NEUROLOGICAL MANIFESTATIONS OF PRIMARY SJOGREN'S SYNDROME (PSS)

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ABSTRACT

Objective: To determine prevalence, clinical patterns and outcomes of neurological involvement in a cohort of primary sjogren's syndrome (PSS) patients presenting to a tertiary care hospital.

Study Design: Observational retrospective cross-sectional case-control study.

Place and Duration of Study: This study was carried out at Neurology department of Pak Emirates Military Hospital, Rawalpindi, from May 2015 to Jun 2016.

Patients and Methods: All patients fulfilling American College of Rheumatology (ACR) criteria of PSS and having neurological involvement, who were admitted in Neurology wards from May 2015 to June 2016, were included in the study. Demographic, clinical and seroimmunological data of the patients was documented.

Results: A total of 26 patients with PSS had some degree of neurological involvement. Mean age was 40.50 years. (SD 14.803, min 22, max 78). Fifteen patients were female and 11 were male. Sicca symptoms (ocular and oral dryness) were present in 38.5%. Serological marker anti Ro and La were present in 76.9% and 42.3% respectively while both Ro and La were present in 34.6%. Lip biopsy was diagnostic in 80.8% and schirmer test was positive in 46.2%. Refractory headache was present in 84.6%. Seizures occurred in 34.6%, which were focal in 23.1% and generalized in 11.5%. Trigeminal neuralgia was present in 26.9%, multiple cranial nerve palsies in 15.4% and recurrent facial nerve palsies in 11.5%. Optic neuritis was seen in 19.2%. Clinical presentation mimicking relapsing and remitting multiple sclerosis was seen in 30.8% of patients among whom 61.5% also met revised McDonald criteria for dissemination in space (DIS) on MRI and 23.1% met criteria for dissemination in time. MRI brain showed cortical lesions in 42.3%. Longitudinally extensive transverse myelitis involving cervical and upper thoracic cords was present in 26.9% of patients.

Conclusion: The diagnosis of neuro-sjogren's syndrome (NSS) can be difficult in the absence of sicca symptoms especially when neurological manifestations precede sicca symptoms by many years. This requires a high index of clinical suspicion and low threshold for investigations like lip biopsy and autoantibody profile for the diagnosis. This study highlights the need to revise the overemphasis of sicca symptoms in various current diagnostic criteria in order to improve early recognition and initiation of treatment.

Keywords: Central Nervous System (CNS), Intracranial Hypertension (ICH), Neuro-Sjogren's syndrome (NSS), Peripheral Nervous System (PNS).

INTRODUCTION

Sjogren's syndrome affects the nervous system in approximately twenty percent of the cases[1,2]. Neurological symptoms may precede years before the onset of dry eyes and dry mouth (sicca symptoms) in 25-92%[3,4], in such cases, the first presentation is often to a neurologist. A little is known about the central nervous system (CNS) manifestations of PSS, as most of the studies have focused on peripheral nervous system (PNS) disease. We will share our experience of CNS manifestations of Sjogren's syndrome which will help neurologists in recognizing these manifestations very early in the course of disease, starting appropriate treatment and preventing severe morbidity and mortality.

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Received: 21 Dec 2017; revised received: 19 Mar 2018; accepted: 28 Mar 2018

PATIENTS AND METHODS

We performed a retrospective review of 26 patients in the inpatient services of neuro-

logy department of Pak Emirates Military Hospital Rawalpindi as having primary Sjogren's syndrome (PSS) between May 2015 and June 2016. All patients fulfilling American college of rheumatology (ACR) criteria of PSS 2012[5] were included with positive serum anti-Ro/SSA and/ or anti-La/SSB antibody testing and presence of focal lymphocytic sialadenitis with a focus score ≥1 focus/4mm^2 (lymphocytic foci containing more than 50 cells/mm^2 labial salivary gland biopsy samples). Complete autoimmune serological marker panel including anti-Ro and La, lip biopsy, schirmer test, cerebrospinal fluid pressure, oligo clonal bands analysis and MRI brain with contrast was performed on all patients. Magnetic resonance imaging (MRI) cervical spine with contrast and visual evoked potentials (VEP's) were done when clinically indicated.

RESULTS

A total of 26 patients with PSS had neurological involvement. Mean age was 40.50 years. (SD 14.803, min 22, max 78), 57.7 %(n=15) were females and 42.3% (n=11) were males. None of the studied patients complained of sicca symptoms but on direct questioning, sicca symptoms (ocular and oral dryness) were present in 38.5%. Serological markers anti Ro and anti La were present in 76.9%and 42.3% respectively, both Ro and La were present in 34.6%. Lip biopsy was diagnostic in 80.8% and schirmer test was positive in 46.2%. The most common neurological symptom was refractory headache being present in 84.6% of patients. All patients underwent cerebrospinal fluid manometry in which 69.2% had intracranial hypertension. Mean CSF pressure was 256.15 (SD 76.529) and CSF oligo clonal bands were present in 61.5% indicating intrathecal synthesis. Seizures occurred in 34.6% which were focal in 23.1% and generalized in 11.5%. Trigeminal neuralgia was present in 26.9%, multiple cranial nerve palsies in 15.4% and recurrent facial nerve palsies in 11.5%. Optic neuritis was seen in 19.2% and prolonged VEPs were present in 26.9%. Clinical presentation mimicking relapsing and remitting multiple sclerosis (MS) was seen in 30.8% of patients in which 61.5% met revised McDonald criteria for dissemination in space (DIS) on MRI and 23.1% met criteria for dissemination in time (DIT), while 15.4% of patients fulfilled both DIS and DIT. MRI brain showed cortical lesions in 42.3%, generalized cerebral atrophy (GCA) in 30.8% and periventricular leucoaraiosis in 11.5%. Longitudinally extensive transverse myelitis involving cervical and upper thoracic cords was present in 26.9% of patients presenting with quadri/para paresis. We could not find any involvement of peripheral nervous system other than cranial nerve palsies. Keeping in view the debilitating and aggressive nature of Neurosjogren's syndrome (NSS), all patients received inpatient care. All patients were given methylprednisolone pulse therapy for five days then intermittently for 06 months (weekly for 8 weeks, twice monthly for two months and monthly for two months). Patients with optic neuritis, longitudinally extensive transverse myelitis, CNS vasculitis and status epilepticus underwent plasma exchange for five sessions and were also given 03 weekly cyclophosphamide 75g/m^2 of body surface area with a median cumulative dose of 7 to 10gms. After pulse cyclophosphamide therapy, the remission was maintained with azathioprine 2.5 to 3mg/kg/day, methotrexate 20-25gm/week or mycophenolate motefil 2gm daily depending upon patient's preference, affordability and tolerance. All patients also received prophylaxis for Pneumocystis Jirovici Pneumonia (PJP). Patients found to be having latent tuberculosis also received prophylactic anti tuberculous treatment (ATT). Out of all the patients who received immunosuppressive therapy, only two patients developed cytopenias requiring delay in dose of cyclophosphamide. None of the patients who received cyclophosphamide in our cohort developed hemorrhagic cystitis. All of the patients improved clinically, with no mortality in this cohort till the time of culmination of this study.

DISCUSSION

Primary Sjogren's syndrome (PSS) can have central nervous system (CNS) as well as peripheral nervous system (PNS) manifestations[6]. The prevalence of neurological manifestations ranges between zero and 70%[7]. This wide variation is likely due to the heterogeneity of the diagnostic criteria's as well the different hospitals where patients were managed. In a study by Lafitte *et al*[8] in which he studied neurological involvement in Sjogren patients, overall 40% of patients had neurological manifestations. Classical Sicca symptoms may precede neurological manifestations in 40 to 93% of cases[6]. NSS is an underdiagnosed condition in the subcontinent as physicians and neurologists here are not familiar with its clinical presentations. It is also falsely believed that sjogren syndrome is a disease of western population. Yadav *et al*[9] reported a series of six patients with NSS from a tertiary care hospital in india discussing neurological manifestation of sjogren syndrome. In their study all of the patients had only PNS disease contrary to our observation of CNS involvement in almost all our patients. NSS is a difficult entity to diagnose because, firstly there are no diagnostic criteria and secondly young patients with CNS involvement usually do not manifest sicca symptoms. It is imperative that we are aware of its manifestations so that we are able to recognize and start appropriate treatment very early in the course of disease thereby preventing dreadful outcomes. We observed that certain patients with central nervous system involvement turned out to have positive serology for sjogren syndrome but were without anysymptoms of dry eyes or mouth. We performed a lip biopsy of these patients which, to our surprise, was positive with lymphocytic infiltrate. The American college of rheumatology approved a new set of criteria[5] for Sjogren's syndrome (SS) emphasizing the importance of objective evidence of glandular involvement using specific autoantibody positivity, ocular staining scores, and histological evidence of minor salivary gland.

- SS requires at least two of the following three findings:

Table: Clinical and seroimmunological characteristic of PSS patients having neurological manifestations.

Clinical & Seroimmunological Characteristic		Present	Absent
Sicca symptoms (On direct questioning)		38.5% (n=10)	61.5% (n=16)
Refractory headache		84.6% (n=22)	15.4% (n=4)
Seizure		34.6% (n=9)	65.4% (n=17)
Trigeminal Neuralgia		26.9% (n=7)	73.1% (n=19)
Optic Neuritis		19.2% (n=5)	80.8% (n=21)
Intracranial hypertension		69.2% (n=18)	30.8% (n=8)
Mimicking MS		30.8% (n=8)	69.2% (n=18)
Prolonged VEP's		26.9% (n=7)	73.1% (n=19)
CSF Oligoclonal band		61.5% (n=16)	38.5% (n=10)
MRI findings	Cortical Lesions	42.3% (n=11)	57.7% (n=15)
	Generalized Cerebral Atrophy	30.8% (n=8)	69.2% (n=18)
	Periventricular Leucoaraisosis	11.5% (n=3)	88.5% (n=23)
Anti Ro		76.9% (n=20)	23.1% (n=6)
Anti La		42.3% (n=11)	57.7% (n=15)
Both anti Ro & anti La		34.6% (n=9)	65.4% (n=17)
Diagnostic Lip biopsy		80.8% (n=21)	19.2% (n=5)
Schirmer Test (Positive)		46.2% (n=12)	53.8% (n=14)

1. Positive serum anti-Ro/SSA and/or anti-La/SSB antibody testing OR a positive rheumatoid factor and an antinuclear antibody (ANA) titer ≥1:320
2. Ocular staining score ≥3 (Provided the individual is not concurrently using daily eye drops)
3. Presence of focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm^2 in labial salivary gland biopsy samples[10].

Using the above criteria we classified patients as having neuro-sjogren syndrome (NSS) if the patient had neurological involvement with positive serological test plus positive lip biopsy. The most common clinical manifestation of NSS was headache in our cohort., Escudero *et al* also reported that headache was the major CNS presentation in NSS in their study[11]. Focal encephalic involvement is the main pathological CNS manifestation in NSS. These focal disorders can include motor and sensory loss with hemiparesis, aphasia, dysarthria, seizures, movement disorders, and cerebellar syndrome. The most common focal presentation in our patients was seizures which occurred in 34.6% of our patients. One patient also developed refractory status epilepticus requiring ventilator support. Clinical presentation of focal neurological deficitscan be acute, insidious or recurring resembling multiple sclerosis. It's important to mention here that cortical lesions present in NSS which are not very common in multiple sclerosis[12]. Neuro myelitis optica spectrum disorders (NMOSD) and NSS associated optic neuritis and myelitis clearly share many features in common. It's not clear whether they are associated or their co-occurrence is only by chance. Alexander *et al*[13] reported seven cases of retro bulbar optic neuropathy in NSS patients. In our study optic neuritis was seen in 19.2% of patients and prolonged VEPs were present in 26.9% suggesting asymptomatic episodes of previous optic neuritis. Longitudinally extensive transverse myelitis involving more than three vertebral segments was seen in 26.9%. Other spinal cord disorders documented in literature in NSS include chronic progressive myelopathies, lower motor neuron disease, or neurogenic bladder[14]. CNS involvement can also be diffuse presenting with encephalopathy, cognitive dysfunction, dementia, psychiatric abnormalities, and aseptic meningoencephalitis[15]. Lafitte *et al*. reported 8 cases from 36 patients of NSS patients with cognitive dysfunction, characterized by frontal lobe dysfunction, impairment attention and intellectual deterioration. Cognitive impartment is not correlated with CSF abnormalities or MRI findings[16]. Peripheral neuropathy is the most common peripheral neurological complication of NSS. It can be present among 20 to 50% of patients as revealed by electrophysiological study[17] but when demonstrated clinically, it ranges from 10 to 32%[18]. In 1962, Kaltreider and Talal *et al*[19] described, for the first time, the prevalence of neurological involvement in NSS. In this series, 8.3% of 109 patients presented with neuropathies. PNS disease includes axonal polyneuropathies (distal axonal sensory and sensorimotor), neuropathies, mononeuropathies, cranial nerves involvement (mainly trigeminal neuropathy), and autonomic system involvement. Axonal polyneuropathies were the commonest manifestations of PNS involvement found in 50% of Sjogren syndrome cases in one study[20]. Our findings of PNS were restricted to cranial nerve involvement and trigeminal neuralgia. Treatment options for NSS are limited by varied response to different treatment options as they are largely based on case reports and expert opinion[21]. Acute myelopathies and vasculitic neuropathies should be treated with intravenous glucocorticoids, plasma exchange and cyclophosphamide as partial to complete recovery may be expected. Specific cyclophosphamide regimens range between 6 and 24 months of monthly pulses, depending on response to treatment. We treated with three weekly pulse therapies for total of 7 to 10gms as remission induction borrowed from rheumatologists' experience in treating systemic lupus

erythematosus. All our patients had severe organ-threatening disease but they showed good response to early, aggressive, high-dose corticosteroids combined with plasma exchange, followed by cyclophosphamide. Other therapeutic options that have been shown to be beneficial are azathioprine and methotrexate. Finally, rituximab appears promising as a recent therapeutic breakthrough, but its overall benefit is yet to be substantiated[22]. A limitation of our study was the lack of data on the prevalence of NSS and its neurologic complications at our center, small sample size and patient selection bias as these may not represent actual prevalence. Despite this our case series raises important issues about difficulty in diagnosing NSS in Pakistani patients who present with complex neurological issues and positive serology and biopsy fulfilling the diagnostic criteria.

CONCLUSION

Neuro-sjogren's syndrome (NSS) with its diverse clinical laboratory and radiological manifestations can become a diagnostic challenge in the absence of sicca symptoms. Neurological manifestations often precede sicca symptoms by many years. This warrants a high index of clinical suspicion and a low threshold for investigations with lip biopsy and autoantibody profile for the diagnosis and early initiation of appropriate treatment to prevent morbidity and mortality.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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