CASE REPORT

Bilateral Internuclear Ophthalmoplegia as a Presenting Manifestation of Primary Sjögren's Syndrome

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ABSTRACT

Bilateral internuclear ophthalmoplegia has been linked with various pathological conditions of the central nervous system (CNS), such as multiple sclerosis, stroke, tumours, and brainstem inflammatory processes. Herein the authors report a case of a 45-year-old female patient who presented with diplopia due to bilateral internuclear ophthalmoplegia, with no evidence of brainstem lesion in brain magnetic resonance imaging (MRI) and was diagnosed with primary Sjögren's syndrome.

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease that usually affects salivary and lacrimal glands with a variety of neurological manifestations. Both peripheral and central nervous system (CNS) symptoms have been reported in the setting of pSS with various clinical presentations, making the diagnosis very difficult. Our patient presented with subacute diplopia due to bilateral internuclear ophthalmoplegia (INO). Unilateral INO has been rarely reported as a CNS symptom of pSS,^{1,2} and as far as we know, this is the first report of bilateral INO as the presenting symptom of pSS.

Case report

A 45-year-old female presented to the emergency department with diplopia that started insidiously 1 month prior to admission. Her previous medical history was remarkable only for multiple episodes of inflammation of the right parotid gland 7 years ago.

On clinical examination, her visual acuity was intact and her pupils were equal with normal pupillary reflexes. Eye movement testing revealed asymmetrical bilateral internuclear ophthalmoplegia. On left

lateral gaze, her right eye had impaired adduction and the left eye presented horizontal nystagmus. Similarly on right lateral gaze, her left eye had impaired adduction, although less obvious than in the other side, and her right eye presented horizontal nystagmus, whereas convergence was preserved. The rest of the neurological examination was normal.

Brain magnetic resonance imaging (MRI) scan showed a small demyelinating lesion in the subcortical white matter of the left frontal lobe (Figure 1A) and no signs of brainstem pathology (Figure 1B). MRI scan was performed on a 1.5-T scanner (GE GoldSeal Certified Signa HD 1.5T). Axial, coronal, and sagittal cuts were taken with slice thickness of 5, 3, and 1.4 mm, before and after gadolinium administration, and no focal lesion was detected.

Magnetic resonance angiography (MRA) of the brain, visual and somatosensory evoked potentials, cardiac ultrasound, and Holter monitoring were found normal, and cerebrospinal fluid (CSF) examination for viruses and oligoclonal bands was negative. Immunological blood tests were positive for antinuclear antibody (ANA), anti-dsDNA, rheumatoid factor (RF; 28.2 IU/mL), and anti-SS-A (Ro) antibodies (184.72 U/mL). Furthermore, mildly increased erythrocyte sedimentation rate (ESR; 28 mm) and

Figure 1. (A) Axial FLAIR image showing one small high-signal lesion in the subcortical white matter of the left frontal lobe. (B) Axial T2-weighted image showing no evidence of brainstem pathology. (C) Axial T1-weighted post-gadolinium image showing no pathology of the upper pons.

chronic disease anaemia (haematocrit [Ht]: 36%, normal mean corpuscular volume [MCV] and mean corpuscular haemoglobin [MCH]) were found. Although there was no history of dryness of the eyes, a tear break-up time (TBUT) test was positive (<10 s) for xerophthalmia. The histological examination of the lower lip biopsy sample revealed a normal epidermis and within the dermis a minor accessory salivary gland, generally preserving its lobular architecture and presenting moderate to quite dense nodular or diffuse lymphoplasmacytic infiltrations. These amounted to >3 aggregates per lobule and >1 per 4 mm² (aggregate = approximately 50 inflammatory round cells), findings that were graded as Tarpley's class 2 and focus score (FS) >1. Immunostaining for CD45/Leukocyte Common Antigen (LCA) highlighted the lymphocytic infiltrate, whereas markers for CD38 and κ/λ light chains stained a moderate number of plasma cells with a ratio of $\kappa:\lambda = 4:1$. A small degree of focal fibrosis was also observed (Figure 2).

According to the revised classification criteria for Sjögren's syndrome (SS) proposed by the American-European Consensus Group,³ the diagnosis of primary Sjögren's syndrome was well established. A high-dose intravenous methylprednisolone course

for 5 days was administered, with partial improvement of the symptoms, and the patient was prompted to a rheumatologist for further evaluation.

Discussion

SS is a chronic systemic autoimmune disease characterised by lymphocytic infiltration of exocrine glands and frequent involvement of other organs and systems such as musculoskeletal system, lungs, kidneys, liver, and central and peripheral nervous systems. Depending on the absence or presence of other underlying autoimmune rheumatic disorders, it is called primary or secondary, respectively. The prevalence of SS in the general population ranges from 1% to 3%, with a female predominance (female to male ratio about 9:1)^{4–6} and a mean age of onset between 40 and 50 years.^{6,7}

The clinical hallmark of SS is the presence of sicca syndrome of the eyes (xerophthalmia—dryness of the eyes) and mouth (xerostomia—dryness of the mouth). Additional systemic clinical features are arthralgias, Raynaud's phenomenon, glomerulonephritis, primary biliary cirrhosis, dyspareunia, and neuropsychiatric symptoms.

Figure 2. Lymphocytic infiltrations in salivary gland biopsy with a focus score >1. (A) $\times 100$; (B) $\times 100$; (C) $\times 400$.

Peripheral nervous system involvement occurs in about 2–60% of the patients.⁸ Clinical manifestations include sensory axonal polyneuropathy, sensory ataxic neuropathy or sensory ganglionopathy, painful small fibre sensory neuropathy, axonal sensorimotor polyneuropathy, demyelinating polyradiculoneuropathy, mononeuropathy multiplex, and autonomic neuropathy,⁸ and could be attributed to mononuclear lymphocytic infiltration or an inflammatory vascular response in the dorsal root ganglia, peripheral nerve, or muscle.

CNS symptoms may precede the diagnosis of Sjögren's syndrome by up to 2 years in about 80% of patients,⁹ including focal, diffuse, and spinal symptoms.¹⁰ Among them, the most frequent are headache, movement disorders, seizures, myelopathy, aseptic meningitis, and cognitive dysfunction.^{4,10,11} The pathological processes causing the CNS involvement include mononuclear lymphocytic infiltration in the meninges or parenchyma, microinfarcts, or microhaemorrhages in brain parenchyma.

Alexander et al. described unilateral INO as a symptom of Sjögren's syndrome in one case series.² Additionally, a variety of neuro-ophthalmological manifestations have been reported in the setting of primary Sjögren's syndrome. The most common is binocular or less frequently monocular optic neuritis characterised by exceptional response to steroid or immunosuppressive treatment and high recurrence rate.^{12,13} Pathophysiological mechanisms of Sjögren's-related optic neuritis include immune-mediated small vessel vasculitis or even demyelination.¹⁴ Diplopia due to isolated oculomotor, abducens, or trochlear nerve palsy with favourable clinical course after steroid treatment have also been reported.¹⁴ Bilateral Adie tonic pupil due to autonomic failure^{15,16} and opsoclonus¹⁷ are rare neuro-ophthalmological features of pSS.

To our knowledge, bilateral INO has never been described among the CNS manifestations of Sjögren's syndrome. Interestingly, in our patient, brain MRI scan excluded brainstem lesions in the medial longitudinal fasciculus (MLF) region bilaterally. According to Bolanos et al., about 30% of the patients with unilateral or bilateral INO, in a 65-patient cohort, had no detectable lesions in the MLF region.¹⁸ A possible reason may be the very small size of lesions, making them practically undetectable

by the common MRI techniques. In conclusion, we can expand the phenotype of focal CNS involvement in pSS, adding bilateral INO in it.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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