenchyma. It may be primary or secondary to an inflammatory disease (RA, Lupus, Scleroderma, etc.). Neurological damage, alongside renal, pulmonary and hepatic damage, is the most serious aspect of the disease, as it affects the functional prognosis and is still one of the causes of mortality. Neurological involvement may be inaugural in Gougerot's disease, and may therefore pose problems of differential diagnosis with other disorders of the central and peripheral nervous system. There is no specific neurological involvement, but the most suggestive manifestations of primary Gougerot Sjögren's are mainly neuropathy, myelopathy and focal involvement of the central nervous system, due to their prevalence in primary Gougerot. Polyneuropathies are frequently associated with Gougerot Sjögren's syndrome. Polyradiculoneuritis, epilepsy, headache and cognitive disorders are uncommon.

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