Magnetic Resonance Imaging for Sjögren's Syndrome

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Primary Sjögren's Syndrome (pSS) is a chronic autoimmune exocrinopathy affecting 0.3–3.0% of the population. Its main clinical hallmarks are the sicca symptoms (mucosal dryness manifesting mainly ocularly and orally) and extra-glandular symptoms, among which joint pain and chronic fatigue are the most important. Besides these symptoms, pSS may also manifest in the central nervous system (CNS), as noted in the original description of the disease by Sjögren himself in 1933. The most common radiological lesions in pSS are white matter hyperintensities (WMH), scattered alterations hyperlucent on T2 and FLAIR sequences, typically located periventricularly and subcortically. Cortical atrophy and ventricular dilatation can also occur in pSS. Whilst these conditions are thought to be more common in pSS than healthy controls, diffusion tensor imaging (DTI) and resting-state functional magnetic resonance imaging (fMRI) alterations demonstrate evident microstructural changes in pSS. As pSS is often accompanied by cognitive symptoms, these magnetic resonance imaging (MRI) alterations are expectedly related to them.

Sjögren's syndrome | magnetic resonance imaging | white matter hyperintensities

1. Conventional MRI

1.1. White Matter Hyperintensities (WMHs)

The most characteristic MRI finding in primary Sjögren's syndrome (pSS) is the white matter hyperintensities (WMHs). These are hyperintense foci on T2 weighted and FLAIR images typically located periventricularly and subcortically. These lesions can mimic the radiological properties of multiple sclerosis (MS).

In a related study, four of twelve patients (33%) had such alterations, but neither the location nor the size could be correlated with any clinical central nervous system (CNS) symptoms [1]. Moreover, regarding the immunological parameters, serum IgG, rheumatoid factor levels, and anticardiolipin antibodies do not correlate with WMHs properties [2]. There have also been investigations showing that the presence of WMHs on cerebral MRI between pSS patients and age and gender-matched controls do not differ statistically; therefore, they cannot be considered signs of CNS involvement but marks of physiological ageing [3]. However, this may also mean that the role of WMHs is underestimated because of the lack of proper diagnostical modalities [4].

The clinical correlations of WMHs are also controversial. Coates et al. deny any significant clinical correlations of cerebral white matter lesions in pSS [2]. There is no connection between the number of pSS criteria fulfilled, extraglandular symptoms [1][3][5], fatigue [6][7] or depression [6] and WMHs. Patient age is found as the only clinical data significantly correlating with the number of WMHs [8]. More WMHs are to be found in younger patients [5], and pSS patients with WMHs tend to be younger than controls with WMHs [9]. Another study describes that whilst WMHs with demyelinating characteristics are more frequent with younger age and altered glomerular filtration rate, the total number of WMHs, however, is associated with higher age (contrary to the findings of Govoni et al.) as well as lower prevalence of leukopenia and anti-SSB (anti-La) autoantibodies, higher prevalence of hypertension, diabetes mellitus, metabolic syndrome and lower use of antimalarial drugs [10]. Disease duration is significantly associated with WMHs [9][11].

Results of resting-state fMRI and other imaging techniques also showed correlations with WMHs: the association of asymmetrical hypoperfusion verified by single-photon emission computerized tomography (SPECT) and subcortical WM lesions is statistically proven [12]. Furthermore, fMRI studies have detected a positive correlation in mean diffusivity (MD) in pSS patients in the anterior thalamic radiation, the corticospinal tract, the cingulum, the forceps minor and major, the inferior fronto-occipital fasciculus, the superior and inferior longitudinal fasciculus and the uncinate fasciculus [6]. Longitudinal studies and follow-up reports are available in a very limited number; the available data suggests that these lesions remain unchanged over time without progression [10][13], and patients with WMHs do not develop MS [2].

1.2. Atrophy

Signs of atrophy are also typical in CNS imaging in pSS. Atrophy is not always present though: when directly measuring the cortical thickness of pSS patients, Segal et al. did not find any differences between pSS and healthy controls [14]. Cortical atrophy of 2 patients is reported based on CT scans [15]. The same condition was identified in 6 patients in an investigation involving 15 participants (31.25%). Focal alterations in the cortex were not seen [16]. The lack of focal atrophy was confirmed and extended to the WM: Lauvsnes et al. reported general atrophy both in the grey and white matter without any focal enhancement [17]. The mechanism of the atrophy is probably due to cortical hypoperfusion and the consequential lowered glucose metabolism that is present in pSS CNS. This hypoperfusion is established with SPECT studies [4][13][18] and possibly can be derived back to the vascular pathology mentioned before. An important unanswered question regarding this hypoperfusion is the problem of lateralization: the hypoperfused areas are more common on the left side, exhibiting asymmetry [4].

2. Volumetric and Morphometric MRI

The total volume of pSS patients' brains is not significantly different compared to patients with migraine. However, ventricular volume was significantly higher in pSS with age covariation correction. This ventricular dilatation was associated with attention disturbance [19]. These alterations correlate with neuropsychological and psychiatric symptoms; thus, together with the previously mentioned single-photon emission computerized tomography (SPECT) studies would support an organic aetiology for these manifestations of pSS. Tzarouchi et al. performed

the first voxel-based morphometric study in pSS. According to the results, the volume of both grey and white matter is reduced in the pSS group. In the grey matter (GM), the cortical regions were bilaterally affected, mainly in the occipital, parietal and frontal lobes; furthermore, the thalamus, caudate nucleus and cerebellar hemispheres were diminished. As for the WM, small areas with decreased volume could be observed throughout the brain, especially in the frontal and occipital lobes, cerebellum and corpus callosum (splenium, genu) [9]. On the contrary, a more recent study identified diffuse cerebral white matter loss in pSS patients but demonstrated the lack of GM or WM atrophy in specific areas of the brain [17]. In the search for an association between fatigue and brain volume, Hammonds et al. found no structural changes either in GM or WM that could be related to fatigue. These results apply to global volumes and individual brain regions [7].

3. DTI

Diffusion tensor imaging (DTI) is an MRI-based technology based on the diffusion of water molecules, arranging the measure of the microstructural integrity of fibre tracts. Subtle tissue alterations that impact the integrity of the brain's structural networks and interregional information transfer are visualized via DTI [20]. DTI revealed significant alterations between pSS patients with and without cognitive impairment and healthy controls in the inferior frontal WM. Lower fractional anisotropy (FA) and higher mean diffusivity (MD) reflecting the deterioration of physiological brain tissue microstructure were observed in the cognitively impaired pSS group [14]. Compared with control subjects, pSS patients turned out to have decreased FA bilaterally in the corticospinal tract, superior longitudinal fasciculus, anterior thalamic radiation, inferior fronto-occipital fasciculus, uncinate fasciculus and inferior longitudinal fasciculus. Voxelwise-based group comparison of MD, axial diffusivity (AD) and radial diffusivity (RD) between patients and healthy controls showed increased MD and RD and decreased AD in the CNS of pSS patients in an extensive, diffuse pattern involving most of the major WM tracts throughout the brain [21]. In another Greek study, pSS patients were divided into two groups: with and without depression. Patients with depression showed increased AD, RD and MD and decreased FA; those without depression showed decreased AD in major WM tracts (superior longitudinal fasciculus, inferior longitudinal fasciculus, corticospinal tract, anterior thalamic radiation, inferior fronto-occipital fasciculus, cingulum, uncinate fasciculus and forceps minor-major) [6]. Finally, in a paper published this year focusing on structural connectivity (SC), 12 connections were significantly different between pSS patients and healthy controls. Decreased SC in the frontal and parietal lobes and some parts of the temporal and occipital lobes were present in pSS patients. Furthermore, increased SC between the right caudate nucleus and the right median cingulate/paracingulate gyri was reported. The reduced SC between the left middle temporal gyrus and the left middle occipital gyrus was negatively associated with WMHs [22].

4. Resting-State fMRI

Functional magnetic resonance imaging (fMRI) has been crucial to the current understanding of brain function. During task performance or in response to a stimulus, specific regions of the brain are activated and detected by fMRI. More recently, the modality has been developed for use at rest, termed resting-state fMRI or functional connectivity (FC) MR imaging. Resting-state fMRI investigates synchronous activations between regions that are

distinct in space, appearing without a task or stimulus, to identify resting-state networks [23]. Thus, resting-state fMRI can provide valuable information about brain networks in pSS. The first fMRI study published on pSS was performed on 14 patients. The data were processed by regional homogeneity (ReHo) analysis. ReHo is the time consistency of the blood oxygenation level-dependent signal of local brain tissue [24]. The ReHo values were increased in the right cerebral hemisphere, left limbic lobe, right middle temporal gyrus and the inferior parietal lobe in pSS patients compared to controls. However, ReHo values were significantly decreased in the right lingual gyrus, left cuneiform lobe, left superior occipital gyrus, bilateral middle occipital gyrus and the bilateral fronto-parietal junction area [25]. Additionally, pSS patients were found to show decreased brain activation compared to controls in the sensorimotor network. No FC changes occurred when comparing patients with or without depression or fatigue and controls [6]. Another study focusing on the hippocampus revealed that hippocampal FC is decreased between the left hippocampus and the right inferior occipital and inferior temporal cortex, as well as between the right hippocampus and right inferior occipital and middle occipital GM, left middle occipital and left middle temporal GM. In addition, increased hippocampal FCs were detected between the left hippocampus and left putamen, as well as between the right hippocampus and right cerebellar posterior lobe.

5. Summary

5.1. Etiopathogenesis of WMHs

The etiopathogenesis and exact histological structure and, thus, the possible classification of the WMHs remain controversial. It is complicated by the fact that WMH appearance is rather heterogenous in terms of their number, size and location. Many attempts have been made to find out the way of the emergence of these lesions. These theories included myelin pallor, dilatation of perivascular (Virchow–Robin) spaces, periventricular gliosis, arteriosclerosis and infarction [2]. It has recently been established that the two main pathways, which most likely interfere, are the vascular and demyelinating/inflammatory pathways. Microinfarcts or microhaemorrhages associated with a small-vessel cerebral vasculopathy have been demonstrated as pathogenic factors of WMHs. It was described in the case of similar foci observed in MS; however, in their case, there was no clinical sign of demyelination [26]. Abnormal cerebral blood flow was also detected in pSS: hypoperfusion in the parietal and temporal lobe was reported based on SPECT studies [13][18]. The hypoperfusion is asymmetrical and focal [4][12] and, due to the subsequent diminished glucose metabolism, is connected not only to WMHs but to atrophy too, which itself may be able to trigger WMH formation via Wallerian degeneration (see below). Cerebrovascular risk factors, such as hypertension, increase the incidence of WMHs, which also supports vascular origin [10]. Haemodynamic changes are also registered in pSS brains: higher mean pulsatility index and systolic–diastolic ratio was found in patients compared to controls, in correlation with anti-SSA autoantibodies. This suggests that the autoimmune response is involved in early cerebral haemodynamic dysfunctions. Additionally, functional impairment of the endothelium was established, which is possibly responsible for vasomotor dysfunction before any organic damage [8]. The importance of functional impairment prior to organic damage, and the role of the autoimmune response in CNS pathology is enhanced by a study examining somatosensory-evoked potentials (SEP) among 33 pSS patients without clinical features of CNS damage and normal head computed tomography scan. The

relationship between SEP parameters and pSS disease duration, duration of arthralgia and presence of anti-SSA and SSB antibodies is also described in the study [27]. The same research group revealed abnormal brainstem auditory-evoked potentials (BAEP) investigating pSS patients without CNS involvement [28]. These bioelectrical activity dysfunctions may be a consequence of ongoing inflammatory and/or immunological processes, anticipating the detectable morphological changes. Vasculitis has been described in the brains of pSS patients [29][30][31]. Therefore, one may consider vasculitis as a pathogenic factor for WMH formation. It probably has low importance though: pSS is not a vasculitic disease despite the occurrence of small vessel vasculitis in some cases. The fact that pSS patients do not have more cerebral infarcts than healthy controls also provides evidence against vasculitis as a pathogenic factor [3][17]. In summary, vascular impairment is important but not the exclusive pathogenic mechanism in the aetiology of CNS involvement in pSS.

The other main pathway settles on inflammation and demyelination, with a high resemblance to MS [10][21][32][33]. Although it may be difficult to distinguish between MS-like and true-MS symptoms based on MRI, it is crucial since MRI may be the most important diagnostic tool to rely on in the differential diagnosis, especially at the beginning of the symptoms [34]. The differences in the etiopathogenesis of pSS and MS may also lead to different neuropathological and neuroradiological hallmarks: focal lesions are more common in pSS, as well as lesions of vascular origin without clinical signs of demyelination. Furthermore, demyelinating lesions are not necessarily present in the brain of pSS patients. Clinical investigations can support the differential diagnosis; cerebrospinal fluid (CSF) analysis detects only one or two bands in pSS as opposed to the oligoclonal pattern found in MS [35].

Young age and lower prevalence of hypertension are significant variables for inflammatory/demyelinating lesions when it comes to the differentiation between vascular and inflammatory/demyelinating WMHs [10]. The presence of anti-aquaporin-4 (anti-AQP4) autoantibody in pSS is a predictive sign for demyelinating lesions; brain lesions fulfilling Barkhof's criteria were found only in anti-AQP4 antibody-positive patients among 22 participants [36].

Similarly to anti-AQP4 antibodies, which are direct insults to the myelin, the autoimmune response itself can damage the CNS-promoting WMH formation. B-cell dysfunction is a key feature of pSS. The excessive B-cell activating factor (BAFF) production is a pathological mechanism in pSS [37]. Nonlymphoid cells, such as astrocytes, can express BAFF and trigger CNS manifestations.

5.2. MRI Findings and Cognitive Functions

The obvious neuropsychological and cognitive symptoms of pSS have drawn the attention of the scientific community in recent decades [38][39]. There is a wide range of cognitive involvement in pSS, from mild cognitive impairment (MCI) to severe dementia. There have been studies analysing cognitive functions and MRI findings together. Their results, however, often contradict each other, which brings into question whether the cognitive impairments correlate with MRI abnormalities. On the other hand, there is concordance in the nature of cognitive manifestations in pSS. These are, for the most part, attention deficits, visual and verbal memory (working and long-term), psychomotor function and processing speed abnormalities. Possibly the immune system itself plays a role in

these conditions; in patients with anti-SSA antibody positivity, higher cognitive function disorders can be observed [3][12][40][41].

The correlation of the cognitive symptoms, MRI findings and the atrophy typical for pSS described above all support the organic origin of mental health impairment in the disease. The reason for the asymmetricity of the blood flow is an interesting and open question. Nevertheless, these procedures may cause detectable cognitive decline that can reach the threshold of clinical dementia [12][42]. Nation-wide, population-based studies also have confirmed that pSS patients have a higher risk for dementia [43][44].

5.3. Involvement of Brain Regions

A typical pattern or location of brain lesions has yet to be described in pSS. However, there are interesting findings regarding the involvement of certain territories of the brain. The first such area is the visual cortex, where Tzarouchi et al. found atrophy [9], and Xing et al. detected abnormal brain activity with resting-state fMRI [25]. This finding can be explained by the association of pSS and neuromyelitis optica (NMO) [45], which may result in the degeneration of the entire circuitry [9].

The other affected region to discuss is the cerebellum. Govoni et al. mentions a >1cm hyperlucent area in the left cerebellar hemisphere of one patient [5]. The bilateral degeneration of cerebellar hemispheres with voxel-based morphometry is also described. WMHs can also appear in the cerebellum [10]. An autopsy showed high Ro52/TRIM21 expression in the Purkinje cells in the histological sections of the cerebellum in a patient with cerebellar degeneration. This may indicate that anti-Ro/SSA antibodies are the antineuronal antibodies involved in the cerebellar degeneration of patients with SS. This finding, besides the possible use of CSF as a biomarker in pSS, suggests that the autoimmune response linked to pSS causes cerebellar degeneration [46]. In conclusion, it is most likely that these are not sporadic cases; cerebellar impairment is possibly a rare but notable symptom of pSS.

References

1. Manthorpe, R.; Manthorpe, T.; Sjöberg, S. Magnetic resonance imaging of the brain in patients with primary Sjögren's syndrome. Scand. J. Rheumatol. 1992, 21, 148–149.
2. Coates, T.; Slavotinek, J.P.; Rischmueller, M.; Schultz, D.; Anderson, C.; Dellamelva, M.; Sage, M.R.; Gordon, T.P. Cerebral white matter lesions in primary Sjogren's syndrome: A controlled study. J. Rheumatol. 1999, 26, 1301–1305.
3. Harboe, E.; Beyer, M.K.; Greve, O.J.; Gøransson, L.G.; Tjensvoll, A.B.; Kvaløy, J.T.; Omdal, R. Cerebral white matter hyperintensities are not increased in patients with primary Sjögren's syndrome. Eur. J. Neurol. 2009, 16, 576–581.
4. Le Guern, V.; Belin, C.; Henegar, C.; Moroni, C.; Maillet, D.; Lacau, C.; Dumas, J.L.; Vigneron, N.; Guillevin, L. Cognitive function and 99mTc-ECD brain SPECT are significantly correlated in

patients with primary Sjögren syndrome: A case-control study. Ann. Rheum. Dis. 2010, 69, 132–137.

5. Govoni, M.; Bajocchi, G.; Rizzo, N.; Tola, M.R.; Caniatti, L.; Tugnoli, V.; Colamussi, P.; Trotta, F. Neurological involvement in primary Sjögren's syndrome: Clinical and instrumental evaluation in a cohort of Italian patients. Clin. Rheumatol. 1999, 18, 299–303.
6. Andrianopoulou, A.; Zikou, A.K.; Astrakas, L.G.; Gerolymatou, N.; Xydis, V.; Voulgari, P.; Kiortsis, D.N.; Argyropoulou, M.I. Functional connectivity and microstructural changes of the brain in primary Sjögren syndrome: The relationship with depression. Acta Radiol. 2020, 61, 1684–1694.
7. Hammonds, S.K.; Lauvsnes, M.B.; Dalen, I.; Beyer, M.K.; Kurz, K.D.; Greve, O.J.; Norheim, K.B.; Omdal, R. No structural cerebral MRI changes related to fatigue in patients with primary Sjögren's syndrome. Rheumatol. Adv. Pract. 2017, 1, rkx007.
8. Morreale, M.; Francia, A.; Marchione, P.; Manuppella, F.; Giacomini, P. Intracranial hemodynamic changes in primary Sjögren Syndrome: A transcranial doppler case–control study. Neurol. Sci. 2015, 36, 1589–1595.
9. Tzarouchi, L.C.; Tsifetaki, N.; Konitsiotis, S.; Zikou, A.; Astrakas, L.; Drosos, A.; Argyropoulou, M.I. CNS involvement in primary Sjögren syndrome: Assessment of gray and white matter changes with MRI and voxel-based morphometry. AJR. Am. J. Roentgenol. 2012, 197, 1207–1212.
10. Akasbi, M.; Berenguer, J.; Saiz, A.; Brito-Zerón, P.; Pérez-De-Lis, M.; Bové, A.; Diaz-Lagares, C.; Retamozo, S.; Blanco, Y.; Perez-Alvarez, R.; et al. White matter abnormalities in primary Sjögren syndrome. QJM Int. J. Med. 2012, 105, 433–443.
11. Šarac, H.; Markeljević, J.; Erdeljić, V.; Josipović-Jelić, Z.; Hajnšek, S.; Klapan, T.; Batinica, M.; Baršić, I.; Sertić, J.; Dintinjana, R.D. Signal hyperintensities on brain magnetic resonance imaging in patients with primary Sjögren syndrome and frequent episodic tension-type headache: Relation to platelet serotonin level and disease activity. J. Rheumatol. 2013, 40, 1360–1366.
12. Yoshikawa, K.; Hatate, J.; Toratani, N.; Sugiura, S.; Shimizu, Y.; Takahash, T.; Ito, T.; Fukunaga, R. Prevalence of Sjögren's syndrome with dementia in a memory clinic. J. Neurol. Sci. 2012, 322, 217–221.
13. Massara, A.; Bonazza, S.; Castellino, G.; Caniatti, L.; Trotta, F.; Borrelli, M.; Feggi, L.; Govoni, M. Central nervous system involvement in Sjögren's syndrome: Unusual, but not unremarkable—Clinical, serological characteristics and outcomes in a large cohort of Italian patients. Rheumatology 2010, 49, 1540–1549.
14. Segal, B.M.; Mueller, B.A.; Zhu, X.; Prosser, R.; Pogatchnik, B.; Holker, E.; Carpenter, A.F.; Lim, K.O. Disruption of brain white matter microstructure in primary Sjögren's syndrome: Evidence from diffusion tensor imaging. Rheumatology 2010, 49, 1530–1539.

15. Alexander, E.L.; Malinow, K.; Lejewski, J.E.; Jerdan, M.S.; Provost, T.T.; Alexander, G.E. Primary Sjögren’s syndrome with central nervous system disease mimicking multiple sclerosis. Ann. Intern. Med. 1986, 104, 323–330.
16. Pierot, L.; Sauve, C.; Leger, J.M.; Martin, N.; Koeger, A.C.; Wechsler, B.; Chiras, J. Asymptomatic cerebral involvement in Sjögren’s Syndrome: MRI findings of 15 cases. Neuroradiology 1993, 35, 378–380.
17. Lauvsnes, M.B.; Beyer, M.K.; Appenzeller, S.; Greve, O.J.; Harboe, E.; Gøransson, L.G.; Tjensvoll, A.B.; Omdal, R. Loss of cerebral white matter in primary Sjögren’s syndrome: A controlled volumetric magnetic resonance imaging study. Eur. J. Neurol. 2014, 21, 1324–1329.
18. Kao, C.H.; Ho, Y.J.; Lan, J.L.; Changlai, S.P.; Chieng, P.U. Regional cerebral blood flow and glucose metabolism in Sjögren’s syndrome. J. Nucl. Med. 1998, 39, 1354–1356.
19. Mataró, M.; Escudero, D.; Ariza, M.; Sánchez-Ojanguren, J.; Latorre, P.; Junqué, C.; Mercader, J.M. Magnetic resonance abnormalities associated with cognitive dysfunction in primary Sjögren syndrome. J. Neurol. 2003, 250, 1070–1076.
20. Oishi, K.; Mielke, M.M.; Albert, M.; Lyketsos, C.G.; Mori, S. DTI Analyses and clinical applications in Alzheimer’s disease. J. Alzheimer’s Dis. 2011, 26, 287–296.
21. Tzarouchi, L.C.; Zikou, A.K.; Tsifetaki, N.; Astrakas, L.G.; Konitsiotis, S.; Voulgari, P.; Drosos, A.; Argyropoulou, M.I. White matter water diffusion changes in primary Sjögren syndrome. Am. J. Neuroradiol. 2014, 35, 680–685.
22. Zhang, X.-D.; Li, J.-L.; Zhou, J.-M.; Lu, Z.-N.; Zhao, L.-R.; Shen, W.; Xu, J.-H.; Cheng, Y. Altered white matter structural connectivity in primary Sjögren’s syndrome: A link-based analysis. Neuroradiology 2022, 64, 2011–2019.
23. Lee, M.H.; Smyser, C.D.; Shimony, J.S. Resting-state FMRI: A review of methods and clinical applications. AJNR Am. J. Neuroradiol. 2013, 34, 1866–1872.
24. Xu, Z.; Lai, J.; Zhang, H.; Ng, C.H.; Zhang, P.; Xu, D.; Hu, S. Regional homogeneity and functional connectivity analysis of resting-state magnetic resonance in patients with bipolar II disorder. Medicine 2019, 98, e17962.
25. Xing, W.; Shi, W.; Leng, Y.; Sun, X.; Guan, T.; Liao, W.; Wang, X. Resting-state FMRI in primary Sjögren syndrome. Acta Radiol. 2018, 59, 1091–1096.
26. Alexander, E.L.; Beall, S.S.; Gordon, B.; Selnes, O.A.; Yannakakis, G.D.; Patronas, N.; Provost, T.T.; McFarland, H.F. Magnetic resonance imaging of cerebral lesions in patients with the Sjögren syndrome. Ann. Intern. Med. 1988, 108, 815–823.
27. Dziadkowiak, E.; Sebastian, A.; Wieczorek, M.; Kusińska, E.; Waliszewska-Prosół, M.; Wiland, P.; Ejma, M. Parameters of somatosensory evoked potentials in patients with primary Sjögren’s

syndrome: Preliminary results. J. Immunol. Res. 2018, 2018, 8174340.

28. Waliszewska-Prosół, M.; Sebastian, A.; Wiland, P.; Budrewicz, S.; Dziadkowiak, E.; Ejma, M. Brainstem auditory evoked potentials in patients with primary Sjögren’s syndrome without central nervous system involvement. Clin. Rheumatol. 2021, 40, 991–997.
29. Gerraty, R.P.; McKelvie, P.A.; Byrne, E. Aseptic meningoencephalitis in primary Sjögren’s syndrome. Acta Neurol. Scand. 1993, 88, 309–311.
30. Belin, C.; Moroni, C.; Caillat-Vigneron, N.; Debray, M.; Baudin, M.; Dumas, J.L.; Moretti, J.L.; Delaporte, P.; Guillevin, L. Central nervous system involvement in Sjögren’s syndrome: Evidence from neuropsychological testing and HMPAO-SPECT. Ann. Med. Interne 1999, 150, 598–604.
31. Huang, W.S.; Chiu, P.Y.; Kao, A.; Tsai, C.H.; Lee, C.C. Detecting abnormal regional cerebral blood flow in patients with primary Sjögren’s syndrome by technetium-99m ethyl cysteinate dimer single photon emission computed tomography of the brain—A preliminary report. Rheumatol. Int. 2003, 23, 174–177.
32. Al-Watban, J.; Patay, Z.; Bohlega, S.; Larsson, S. Magnetic resonance imaging of central nervous system involvement in primary Sjögren’s syndrome. Riv. Neuroradiol. 1998, 11, 51–54.
33. Anaya, J.M.; Villa, L.A.; Restrepo, L.; Molina, J.F.; Mantilla, R.D.; Vargas, S. Central nervous system compromise in primary Sjögren’s syndrome. J. Clin. Rheumatol. 2002, 8, 189–196.
34. Kapadia, M.; Sakic, B. Autoimmune and inflammatory mechanisms of CNS damage. Prog. Neurobiol. 2011, 95, 301–333.
35. Ömerhoca, S.; Yazici Akkaş, S.; Kale Içen, N. Multiple Sclerosis: Diagnosis and differential diagnosis. Arch. Neuropsychiatry 2018, 55, S1.
36. Estiasari, R.; Matsushita, T.; Masaki, K.; Akiyama, T.; Yonekawa, T.; Isobe, N.; Kira, J.I. Comparison of clinical, immunological and neuroimaging features between anti-aquaporin-4 antibody-positive and antibody-negative Sjogren’s syndrome patients with central nervous system manifestations. Mult. Scler. 2012, 18, 807–816.
37. Cikes, N.; Bosnic, D.; Sentic, M. Non-MS Autoimmune demyelination. Clin. Neurol. Neurosurg. 2008, 110, 905–912.
38. Malinow, K.L.; Molina, R.; Gordon, B.; Selnes, O.A.; Provost, T.T.; Alexander, E.L. Neuropsychiatric dysfunction in primary Sjögren’s syndrome. Ann. Intern. Med. 1985, 103, 344–350.
39. Mauch, E.; Völk, C.; Kratzsch, G.; Krapf, H.; Kornhuber, H.H.; Laufen, H.; Hummel, K.J. Neurological and neuropsychiatric dysfunction in primary Sjögren’s syndrome. Acta Neurol. Scand. 1994, 89, 31–35.

40. Morreale, M.; Marchione, P.; Giacomini, P.; Pontecorvo, S.; Marianetti, M.; Vento, C.; Tinelli, E.; Francia, A. Neurological involvement in primary Sjögren syndrome: A focus on central nervous system. PLoS ONE 2014, 9, e84605.
41. Koçer, B.; Tezcan, M.E.; Batur, H.Z.; Haznedaroğlu, Ş.; Göker, B.; İrkeç, C.; Çetinkaya, R. Cognition, depression, fatigue, and quality of life in primary Sjögren’s syndrome: Correlations. Brain Behav. 2016, 6, e00586.
42. Caselli, R.J.; Boeve, B.F.; Scheithauer, B.W.; O’Duffy, J.D.; Hunder, G.G. Nonvasculitic Autoimmune inflammatory meningoencephalitis (NAIM): A reversible form of encephalopathy. Neurology 1999, 53, 1579–1581.
43. Liliang, P.C.; Liang, C.L.; Lu, K.; Yang, S.N.; Hsieh, M.T.; Tai, Y.C.; Wang, K.W. Population-based study suggests an increased risk of Alzheimer’s disease in Sjögren’s syndrome. Clin. Rheumatol. 2018, 37, 935–941.
44. Chen, H.H.; Perng, W.T.; Chiou, J.Y.; Wang, Y.H.; Huang, J.Y.; Wei, J.C.C. Risk of dementia among patients with Sjogren’s syndrome: A nationwide population-based cohort study in Taiwan. Semin. Arthritis Rheum. 2019, 48, 895–899.
45. Shahmohammadi, S.; Doosti, R.; Shahmohammadi, A.; Mohammadianinejad, S.E.; Sahraian, M.A.; Azimi, A.R.; Harirchian, M.H.; Asgari, N.; Naser Moghadasi, A. Autoimmune diseases associated with neuromyelitis optica spectrum disorders: A literature review. Mult. Scler. Relat. Disord. 2019, 27, 350–363.
46. Tetsuka, S.; Suzuki, T.; Ogawa, T.; Hashimoto, R.; Katoa, H. Anti-Ro/SSA antibodies may be responsible for cerebellar degeneration in Sjogren’s syndrome. J. Clin. Med. Res. 2021, 13, 113–120.