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Neuromyelitis Optica Spectrum Disorder and Neurosyphilis Coexist in A Chinese Woman

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Abstract

Background: Neuromyelitisoptica spectrum disorder (NMOSD) is a series of central nervous system diseases with positive aquaporin-4 antibody. And neurosyphilis is a manifestation of the late syphilis. Although Neuromyelitisoptica (NMO) following syphilis has been previously reported, transverse myelitis and neurosyphilis in the same patient with positive aquaporin-4 antibody has never been mentioned.

Method: We presented the coexistence of NMOSD and syphilis in a 72-year-oldChinese woman and analyzed the relationship of these two diseases. The pertinent literatures were also reviewed.

Result: Previous studies showed that syphilitic myelitis might be more frequent in male than in female and it tended to be asymptomatic. However our case was a woman who experienced acute attack, with positive AQP4 antibody. Therefore, her myelitis occurrence mainly associated with AQP4 antibodies autoimmunity, and neurosyphilis might be an asymptomatic episode in our case. Although there was no evidence that treponema pallidum subspecies pallidum involved in the pathogenesis of NMO, it seemed that anti-syphilitic treatment was helpful to attenuate disability in our present case.

Conclusion: Anti-NMO and anti-syphilitic treatment should be used together to treat the patient with both NMOSD and neurosyphilis.

Keywords: Myelitis; Neuromyelitisoptica spectrum disorder; Neurosyphilis; Aquaporin-4

Introduction

Transverse myelitis (TM) is an inflammatory demyelinating disorder of the spinal cord that has various manifestations [1]. TM has several subtypes according to origin but, in China, most of them are associated with neuromyelitisoptica (NMO) and multiple sclerosis (MS) [1]. However, the exact etiologies of inflammatory demyelinating TM are unclear and the details of their pathogenesis are unknown. NMO immunoglobulin G (IgG), selectively targeting to the antigen of aquaporin-4 (AQP4) that localizes in the central nervous system (CNS) microvessels, pia, subpia, and Virchow-Robin space has been considered as an biomarker to some TM [2], which is defined as NMO spectrum disorder (NMOSD). Previous studies have revealed this autoantibody as an important contributor to TM pathology.

Viral or bacterial infections [3,4] may be prodromal factors of TM, commonly stimulating an inappropriate immune attack in spinal cord. On the other hand, many infections can induce direct neuronal invasion, resulting in spinal cord injury. Neurosyphilis has traditionally been divided into distinct syndromes. Sometimes, it involves in the spinal cord that may manifest itself as tabesdorsalis, meningomyelitis, spinal vascular syphilis, hypertrophic pachymeningitis, and even development of extramedullary location [5].

Although NMO following syphilis has been previously reported [6,7], TM and neurosyphilis in the same patient with positive AQP4 antibody has never been mentioned. We present the revelation of NMOSD in a 72-year-old Chinese woman and the pertinent literatures are reviewed.

Case Report

The patient was a 73-year-old Chinese woman, who developed TM in July, 2013. She experienced the severe attack with quadriplegia, sphincter dysfunction, and sensory disturbance, but vision was normal. Three days later, she was transferred to our hospital. Her initial expanded disability status scale (EDSS) was 8.5. She had no feculent sexual behavior and could not recall any symptoms of primary or secondary syphilis.

T2-weighed spinal magnetic resonance imaging (MRI) showed a lesion extending from the third cervical cord to the fifth thoracic cord (C3-T5) without any enhancement. Cranial MRI showed a high T2 signal and fluid attenuated inversion recovery (FLAIR) abnormality involving the pons, corpus callosum, bilateral ependyma around the bilateral ventricle, and the septum pellucidum without any enhancement (Figure 1). Somatosensory evoked potential was

abnormal. But visual-evoked potential and brain-stem auditory evoked potential were normal.

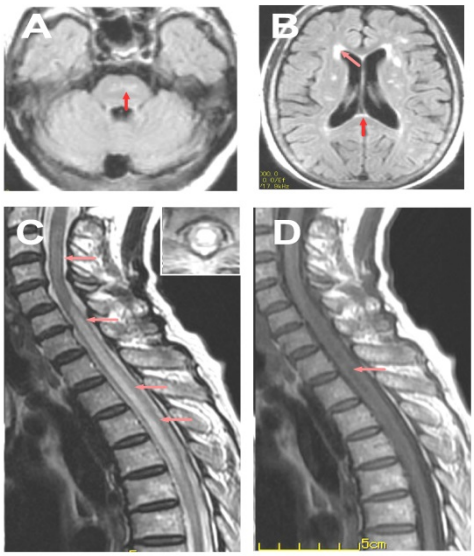

Figure 1: MRI features of the case. A: Lesion in Pons (arrow); B: Brain lesions around the bilateral ventricle (arrow) and in corpus callosum (arrow); C: T2-weighed spinal MRI showed extensive lesion in the cervical and thoracic cord (C3-T5); D: T1-weighed spinal MRI showed hypointensity mainly around the central canal (arrow).

On the lab test, she was tested positive for antinuclear antibody (1:1000), anti-mitochondrial antibody M2 subtype (1:10000), anti-Ro-52 antibody (1:10000), anticardiolipin antibody-IgM (1:1) and anticardiolipin antibody-IgA (1:1). Her erythrocyte sedimentation rate was 64.0 mm/h, anti-thyroglobulin antibody was 140.2 KIU/L(0-50 KIU/L), and antithyroid peroxidase antibody was 44.94 KIU/L (0-35 KIU/L). Anti-AQP-4 antibody was detected in both of the serum (1:10000) and cerebral spinal fluid (1:1000) by cell-based assay. Blood tests for syphilis were positive for toluidine red unheated serum test (TRUST) (1:8 titers) and reactive in specific treponema pallidum particle agglutination assays (TPPA). A lumbar puncture was performed with normal opening pressure. The cerebral spinal fluid (CSF) had elevated cellular count (15×106/L) with slightly elevated protein 0.67 (0.12–0.40 g/L), normal glucose, and chloride. There were no bacteria, fungi and mycobacterium tuberculosis. CSF tests for syphilis were positive for TRUST (1:1 titer) and reactive in specific TPPA.

Based on these results, she was diagnosed as NMOSD and neurosyphilis. She was treated with intravenous methylprednisolone (1 g daily for three days) and intravenous immunoglobulin G (20 g daily for five days). After the treatment, her motor and sensory disturbance did not improve. On neurological examination, the muscle strength in upper limbs was in grade 4 and that in lower limbs was grade 2. Superficial sensations were severely impaired in lower limbs. Two weeks later, she received the penicillin treatment for neurosyphilis in another hospital. About two months later, her muscle strength in four limbs was improved with 5 of EDSS. The titers were decreased for AQP4 antibodies (1:100) and TRUST (1:1) in serum.

Discussion

Although the coexistence of NMO and syphilis has been noted in some previous case reports, to our knowledge, it is the first time to describe NMOSD patients with neurosyphilis. In our case, the diagnosis of these two disorders is clear. The revised diagnostic criteria proposed for NMO requires myelitis, optic neuritis, and at least two of three supportive criteria [8]: (1) contiguous spinal cord MRI lesion extending over ≥3 vertebral segments; (2) brain MRI not meeting diagnostic criteria for multiple sclerosis; (3) NMO-IgG seropositive status. Although our patient did not meet above absolute criteria, according to recent new consensus [9], she clearly had definite NMOSD with positive AQP4 antibodies in both of serum and CSF. In spite of a "gold standard" for the diagnosis of neurosyphilis is not available, the serologic tests, clinical findings and examination of CSF play a major role, especially the testing of CSF. Treponemapallidum haemagglutination/TPPA/ microhemaglutination for Treponemapallidum and/or fluorescent treponemal antibody-absorption tests positive and increased number of mononuclear cells or positive venereal disease research laboratory (VDRL)/rapid plasma reagin (RPR) in CSF are used in the diagnosis of neurosyphilis. A reactive VDRL-CSF test is generally considered definitive evidence of neurosyphilis. Although it's very high specificity, it is difficult to develop VDRL test in most of hospital. The TRUST is a routine serological test for syphilis in China. It is reported that the specificity of the TRUST in neurosyphilis was 100%, which is the same as the VDRL [10]. Therefore, the diagnosis of neurosyphilis is also definite to our present patient because of the positive TPPA and TRUST in CSF.

Infectious causes to spinal cord include viral, bacterial, mycobacterial, fungal, and parasitic agents, commonly are treatable [11]. The spectrum of neurosyphilis is broad and may manifest as meningitis, dementia, stroke, and progressive myelopathy. Syphilitic involvement of the spinal cord may have various manifestation, including tabesdorsalis, meningomyelitis, spinal vascular syphilis, hypertrophic pachymeningitis [5]. Syphilitic myelitis is a rare manifestation of syphilis and a rare cause of myelopathic syndromes in general [11]. On the other hand, we have carried out a literature search for the years 1949–2013 in the context of our case study and found about 25 case reports of syphilitic myelitis (Table 1). It appears that syphilitic myelitis may be more frequent in the male than in the female. However, the most common form of neurosyphilis currently diagnosed is asymptomatic, as our case is a woman who experienced acute attack, with very high sero-AQP4 antibodies titers, and high CSF AQP4 antibodies titers. Therefore, her myelitis occurrence maybe mainly associated with AQP4 antibodies autoimmunity. Although potential infections, such as helicobacter pylori [4,12], were associated with anti-AQP4 antibody positive status, no evidence has showed that syphilis infection was involved in the AQP4 autoimmunity. Therefore, neurosyphilis may be an asymptomatic and isolated episode in our case. When NMOSD meets neurosyphilis, it is critical to differentiate which is the main cause. Certainly, although there is no evidence that treponemapallidum subspecies pallidum involved the pathogenesis of NMO, it seems that anti-syphilitic treatment is helpful to attenuate disability to our present case. Therefore, combined treatment of immunosuppressant and anti-syphilis is recommended in such patients.

In conclusion, TM and neurosyphilis in a patient with positive aquaporin-4 antibody is extremely rare. Although neurosyphilis may be an asymptomatic and isolated episode, combined treatment of immunosuppressant and anti-syphilis is recommended.

Author	Year	Sex	Age	Spinal lesions	AIDS	Therapy
Stratton EK [13]	1949	F	NA	NA	No	PG
Wigfield AS [14]	1970	M	42	NA	No	PG
Fisher M, et al. [15]	1977	M	58	NA	No	PG
Harrigan EP, et al. [16]	1984	F	51	NA	No	PG
Talbot MD, et al. [17]	1985	M	34	NA	No	PG
Tashiro K, et al. [18]	1987	M	31	T3-T4	No	PG
Lowenstein DH, et al. [19]	1987	M	26	NA	No	PG
Janier M [20]	1988	M	26	NA	No	PG
P M Terry, et al. [21]	1989	M	31	NA	No	PG
Berger JR [22]	1992	F	33	T8	Yes	PG
Nabatame H, et al. [23]	1992	M	46	thoracic spinal cord	No	PG
Strom T, et al. [24]	1994	M	28	T5	No	PG
John JF, et al. [25]	1977	F	49	NA	No	PG
	1977	M	45	NA	No	PG
	1977	F	65	NA	PG	PG
Srivastava T, et al. [26]	2000	M	32	T5-T12	No	PG
Bulundwe KK, et al. [27]	2000	M	53	T3-T6	No	Benzyl-PG
Tsui EY, et al. [28],	2002	F	52	whole spinal cord	No	PG
Kikuchi S, et al. [29]	2003	M	36	Whole spinal cord	No	PG
Matijosaitis V, et al. [30]	2006	M	38	T6-T7	No	PG
Chilver-Stainer L, et al. [31]	2009	M	46	T6 - the conus	No	PG
Kayal AK, et al. [32]	2011	M	35	Conusmedullaris	No	NA
	2011	M	38	NA	No	NA
	2011	F	30	whole spinal cord	No	NA
Mebrouk Y [33]	2011	M	40	T2-T4	No	PG

F: Female; M: Male; T: thoracic spinal cord; NA: No application; PG: Penicillin; AIDS: acquired immunodeficiency syndrome

Table 1: Case-reports: syphilitic myelitis in previous literatures (1949–2011)

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