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-old Chinese 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 autoimmune, 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 tabes dorsalis, 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 febrile 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), antcardiolipin antibody-IgM (1:1) and antcardiolipin 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 (15×10^6/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 upper limbs was in grade 4 and that in lower 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/ microhemagglutination 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 syphilitic 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.
Table 1: Case-reports: syphilitic myelitis in previous literatures (1949–2011)

| 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      |
| Nabalamie 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      |
| John JF, et al. [25]          | 1977 | M   | 45  | NA             | No   | PG      |
| John JF, et al. [25]          | 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 |
| Tsuji 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      |
| Matjosalitis 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      |
| Mebrrouk 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

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References

1. Li R, Qiu W, Lu Z, Dai Y, Wu A, et al. (2011) Acute transverse myelitis in demyelinating diseases among the Chinese. J Neurol 258: 2206-2213.
2. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittocck SJ, Lucchinetti CF, et al.(2004) A serum autoantibody marker of neuromyelitisoptica: distinction from multiple sclerosis. Lancet 364: 2106-2112.
3. Ren Z, Wang Y, Duan T, Patel J, Liggett T, et al. (2012) Cross-immunoreactivity between bacterial aquaporin-Z and human aquaporin-4: potential relevance to neuromyelitisoptica. J Immunol 189: 4602-4611.
4. Long Y, Gao C, Qiu W, Hu X, ShuY, et al. (2013) Helicobacter pylori infection in NeuromyelitisOptica and Multiple Sclerosis. Neuroimmunomodulation 20: 107-112.
5. Berger JR (2011)Neuropsychitis and the spinal cord: then and now. J NervMenDis 199: 912-913.
6. Vidal MF, Garcia SV, Gonzalez J, Richart JC(1989) Devic's syndrome during secondary syphilis. An Med Interna 6: 497-498.
7. Wilcox RA, Burrow J, Skee M, Craig J, Thyagarajan D (2008) Neuromyelitisoptica (Devic's disease) in a patient with syphilis. MultiScler 14: 268-271.
8. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittocck SJ, Weinsenker BG (2007)The spectrum of neuromyelitisoptica. Lancet Neurol 6: 805-815.
9. Fujihara K, Sato DK (2014) AQP4 antibody serostatus: Is its luster being lost in the management and pathogenesis of NMO. Neurology 81: 1186-1188.
10. Jiang Y, Chen X, Ma X, Yang Y, Peng F, et al. (2011) The usefulness of toluidine red unheated serum test in the diagnosis of HIV-negative neurosyphilis. Sex Transm Dis 38: 244-245.
11. Chilver-Stainer L, Fischer U, Hauf M, Fux CA, Sturzenegger(2009) M. Syphilitic myelitis: rare, nonspecific, but treatable. Neurology 72: 673-675.
12. Yoshimura S, Isebe N, Matsushita T, Yonekawa T, Masaki K, et al. (2013) Distinct genetic and infectious profiles in Japanese neuromyelitisoptica patients according to anti-aquaporin 4 antibody status. J NeuroImmunospsych Psychiatry 84: 29-34.
13. Stratton EK (1949)Meningovascular myelitis in early syphilis. Calif Med 70: 209.
14. Wigfield AS (1970)Tabes dorsalis of sudden onset associated with possible transverse myelitis. Br J Vener Dis 46: 262-263.
15. Fisher M, Poser CM(1977) Syphilitic meningomyelitis. A case report. Arch Neurol 34: 785.
16. Harrigan EP, McLaughlin TJ, Feldman RG (1984) Transverse myelitis due to meningovascular syphilis. Arch Neurol 41: 337-338.
17. Talbot MD, Morton RS (1985)Neurosyphilis: the most common things are most common. Genitourin Med 61: 95-98.
18. Tashiro K, Moriwaka F, Sudo K, Akino M, Abe H (1987) Syphilitic myelitis with its magnetic resonance imaging (MRI) verification and successful treatment. Jpn J Psychiatry Neurol 41: 269-271.
19. Lowenstein DH, Mills C, Simon RP(1987) Acute syphilitic transverse myelitis: unusual presentation of meningovascular syphilis. Genitourin Med 63: 333-338.
20. Janier M(1988) Acute syphilitic myelitis in a young man. Genitourin Med 64: 206.
21. Perry PM, Glancy GR, Graham A (1989)Meningovascular syphilis of the spinal cord presenting with incomplete Brown-SEQUARD syndrome: case report. Genitourin Med 65: 189-191.
22. Berger JR (1992) Neurosyphilis and the spinal cord: then and now. J NervMenDis 199: 912-913.
23. Nabatame H, Nakamura K, Matuda M, Fujimoto N, Dodo Y, et al (1992) MRI of syphilitic myelitis. Neuroradiology 34: 105-106.
24. Strom T, Schneck SA. Syphilitic meningomyelitis (1991) Neurology 41: 325-326.
25. John JF Jr, Cuetter AC (1977) Spinal syphilis: the problem of fluorescent treponemal antibody in the cerebrospinal fluid. South Med J 70: 309-311.
26. Srivastava T, Thussu A (2000) MRI in syphilitic meningomyelitis. Neurol India 48: 196-197.
27. Bulundwe KK, Myburgh CJ, Gledhill RF(2000) Syringomyelia complicating syphilitic spinal meningitis: a case report. Eur J Neurol 7: 231-236.
28. Tsui EY, Ng SH, Chow L, Lai KF, Fong D, et al.(2002) Syphilitic myelitis with diffuse spinal cord abnormality on MR imaging. EurRadiol 12: 2973-2976.
29. Kikuchi S, Shinpo K, Niino M, Tashiro K (2003) Subacute syphilitic meningomyelitis with characteristic spinal MRI findings. J Neuro 250: 106-107.
30. Matijosaitis V, Vaitkus A, Pauza V, Valiukeviene S, Gleizniene R (2006) Neurosyphilis manifesting as spinal transverse myelitis. Medicina (Kaunas) 42: 401-405.
31. Chilver-Stainer L, Fischer U, Hauf M, Fux CA, Sturzenegger M (2009) Syphilitic myelitis: rare, nonspecific, but treatable. Neurology 72: 673-675.
32. Kayal AK, Goswami M, Das M, Paul B (2011) Clinical spectrum of neurosyphilis in North East India. Neurol India 59: 344-350.
33. Mebrouk Y, Chraa M, McMaughey C, Kissani N (2011) Syringomyelia associated with syphilitic spinal meningitis: real complication or possible association. Spinal Cord 49: 757-760.