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Suspect recurrent transient ischemic attack ec Sjogren's Syndrome: A case report

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Abstract---Sjogren's Syndrome is a chronic systemic autoimmune disorder that is usually accompanied by dry eyes and mouth due to inflammation and abnormalities in the lacrimal and salivary glands. This disease can cause a decrease in the production of secretions in other organs that need moisture, such as the nose, throat, respiratory tract, and skin. The prevalence in the general population is not yet known, but the prevalence in the Americas is 0.05-4.8% of the population. Sixty percent of Sjogren's Syndrome patients have disease secondary to accompanying autoimmune disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or systemic sclerosis.

Keywords---Sjogren's Syndrome, autoimmune, dry eyes, transient ischemic attack, transient monocular visual loss.

Introduction

The clinical picture of Sjogren's Syndrome is very broad, which can be in the form of exocrinopathy accompanied by systemic or extra-glandular symptoms. The most common complaints experienced by people with Sjogren's syndrome are dry eyes and mouth. The most common complaints experienced by people with Sjogren's syndrome are dry eyes and mouth. The diagnosis of Sjogren's syndrome is made through the examination of the secretory function of the glands, especially the lacrimal and salivary glands, histopathological examination, radiology, and laboratory. Laboratory tests include complete blood count, ESR, CRP, liver function, kidney function, rheumatoid factor, TSH, ds-DNA, complement, viral hepatitis markers, and ANA examination.

Case

A 35-year-old female patient who was referred from a hospital came to the Neurology Clinic of Dr. Hasan Sadikin General Hospital with transient monocular visual loss ec suspected embolism. The patient complained of intermittent headaches since 6 months before admission, complaints accompanied by dry, blurry eyes, and burning sensation since $\pm$ 2 months before admission. The patient admitted that her vision in the right eye could only see the center of the visual field for $\pm$ 2 months before admission, it recovered for $\pm$ 1 minute, and repeated 5 times a day. Momentary dark vision (+), 2 months history of hypertension with mean systolic blood pressure of 160.

On physical examination, visual acuity ocular dextra (OD) 20/40, ocular sinistra (OS) 20/30. No abnormalities were found on neurological examination. The patient's working diagnosis was a recurrent transient ischemic attack (TIA) with risk factors for hypercoagulability, then she was given warfarin 2 mg and checked for PT and INR.

The result of fundoscopic examination was well-defined papillae, arterial-venous ratio 2/3, no bleeding, no exudate. The result of carotid artery Doppler examination was no plaque in the bilateral common carotid arteries. The patient was then referred to the Rheumatology Clinic and warfarin therapy was stopped.

The patient was examined for platelet aggregation with normal aggregation result. Contrast CT scan result showed no signs of bleeding, systemic lesions, space occupying lesions (SOL), and vascular malformations. The result of Schirmer test are below 5 mm/5 minutes, antinuclear antibody indirect immunofluorescence (ANA IIF) result was reactive with a homogeneous pattern. There was increase in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Normal creatinine, alanine aminotransferase (ALT), and urinalysis result. The results of the antinuclear antibody profile examination: RNP/Sm (+), SS-A native (60 kDa) (+++), and Ro-52 recombinant (+++). The patient was suspected as Sjogren's Syndrome.

Discussion

The pathogenesis mechanism of Sjogren's Syndrome is caused by multiple factors, namely environmental factors, genetic predisposition, and epigenetic factors that can trigger abnormal autoimmune responses mediated mainly by T and B lymphocytes. Initially, viral infection causes disruption of epithelial cells which are then recognized by toll-like receptors (TLR) and cause activation of epithelial cells and dendritic cells. In addition to functioning as epithelial cell activation that triggers the activation of B cells or T cells, antigen presenting cells (APCs) also activate dendritic cells that can activate interferon (IFN) types I and II thereby increasing the secretion of pro-inflammatory cytokines such as B-cell activating factor (BAFF) from the tumor necrosis factor (TNF) family. Dendritic cells secrete natural killer (NK) cells and T helper 1 (Th1) cells that increase the production of interferon gamma (IFN- γ) and mediate tissue damage. Interferon alpha (IFN- α) and IFN- γ increase the overproduction of BAFF and activation of B cells and T cells. In individuals susceptible to Sjogren's syndrome, activation of B

cells can promote autoantibody production in germinal center (GC) like structures. Epithelial cells release ribonucleoprotein autoantigens Ro/SSA and La/SSB which participate in the formation of immune complexes and in the continuous activation of the immune system and cause tissue damage (Endaryanto & Nugraha, 2021; Hertanto et al., 2021; Huldani et al., 2022; Kristanti et al., 2021; Nocturne & Mariette, 2013; Parisi et al., 2020; Permatasari et al., 2022).

B cell hyperactivity is an increase in circulating levels of immunoglobulins and autoantibodies against the ribonucleoprotein autoantigens Ro/SS-A and La/SS-B. Anti-La is more specific but less sensitive for Sjogren's syndrome than anti-Ro since the emergence of the autoimmune disease SLE. Circulating antibodies include rheumatoid factor (RF) and anti-fodrine. Cryoglobulin type II (monoclonal with RF activity) is seen in 20% of patients. The pathogenesis of Sjogren's Syndrome is described in Figure 1 as follows (Marofi et al., 2021a; Marofi et al., 2021b; Parisi et al., 2020).

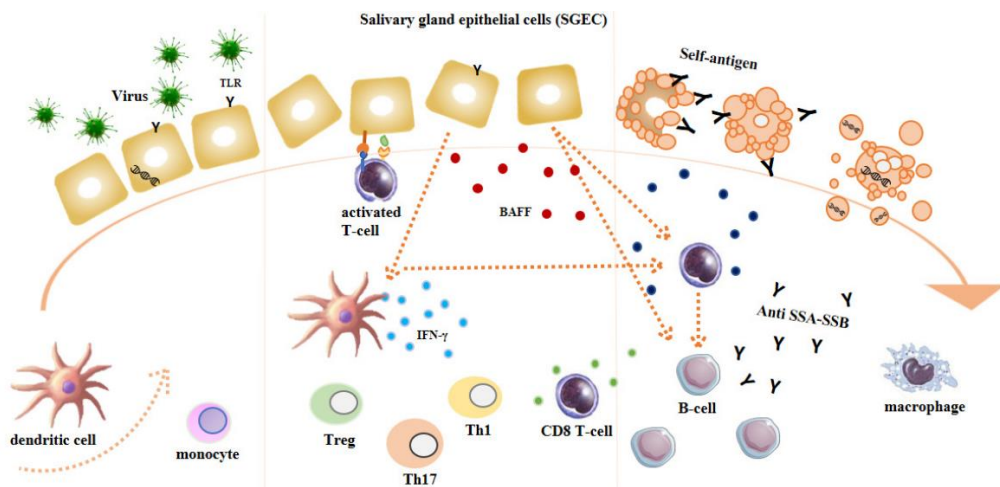


Figure 1 Pathogenesis of Sjogren's Syndrome

Adapted from: Parisi(Parisi et al., 2020)

Description: TLR: Toll-like receptor

BAFF: B-cell activating factor
Th1: T helper type 1
Th17: T helper type 17
Treg: Regulatory T cell

The clinical picture of Sjogren's Syndrome is very broad, which can be in the form of exocrinopathy accompanied by systemic or extra-glandular symptoms. Xerostomia and xerotrachea are features of exocrinopathies of the mouth. The

appearance of exocrinopathy in the eye is dry eyes or kerato-conjunctivitis Sicca due to dry eyes. Extra-glandular manifestations can affect the lungs, kidneys, blood vessels, and muscles. Systemic symptoms found in Sjogren's Syndrome are the same as other autoimmune diseases, including fatigue, fever, muscle aches, and arthritis. Non-erosive polyarthritis is a typical form of arthritis in Sjogren's syndrome. Raynaud's phenomenon is a common vascular disorder, usually without telangiectasia or ulceration of the fingers. Extra-glandular manifestations in Sjogren's Syndrome can be in the form of skin, lung, blood vessel manifestations, and others. Skin manifestations are the most common extra-glandular symptoms. Manifestations of vasculitis on the skin can affect medium or small blood vessels. Vasculitis of the skin is a sign of a poor prognosis. Manifestations of Sjogren's Syndrome also occur in the lungs. The most prominent manifestations are bronchial, bronchiolar, and small airways involvement. Manifestations of blood vessels or vasculitis found in only about 5% of cases can affect medium or small blood vessels with clinical manifestations in the form of purpura. Raynaud's phenomenon is present in 35% of cases and usually appears after years of Sicca syndrome, and is not accompanied by telangiectasia and ulceration. Renal manifestations are only found in about 10% of cases. The most common manifestations are abnormalities in the tubules with subclinical symptoms. The clinical picture can be in the form of hypophosphaturia, hypokalemia, hypocloemic, distal type of renal tubular acidosis (RTA) (Yuliasih, 2014).

Neuromuscular manifestations were caused by vasculitis of the nervous system. Clinical manifestations are usually peripheral neuropathy, but can also be cranial neuropathy. The frequent gastrointestinal manifestations found are dysphagia due to dryness of the oesophagus and mouth, and motility disorders in the oesophagus. Complaints of nausea and epigastric abdominal pain are also common. In the gastric mucosal biopsy of a patient with Sjogren's Syndrome with chronic atrophic gastritis, lymphocytic infiltration was found. Arthritis manifestations are found in 50% of cases of Sjogren's Syndrome. Arthritis appears earlier before the symptoms of Sicca. Other symptoms that may be encountered are arthralgia, joint stiffness, synovitis, chronic polyarthritis. Hematologic manifestations in Sjogren's syndrome are not as specific as in other autoimmune diseases. Usually only mild anemia is found. Leukopenia occurs only in 10% of cases, then there can be an increase in the ESR without a typical increase in CRP (Yuliasih, 2014)

Examination to establish the diagnosis of Sjogren's Syndrome can be divided into examination of the secretory function of the glands, especially the lacrimal and salivary glands, histopathological examination, radiology, and laboratory examinations. Examination of the secretory function of the glands, including the Schirmer test, Rose Bengal Staining, tear film break up time (TBUT), and sialometry test. Biopsy can be done for histopathological examination. The radiological examinations used include sialography tests, scintigraphy tests, chest X-rays. Laboratory tests include complete blood count, ESR, CRP, liver function, kidney function, rheumatoid factor, TSH, ds-DNA, complement, viral hepatitis markers, and ANA examination (Yuliasih, 2014). Based on the ACR-EULAR classification, the diagnosis of Sjogren's Syndrome can be made if the score ≥ 4 .

This patient score was 4, so that Sjogren's Syndrome diagnosis can be made (Shiboski et al., 2017).

The patient was examined for ANA IIF, a screening test to detect antibodies in the serum against self-antigens on components of human nuclear cells. This is qualitative examination and was made using human epithelial cell type-2 (HEp-2) and primate liver cells fixed on glass slides as substrates for attachment of autoantibodies. Fluorescently labeled antibody conjugate (fluorescein isothiocyanate/FITC) was used to mark autoantibodies attached to antigens present in fixed cells. The fluorescent label on this antibody conjugate will glow green when exposed to a fluorescent microscope light. HEp-2 cells were chosen as substrate in ANA IIF assay because they can express 100-150 antigens (Tebo, 2017).

The common fluorescent microscopic staining patterns in nuclear cells, namely homogeneous, diffuse, peripheral, centromere, nucleolar, and cytoplasmic, show the characteristic distribution of various autoantibodies. In Sjogren's Syndrome, the ANA pattern that is commonly found is the Speckled Pattern (Euroimmun, 2020).

Antinuclear antibody profile examination using the line blot immunoassay (LBI) method is qualitative examination by observing the presence of IgG autoantibody reactions in human serum with test strips that have been attached with antigens, including nRNP, Sm, SS-A, Ro52, SS-B, Scl 70, PM-Scl, Jo-1, CENP B, PCNA, dsDNA, nucleosomes, histones, ribosomal p protein, AMA-M2, DFS70. In immunoblot assays, antigens coated on membranes are used as solid phase to detect specific antibodies in patient samples. The test can be performed manually, semi-automatically, or automatically. If the sample contains a specific antibody, the antibody will bind to the membrane-bound antigen. In the next step, antibody-labeled alkaline phosphatase (conjugate) is added, which then binds to the specific antibody. Alkaline phosphatase catalyzes the color reaction by adding nitro blue tetrazolium chloride/5-bromo-4-chloro-3-indolyl phosphate (NBT/BCIP). If specific antibodies are present in a patient's sample, a dark line appears on the respective antigen panel. The intensity of the resulting stain is proportional to the concentration of antibody in the sample (Euroimmun).

Autoantibody SS-A or Ro has a prevalence of 40-95% appearing in patients with Sjogren's Syndrome, autoantibody Ro-52 is 81%, while autoantibody SS-B or La is 40-95% (Euroimmun, 2021). Anti-SSA (soluble substance A/Sjogren's Syndrome A) or Ro antibodies are the main antibodies in Sjogren's Syndrome. These antibodies are found in two-thirds of patients with Sjogren's Syndrome, and half of them also have anti-SSB antibodies. Anti-SSA antibodies are cytoplasmic protein complexes consisting of molecules Y1-, Y2-, Y3, Y4, and Y5-RNA and a protein subunit of 60 kDa) mainly attack the 60 kDa subunit. most often found in patients with Sjogren's syndrome (40 – 95%), systemic lupus erythematosus (20 – 60%) and primary biliary cirrhosis (20%), and sometimes can be found in viral and autoimmune hepatitis. Anti-SS-A antibodies can also be found in 100% of cases of neonatal lupus erythematosus (Infantino et al., 2015). Patients with Sjogren's Syndrome are known to have a number of other antibodies, including rheumatoid factor (RF), anticyclic citrullinated proteins

(CCP), anti- Ku, anti-Sm and anti-RNP antibodies. The association between some of these antibodies and a specific subset of patients has been described. Anti-CCP antibodies have been shown to be associated with articular and pulmonary involvement and have a risk of developing rheumatoid arthritis (RA), whereas anti-Ku antibodies have been associated with muscle involvement (Abbara et al., 2019).

Autoantibody against SS-B (soluble substance A/Sjogren's Syndrome B) is an extractable nuclear antigen (ENA) or an extractable antigen consisting of a 48-kD protein combined with an RNA species. SS-B/La antibodies were found mainly in patients with Sjogren's Syndrome or SLE which occurred with a frequency of about 60% and 15%, respectively. SS-B/La antibodies are rare in the absence of SS-A/Ro antibodies. Positive results for SS-B/La antibodies are consistent with connective tissue diseases, including Sjogren's Syndrome and SLE (Infantino et al., 2015).

Autoantibodies to Ro-52 were first described in 1988 in patients with Sjogren's syndrome. This protein measures 52 kDa and consists of 475 amino acids. Ro-52 was identified as an interferon-inducible protein (IFN) from the tripartite motif family. Ro-52 has an E3 ligase function that regulates IFN regulatory factors (Infantino et al., 2015). Ribonucleoprotein Ro/SSA and La/SSB are released by epithelial cells that participate in the formation of immune complexes. The activation of the immune system occurs continuously causing tissue damage (Nocturne & Mariette, 2013; Parisis et al., 2020).

Examination of the ANA profile in this patient showed RNP/Sm, SS-A native (60 kDa), and Ro-52 recombinant. Anti-RNP antibodies target proteins belonging to the U1 small nuclear ribonucleoproteins (snRNP) complex, namely core proteins A, C and 70 kDa protein subunits; anti-RNP was considered specific (specificity ranging from 84% to 100%) in mixed connective tissue disease (MCTD). A high autoantibody titer against 27 nRNP/Sm is a typical marker for Sharp's syndrome, a multisymptomatic and multiform mixed connective tissue disease (MCTD) with a combination of characteristics of rheumatoid arthritis, SLE, SSc and polymyositis with a sensitivity of 95-100%. Anti-nRNP/Sm autoantibodies can also be found in SLE (15 – 40%) and SSc (2 – 12%). Positive results for anti-RNP antibodies are associated with more active systemic disease, particularly in organ-specific diseases such as myositis (10 times more frequent) and pulmonary involvement (4 times more frequent), and with elevated B cell levels. Anti-RNP antibodies were also more common in patients with anti-SSA positives. Patients with anti-SSA have been shown to have a higher prevalence of systemic manifestations, but patients with positive anti-RNP results are associated with a more active disease state. Nucleic acids containing RNPs can associate with TLRs and stimulate signaling. The implications of TLR-7 signaling can be found in Sjogren's syndrome, SLE, and MCT (Infantino et al., 2015).

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References

- Abbara, S., Seror, R., Henry, J., Chretien, P., Gleizes, A., Abina, S. H. B., Mariette, X., & Nocturne, G. (2019). Anti-RNP positivity in primary Sjögren's syndrome is associated with a more active disease and a more frequent muscular and pulmonary involvement. *Rheumatic & Musculoskeletal Diseases*, 5(2), 1-7. <https://doi.org/10.1136/rmdopen-2019-001033>
- Carsons, S. E., & Patel, B. C. (2021). Sjogren Syndrome. Statpearls Publishing. <https://doi.org/https://www.ncbi.nlm.nih.gov/books/NBK431049/>
- Endaryanto A, Nugraha RA. Indonesia-Based Study of the Clinical and Cost-Saving Benefits of Subcutaneous Allergen Immunotherapy for Children with Allergic Rhinitis in Private Practice. *Cells*. 2021 Jul 20;10(7):1841. DOI: 10.3390/cells10071841.
- Euroimmun. (2020). ANA Diagnostics Using Indirect Immunofluorescence. PerkinElmer Company.
- Euroimmun. (2021). Strategy for the Determination of Autoantibody against Cell Nuclei (ANA) and Cytoplasm Components. Medizinische Labordiagnostika AG.
- Euroimmun. Immunoblot. Retrieved 17 Juni from <https://www.euroimmun.com/products/techniques/immunoblot/>
- Fox, R. I., & Fox, C. M. (2020). Sjogren's syndrome: past, present, and future. In F. B. Vivino (Ed.), *Sjogren Syndrome - A Clinical Handbook*. Elsevier.
- Hertanto, D. M., Wiratama, B. S., Sutanto, H., & Wungu, C. D. K. (2021). Immunomodulation as a potent COVID-19 pharmacotherapy: Past, present and future. *Journal of Inflammation Research*, 14, 3419-3428. DOI: 10.2147/JIR.S322831
- Huldani, H., Abdalkareem Jasim, S., Olegovich Bokov, D., Kamal Abdelbasset, W., Nader Shalaby, M., Thangavelu, L., Margiana, R., & Qasim, M. T. (2022). Application of extracellular vesicles derived from mesenchymal stem cells as potential therapeutic tools in autoimmune and rheumatic diseases. *International Immunopharmacology*, 106, 108634. DOI: 10.1016/j.intimp.2022.108634
- Infantino, M., Meacci, F., Grossi, V., Benucci, M., Morozzi, G., Tonutti, E., Tampoia, M., Ott, A., Meyer, W., Atzeni, F., Puttini, P. S., Manfredi, M., & Bizzaro, N. (2015). Serological epitope profile of anti-Ro52-positive patients with systemic autoimmune rheumatic diseases. *Arthritis Research & Therapy*, 17, 365. <https://doi.org/10.1186/s13075-015-0871-3>
- Kassan, S. S., & Moutsopoulos, H. M. (2004). Clinical manifestations and early diagnosis of Sjögren syndrome. *Archives of Internal Medicine*, 164(12), 1275-1284. <https://doi.org/10.1001/archinte.164.12.1275>
- Kristanti, R. A., Bramantoro, T., Soesilawati, P., Setiawatie, E. M., & Purwanto, B. (2021). Periodontitis Affects Skeletal Muscle Metabolism Through an Increase in Proinflammatory Cytokines. *Journal of International Dental and Medical Research*, 14(4), 1623-1628.
- Maciel, G., Crowson, C. S., Matteson, E. L., & Cornec, D. (2017). Incidence and Mortality of Physician-Diagnosed Primary Sjögren Syndrome: Time Trends Over a 40-Year Period in a Population-Based US Cohort. *Mayo Clinic Proceedings*, 92(5), 734-743. <https://doi.org/10.1016/j.mayocp.2017.01.020>
- Marofi F, Abdul-Rasheed OF, Rahman HS, Budi HS, Jalil AT, Yumashev AV, Hassanzadeh A, Yazdanifar M, Motavalli R, Chartrand MS, Ahmadi M, Cid-

- Arreguid A, Jarahian M. CAR-NK cell in cancer immunotherapy; A promising frontier. *Cancer Sci.* 2021;112(9):3427-3436. DOI: 10.1111/cas.14993.
- Marofi F, Rahman HS, Achmad MH, Sergeevna KN, Suksatan W, Abdelbasset WK, Mikhailova MV, Shomali N, Yazdanifar M, Hassanzadeh A, Ahmadi M, Motavalli R, Pathak Y, Izadi S, Jarahian M. A Deep Insight Into CAR-T Cell Therapy in Non-Hodgkin Lymphoma: Application, Opportunities, and Future Directions. *Front Immunol.* 2021b;12:681984. DOI: 10.3389/fimmu.2021.681984.
- Nocturne, G., & Mariette, X. (2013). Advances in understanding the pathogenesis of primary Sjögren's syndrome. *Nature Review Rheumatology*, 9(9), 544-556. <https://doi.org/10.1038/nrrheum.2013.110>
- Parisis, D., Chivasso, C., Perret, J., Soyfoo, M. S., & Delporte, C. (2020). Current State of Knowledge on Primary Sjögren's Syndrome, an Autoimmune Exocrinopathy. *Journal of Clinical Medicine*, 9(7), 2299. <https://doi.org/10.3390/jcm9072299>
- Paul Kruszka 1, R. J. O. B. (2009). Diagnosis and management of Sjögren syndrome. *American Family Physician*, 79(6), 465-470. <https://pubmed.ncbi.nlm.nih.gov/19323359/>
- Permatasari, C. A., Zahraini, H., Marpaung, F. R., & Aryati (2022). Hypokalemic periodic paralysis and renal tubular acidosis in a patient with hypothyroid and autoimmune disease. *Annals of medicine and surgery* (2012), 75, 103389. DOI: 10.1016/j.amsu.2022.103389
- Dwijaya, A., & Atmaja, M. H. S. (2022). Clinical and imaging findings of klippel-trenaunay syndrome: A case report. *International Journal of Health & Medical Sciences*, 5(1), 145-149. <https://doi.org/10.21744/ijhms.v5n1.1860>
- Shiboski, C. H., Shiboski, S. C., Seror, R., Criswell, L. A., Labetoulle, M., Lietman, T. M., Rasmussen, A., Scofield, H., Vitali, C., Bowman, S. J., & Mariette, X. (2017). 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. *Arthritis & Rheumatology*, 69(1), 35-45. <https://doi.org/10.1002/art.39859>
- Suryasa, I. W., Rodriguez-Gámez, M., & Koldoris, T. (2022). Post-pandemic health and its sustainability: Educational situation. *International Journal of Health Sciences*, 6(1), i-v. <https://doi.org/10.53730/ijhs.v6n1.5949>
- Tebo, A. E. (2017). Recent Approaches To Optimize Laboratory Assessment of Antinuclear Antibodies. *American Society for Microbiology*, 24(12), 1-10. <https://doi.org/https://doi.org/10.1128/CVI.00270-17>
- Yuliasih. (2014). Sindrom Sjogren In S. Setiati, I. Alwi, A. W. Sudoyo, M. S. K, B. setiyohadi, & A. F. Syam (Eds.), *Buku Ajar Ilmu Penyakit Dalam* (pp. 3160-3166). Internal Publishing.