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The Clinical Characteristics of Primary Sjogren's Syndrome With Neuromyelitis Optica Spectrum Disorder in China

A STROBE-Compliant Article

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Abstract: The aim of the present study was to analyze the clinical characteristics of primary Sjogren's syndrome (pSS) with neuromyelitis optica spectrum disorder (NMOSD). We retrospectively reviewed the medical records of 616 patients who were admitted to the Peking Union Medical College Hospital from 1985 to 2013. Of these patients, 43 developed NMOSD. The median duration of symptoms was 60 months and 72% of the patients experienced neurological complications onset in the pSS with NMOSD group. Twenty-one out of 43 patients had neuromyelitis optica (NMO), and 22 exhibited a limited form of NMO. Serum anti-aquaporin-4 (AQP4) antibody positivity was detected in 89.3% of the patients. A total of 60.5% of the patients (26 patients) complained of dry mouth, 72.1% were positive for objective xerostomia, 53.5% complained of dry eyes, and 74.4% had a positive ocular test. Biopsy of the minor salivary glands was performed in 33 patients, 28 of whom (84.8%) had a lymphocytic focus score of $\geq$1. Anti-Ro/SSA or anti-La/SSB antibodies were detected in 41 patients (95.3%). Compared with the pSS patients without NMOSD, the incidences of xerophthalmia, xerostomia, arthritis, interstitial lung disease, and renal tubular acidosis were significantly lower in the patients with NMOSD.

NMOSD is a neurologic complication of pSS. The presence of anti-AQP4 antibody may be a predictor for pSS patients with NMOSD. Neurological manifestations are prominent in these patients. In clinical scenarios involving pSS or NMOSD, rheumatologists and neurologists should be aware of this association and perform the appropriate tests.

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Abbreviations: ACA = anti-centromere antibody, ANA = antinuclear antibody, AQP4 = aquaporin-4, AQP5 = aquaporin-5, CNS = central nervous system, CSF = cerebrospinal fluid, LETM = longitudinal extensive transverse myelitis, MRI = magnetic resonance imaging, NMO = neuromyelitis optica, NMOSD = neuromyelitis optica spectrum disorder, ON = optic neuritis, pSS = primary Sjogren's syndrome.

INTRODUCTION

Primary Sjogren's syndrome (pSS) is a chronic systemic autoimmune disease that is characterized by exocrine involvement.[1] Approximately 20% to 25%[2,3] of patients also have neurological manifestations, but the exact prevalence of central nervous system (CNS) involvement remains controversial. Neuromyelitis optica (NMO), also known as Devic's syndrome, is a severely disabling CNS disorder that is thought to have an autoimmune etiology and predominantly affects the optic nerves and spinal cord.[4] However, NMO is now recognized as a spectrum disease that affects other regions of the CNS and includes more diverse clinical presentations because of the identification of a disease-specific autoantibody against aquaporin-4 (AQP4).[5] With increased numbers of emerging pSS patients with neuromyelitis optica spectrum disorder (NMOSD) cases reports,[6–8] studies of large Chinese populations have been rare. The aim of the present study was to assess the clinical characteristics, seroimmunological correlations, and risk factors for pSS with NMOSD in a Chinese cohort at a single center. To our knowledge, this is the largest pSS patients with NMOSD cohort in the literature.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the clinical charts of 616 Chinese patients who were diagnosed with pSS and admitted to Peking Union Medical College Hospital (PUMCH) in Beijing, China, between January 1985 and December 2013, as shown in Figure 1. The diagnosis of pSS was based on the revised version of the diagnostic criteria of the American-European Consensus Group.[9] Clinical symptoms of sicca complex, including dry mouth, recurrent parotid enlargement, and rampant caries, were evaluated. Ocular involvement was documented by the Schirmer test or the Rose Bengal score.[10] Objective xerostomia was confirmed by an abnormal salivary scintigraphy[11] or unstimulated salivary flow. Biopsy samples of the minor salivary glands with lymphocytic focus scores of at least 1 were considered suggestive of Sjogren's syndrome.[12] Screening for autoantibodies to Ro/SSA and La/SSB was systematically performed by Ouchterlony double-gel immunodiffusion and in some cases by Western blotting. All tests were performed at the clinical rheumatology immunology laboratory at PUMCH.

Of the 616 pSS patients, 43 were identified as having NMOSD during the study period. Patients were considered to have NMO/NMOSD simultaneously if they fulfilled the

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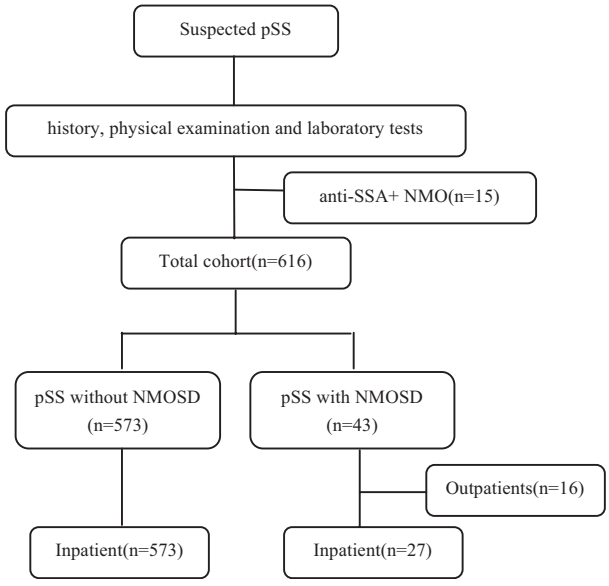

FIGURE 1. Inclusion and exclusion criteria.

Wingerchuk criteria[5,13] (Figure 2). Longitudinal extensive transverse myelitis (LETM) was defined as T2 enhancement on spinal magnetic resonance imaging (MRI) in 3 or more contiguous vertebral segments. Optic neuritis (ON) was diagnosed by a board-certified neurologist or neuro-ophthalmologist. Depending on the clinical findings, patients with NMOSD underwent brain or spinal MRI and cerebrospinal fluid (CSF) assessment. Indirect immunofluorescence analysis was performed to detect anti-AQP4 antibody at the PUMCH clinical neuroimmunological laboratory. Transfection of HEK-293 cells with AQP4 was performed as originally reported by Lennon et al.[14,15] We selected the remaining pSS patients without NMOSD as controls. Extraglandular manifestations other than neurologic involvement were also recorded for all patients. A comparison of the clinical features of the pSS patients with and without NMOSD was performed. The institutional review board of PUMCH approved this study. The requirement for written informed consent was waived because this study was retrospective and only involved the review of records.

Statistical Analysis

Statistical analysis was performed using SPSS statistical package version 18.0 (IBM, Armonk, NY). Categorical data are presented as numbers (percentages), and continuous variables are presented as the mean and standard deviation (SD) or the median and interquartile range, depending on the type of distribution. The chi-square and Fisher's exact tests were used to analyze categorical variables, and the independent samples *t* test was used to compare quantitative data between the groups. *P* values of <0.05 were considered to be statistically significant.

RESULTS

Demographic Characteristics

A total of 43 pSS patients were identified with NMOSD between January 1985 and December 2013. There were 38 females (88.4%) and 5 males (11.6%), corresponding to a ratio of 7.6 to 1. The mean age at onset of disease was 35.3 ± 12.2 years (range 14–69 years), and the median duration of symptoms before diagnosis was 60.2 months (range 1–252 months). Neurologic complications were the first symptoms in 31 patients (72.1%) in the pSS with NMOSD group. Only 12 patients (27.9%) exhibited sicca symptoms before the onset of neurologic manifestations.

Glandular Features

Of the 43 patients, 26 (60.5%) developed dry mouth, 10 had rampant caries, and 3 presented with recurrent parotid enlargement. A total of 31 patients (72.1%) were positive for objective xerostomia. Twenty-three patients (53.5%) complained of dry eyes, and 32 (74.4%) had a positive ocular test result. Biopsy of the minor salivary glands was performed in 33 patients, and 28 (84.8%) had a lymphocytic focus score of 1 or more. Anti-Ro/SSA or anti-La/SSB antibodies were detected in 41 patients (95.3%).

Neurological Findings

Of the 43 pSS patients with NMOSD, 32 (74.4%) had optic nerve involvement including visual loss (29 patients, 67.4%), visual field defects (13 patients, 30.2%), or diplopia (3 patients, 7.0%). Spinal cord involvement was identified in 36 patients (83.7%), 32 (74.4%) of whom had LETM. Peripheral nervous

NMO[9*]	NMOSD[5**]
1.ON	1.NMO
2.Acute myelitis	2.Limited forms of NMO
3.Two of three supportive criteria	a. single or recurrent events of LETM
a. Contiguous spinal cord MRI lesion extending over≥3 vertebral segments	b. Recurrent or simultaneous bilateral ON
b. Brain MRI not meeting diagnostic criteria for MS	3.Asian optic-spinal MS
c. NMO-IgG seropositive status	4.ON or LETM associated with systemic autoimmune disease
	5.ON or myelitis associated with brain lesions typical of NMO (hypothalamic, corpus callosal, periventricular, or brainstem)

FIGURE 2. Definitions of NMO and NMOSD. ∗To be diagnosed, a patient needs to fulfill the first 2 criteria and 2 out of 3 of the supporting criteria. ∗∗Any of the 5 clinical scenarios listed are indicative of NMOSD. LETM = longitudinal extensive transverse myelitis; MS = multiple sclerosis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis.

system involvement was noted in 5 patients (11.6%). The median time between visual and spinal cord involvement was 5.5 months, and 14 patients (32.6%) had both visual and spinal cord manifestations within 1 year. Upon referral to our hospital, there were 21 patients (48.8%) with NMO and 22 (51.2%) with limited forms of NMO (idiopathic single or recurrent events of LETM, 11 patients, 25.6%; recurrent or simultaneous bilateral ON, 11 patients, 25.6%). A comparison of the clinical characteristics among the 3 groups is shown in Table 1. Eleven patients were experiencing their first NMOSD attack, whereas 32 (74.4%) cases involved a recurrent course (range of 1–6 recurrences).

Brain and spinal MRI were performed for all patients. Brain lesions were found in 19 patients, with the areas surrounding the third and fourth ventricles being more frequently involved. A brain stem lesion was noted in 11 patients (25.6%). The spinal cord lesions were predominantly located in the cervical (29 patients, 67.4%) and thoracic cords (27 patients, 62.8%) (Figure 3). Thirty-four patients underwent lumbar puncture. The CSF pressure was 135.9 ± 50.8 mm H_2O (range 75–210 mm H_2O), and it was elevated in 6 patients and depressed in 4. The CSF protein level in these patients was 0.61 g/L (range 0.25–2.13 g/L), and an elevated protein level was noted in 21 patients (61.8%). Activated lymphocytes were found in 10/34 patient samples (29.4%). CSF oligoclonal bands were identified in 12/34 (35.3%) patient sample.

A total of 25/28 patients (89.3%) were positive for serum anti-AQP4 antibody. In addition, this antibody was detected in the CSF of 8/9 seropositive patients (88.9%), and it was not detected in the sera or CSF of 3 patients.

Extraglandular Manifestations Other Than Neurologic Involvement

Among the 43 pSS patients with NMOSD, 9 (20.9%) had arthritis, 5 patients (11.6%) had interstitial lung disease, and 3 (7.0%) had purpura. Extraglandular manifestations also included Raynaud's phenomenon (1 patient, 2.3%), myositis (1 patient, 2.3%), and renal tubular acidosis (1 patient, 2.3%).

Comparison of Clinical Features Between pSS Patients With and Without NMOSD

A total of 573 pSS patients without NMOSD were selected as controls. The clinical features were compared between the pSS patients with and without NMOSD (Table 2). Significant differences were found for dry mouth ($P < 0.001$), dry eyes ($P = 0.024$), recurrent parotid enlargement ($P = 0.003$), rampant caries ($P = 0.002$), objective xerostomia ($P < 0.001$), positive ocular test ($P < 0.001$), Raynaud's phenomenon ($P = 0.009$), arthritis ($P = 0.001$), interstitial lung disease ($P < 0.05$), and renal tubular acidosis ($P < 0.05$). There were no significant differences in gender or the duration of symptoms between the 2 groups.

DISCUSSION

pSS is a systemic autoimmune disease that typically presents with xerophthalmia and xerostomia. Generalized exocrine dysfunction is also typical. Neurological involvement associated with pSS is classified as peripheral nervous system or CNS involvement, but the particular CNS manifestations are still under debate. NMOSD is an inflammatory demyelinating spectrum disorder of the CNS that is characterized by severe attacks of ON and myelitis. In 10% to 40% of patients, this condition is complicated by an autoimmune disease, such as thyroiditis, systemic lupus erythematosus, or pSS[5]. Few studies have attempted to address the relationship between pSS and NMOSD.

Discriminating between pSS and NMOSD is difficult because sicca symptoms can occur after the onset of neurological symptoms. Alhomoud et al[16] have reported that up to 33% of patients who present with pSS with CNS involvement lack sicca symptoms at the time of presentation but that they eventually develop these symptoms over a 5-year follow-up period. In our cohort, neurological manifestations preceded the sicca symptoms in 72.1% of the patients, which is consistent with the findings of other studies.[17–19] This delay in symptoms may lead to the underestimation of the prevalence of pSS in patients with NMOSD. Neurological manifestations were prominent in our study, whereas the frequency of other organ

TABLE 1. Demographic and Clinical Features of pSS Patients With NMOSD

Characteristics	NMO (n = 21)	LETM (n = 11)	RON/BON (n = 11)
Female/male	19/2	9/2	10/1
Average age of diagnosis, y	39.1	44.7	37.1
Duration, mo, median	24	36	36
Dry mouth	10	7	9
Dry eyes	12	5	6
Objective xerostomia*	15	9	7
Positive ocular tests*	16	9	7
Anti-SSA antibodies positive	21	11	9
Anti-SSB antibodies positive	4	3	3
Positive salivary gland biopsy*	13/16	6/7	9/10
Hyperglobulinemia	4	2	0
Extraglandular involvement	10	6	3
CSF-protein, g/L, mean	0.66	0.57	0.44
Anti-AQP4 antibody positive	11/12	4/6	9/9

AQP4 = aquapotin-4; CSF = cerebrospinal fluid; LETM = longitudinal extensive transverse myelitis; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; pSS = primary Sjogren's syndrome; RON/BON = recurrent or simultaneous bilateral optic neuritis.
* Positivity defined according to Vitali et al criteria.[9]

TABLE 2. Clinical Manifestations Between pSS Patients With and Without NMOSD

Characteristics	pSS With NMOSD (n = 43)	pSS Without NMOSD (n = 573)	*P* Value
Female	38 (88.4)	524 (91.4)	0.491
Average age of diagnosis, y*	40.1	49.7	<0.001
Duration, mo, median	36	48	0.258
Dry mouth*	26 (60.5)	484 (84.5)	<0.001
Dry eyes*	23 (53.5)	401 (70.0)	<0.05
Recurrent Parotid enlargement*	3 (7.0)	160 (27.9)	<0.05
Rampant caries*	10 (23.3)	272 (47.5)	<0.05
Objective xerostomia*	31 (72.1)	501/545 (91.9)	<0.001
Positive ocular tests*	32 (74.4)	494/521 (94.8)	<0.001
Positive salivary gland biopsy	28/33 (84.8)	303/334 (90.7)	0.279
ANA positive	37 (86.0)	474/565 (83.9)	0.710
Anti-Ro/SSA positive*	41 (95.3)	474/568 (83.5)	<0.05
Anti-La/SSB positive*	10 (23.3)	231/568 (40.7)	<0.05
Lymphoadenopathy	0 (0.0)	44 (7.7)	0.059
Purpura	3 (7.0)	77 (13.4)	0.224
Raynaud's phenomenon*	1 (2.3)	101 (17.6)	<0.05
Arthritis*	9 (20.9)	274 (47.8)	<0.05
Myositis	1 (2.3)	28 (4.9)	0.444
Interstitial lung disease*	5 (11.6)	116/500 (23.3)	<0.05
Renal tubular acidosis*	1 (2.3)	96 (16.8)	<0.05
Autoimmune thyroiditis	5/21 (23.8)	74/226 (32.7)	0.401
ACA-positive*	1 (2.3)	41/185 (22.2)	<0.05
IgG >20 g/L*	2 (4.7)	330/539 (61.2)	<0.001

ACA = anti-centromere antibody; ANA = antinuclear antibody; NMOSD = neuromyelitis optica spectrum disorder; pSS = primary Sjogren's syndrome.

* All values are n (%) $P < 0.05$.

lesions was low. Accurate diagnosis and management requires a thorough history, physical examination, and laboratory tests, and careful clinical follow-up is recommended.

NMO-IgG is a disease-specific autoantibody for NMO[14]. The NMO antigen is AQP4, which is the predominant water channel protein that is expressed on astrocytes in the CNS[15]. Carvalho DC[19] reviewed 37 cases of pSS patients with NMOSD whose anti-AQP4 antibody serostatus was informed, and showed that it was positive in 32 cases (86.5%). Similarly, 89.3% of the pSS patients with NMOSD were positive for serum anti-AQP4 antibody in our series. CSF positivity for anti-AQP4 antibody was found in 88.9% of the seropositive patients. We also tested 20 patients who had been diagnosed with pSS without NMOSD during the same period, none of whom were positive for this antibody. These findings suggest that anti-AQP4 antibody is also an important marker for pSS patients with NMOSD with a relatively high specificity and sensitivity of detection. Moreover, this marker can be detected in patients with NMOSD in the early stages of the disease who are undetectable by MRI.[20] Thus, the anti-AQP4 antibody may be a predictor of the occurrence of pSS with NMOSD. Park et al[21] have reported that the frequency of anti-AQP4 antibody positivity is significantly higher in anti-Ro/SSA antibody-positive patients with NMOSD than in anti-Ro/SSA antibody-negative patients (90% vs 32.6%, $P < 0.001$). In our experience, anti-Ro/SSA antibody positivity is also closely related to systemic autoimmune diseases, especially pSS. However, we found anti-AQP4 antibody positivity rates of 88% and 100% for the anti-Ro/SSA-positive and anti-Ro/SSA-negative patients, respectively ($P = 0.145$). This discrepancy is likely because of differences in subjects and the limited number of anti-Ro/SSA negative pSS-NMOSD patients in this study (2 patients).

pSS is characterized by mononuclear infiltration and the destruction of salivary and lachrymal glands. Similarly, invasion of visceral organs or vasculitic lesions by mononuclear infiltrates can lead to extraglandular manifestations. However, the precise pathogenesis pSS patients with NMOSD remain unclear. The co-association could be due to common genetic and/or environmental factors that cause a predisposition to autoimmunity. Javed[22] confirmed that 20 NMOSD patients who underwent minor salivary gland biopsy all had evidence of minor salivary gland inflammation. Moreover, a positive labial biopsy is common in pSS patients. In addition, inflammatory lesions in NMO occur in areas with high levels of AQP4 expression, such as the spinal cord and optic nerves.[23] AQP4 is expressed at low levels in the salivary glands, whereas anti-aquaporin-5 (AQP5) is expressed at high levels and plays a major role in salivary gland secretion.[24] The protein sequence identity between AQP4 and AQP5 is approximately 50%.[25] A subset of autoreactive immune cells recognize homologous portions of AQP4 and AQP5, thereby causing inflammation in both the CNS and salivary glands, suggesting a common pathophysiological mechanism between pSS and NMOSD.

To our knowledge, no studies have directly evaluated the optimal therapy for pSS patients with NMOSD. Previous data on the risk of relapse of NMO patients with AQP4 autoantibody positivity have led us to recommend immunosuppressive therapy because of the association with visual impairment and the high risk (>60%) of neurological relapse within 1 year.[26,27] Responders to corticosteroid pulse therapy are more commonly positive for anti-AQP4 antibody than nonresponders.[28]

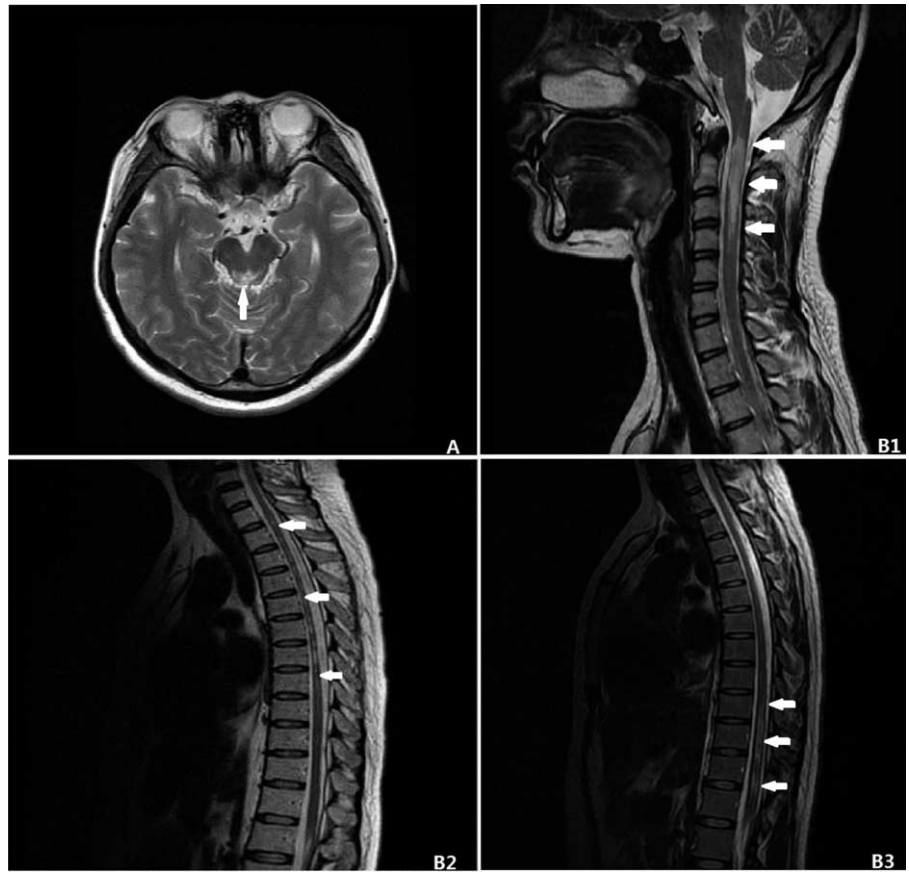

FIGURE 3. Representative cerebral and spinal cord MRI images of 4 pSS patients with NMOSD. (A) Abnormal T2-weighted signal at the midbrain. (B) Sagittal T2-weighted spinal cord MRI showing a high signal intensity long cord lesion; (B1) cervical 1–4, (B2) thoracic 1–8, and (B3) thoracic 10-lumbar1. MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder.

Currently, corticosteroid pulse therapy for early induction and the use of an immunosuppressant (such as cyclophosphamide, azathioprine) for maintenance are recommended. Rituximab and tocilizumab have also demonstrated sustained clinical efficacy in treatment-resistant patients.[29,30] In patients with relapsing disease, lifelong therapy should be considered.[31] However, the standard for the management of pSS patients with NMOSD awaits long-term observation.

Because of the retrospective nature of this study, our results may have been affected by selection bias. The proportion of NMOSD patients in the pSS group is higher compared with previous reports. PUMCH is a university-based hospital and referral center for complicated patients nationwide, and our neurologic department specializes in inflammatory disorders (eg, multiple sclerosis, ON, myelopathy). In addition, the ratio of renal and pulmonary involvement was relatively high in the control group, which may have been because the control group patients were all inpatients, suggesting the presence of relatively severe disease.

In conclusion, NMOSD is a neurologic complication of pSS, and these 2 conditions may share a common pathophysiological mechanism. pSS patients with NMOSD have a distinctive clinical profile that is characterized by relatively severe neurological involvement and mild xerophthalmia, xerostomia, and other extraglandular manifestations. The presence of anti-AQP4 antibody may be a predictor for these patients. Rheumatologists and neurologists should be aware of this association and perform appropriate tests. The early diagnosis of pSS with NMOSD is important for choosing suitable therapies and improving patient prognosis.

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