Neurol Sci (2017) 38:703–706
DOI 10.1007/s10072-016-2718-3

QUIZ CASES

Anti-*N*-methyl-D-aspartate receptor encephalitis associated with intracranial *Angiostrongylus cantonensis* infection: a case report

Yu Peng[1] · Xiaojia Liu[1] · Suyue Pan[1] · Zuoshan Xie[1] · Honghao Wang[1]

Received: 18 April 2016 / Accepted: 15 September 2016 / Published online: 24 October 2016

Abstract Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a recently described paraneoplastic syndrome with prominent neuropsychiatric symptoms. Many of these cases are associated with neoplasma especially teratoma. In addition, a few of cases with anti-NMDAR antibodies triggered by viral infection have been reported, but never by parasitic infection. Here, we report a novel case of NMDA receptor encephalitis in a 51-year-old male related to the development of anti-NMDAR antibodies triggered by *Angiostrongylus cantonensis* infection.

Keywords NMDA receptor encephalitis · *Angiostrongylus cantonensis* · Parasite

Case report

A 51-year-old Chinese male was admitted to our hospital because of psychological and behavioral symptoms for 1 month. He had a past history of chronic osteomyelitis of bilateral lower extremities for many years, and we saw severe skin ulcers around his ankles when he was admitted. 3 weeks before onset, he believed a folk prescription and spread mashed snails on his ankle ulcers. He was an optimistic and conversable man, but 1 month ago, he gradually become apathic, taciturn, and unresponsive. Sometimes, he might make a rigmarolish or irrelevant speech. His mental symptoms became more and more serious, and finally, he was taken to our hospital by his families.

✉ Honghao Wang
wang_whh@163.com

[1] Department of Neurology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

On admission, his vital signs were stable with the temperature of 36.0 °C, blood pressure of 120/80 mmHg, and pulse rate of 80/min. Except for the skin ulcers, physical examination for chest and abdomen had no abnormalities. On neurologic examination, he was apathic and unresponsive. His memory, calculation, and orientation were all decreased. His cranial nerves were normal, and his extremities were powerful. The deep tendon reflexes of all fours were 2+ and symmetrical. Kernig's sign, Brudzinski's sign, and bilateral Babinski's sign were negative.

The routine laboratory tests are showed in Table 1, in which the count of eosinophils increased clearly. Serologic tests were negative for hepatitis B surface antigen, HIV, and TPPA. Other tests which were normal include urine analysis, stool analysis, coagulation test, electrocardiogram, chest X-ray, and abdominal ultrasonogram. Serum AFP, CEA, β2-microglobulin, and series of CA maker for cancer screening all were negative. His electroencephalogram (EEG) was mild abnormal. His MRI of brain revealed multiple patchy hyperintense lesions in bilateral cerebral white matters and right cerebellum on the T2-weighted images and fluid-attenuated inversion recovery images, which were homogeneous enhanced on gadolinium-enhanced T1-weighted images (Fig. 1). These images looked like demyelinating diseases, such as multiple sclerosis at first sight. On lumbar puncture, the opening pressure of CSF was normal (130 mmH_2O), and its analysis revealed a white blood cell count of 125/mm^3, glucose level of 2.66 mmol/L (blood glucose 6.3 mmol/L), and protein concentration of 2.10 g/L. Indian ink stain for cryptococcus, stain for acid fast bacilli, and PCR for Tuberculosis, HSV-1, HSV-2, EBV, CMV, and VZV were negative. The cytological analysis collected 10,000 ± cells in 0.5 ml CSF, in which 25 % were eosinophils (Fig. 2). Therefore, we made a parasite screening and detected IgG antibodies

Table 1 Laboratory tests of the patient

Laboratory tests	Results	Normal range
Potassium	2.90 mmol/L	3.5–5.5 mmol/L
Sodium	140 mmol/L	137–147 mmol/L
Creatinine	87 μmol/L	44–106 μmol/L
Blood urea nitrogen	3.4 mmol/L	2.8–7.2 mmol/L
Albumin	41.3 g/L	40–55 g/L
Alanine aminotransferase	31 U/L	7–40 U/L
Hemoglobin	149 g/L	115–150 g/L
White blood cells count	8390/μL	3500–9500/μL
Eosinophils count	620/μL	20–500/μL
Platelets count	270,000/μL	125,000–350,000/μL
C-reaction protein	2.3 mg/L	0.0–5.0 mg/L
Erythrocyte sedimentation rate	23 mm/1 h	0–20 mm/1 h

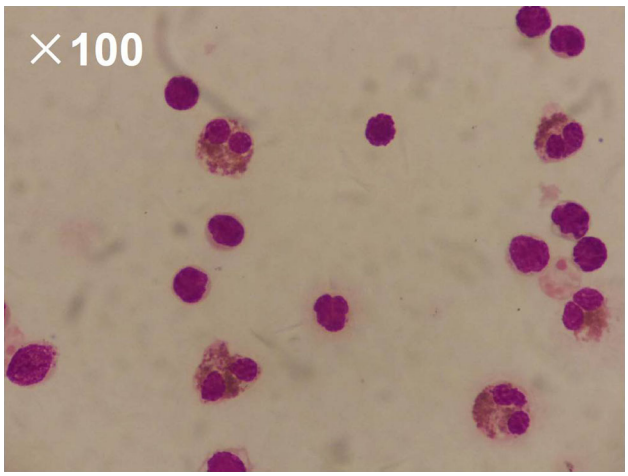

Fig. 2 The cytological analysis of cerebral-spinal fluids. Significantly increased proportion of eosinophils were found

of *Angiostrongylus cantonensis* both in serum and CSF by enzyme-linked immunosorbent assay (ELISA) with crude antigen. The serum optical density of *A. cantonensis* antibody was 1.526 but decreased to 0.593 one month later after treatment. The serum and CSF parasite antibodies screening also presented positive for cysticercosis, schistosomiasis, hydatidosis, sparganosis, and negative for paragonimiasis and distomiasis. All these antibodies in serum became negative 1 month later except *A. cantonensis*. At the same time, we detected anti-NMDAR antibodies both in serum and CSF, which gave us a big surprise. Other autoimmune antibodies, such as anti-AQP4, anti-dsDNA, anti-Sm, ANA, all were negative. The patient was diagnosed as NMDA receptor encephalitis associated with *A. cantonensis* infection. Therefore, the patient was given intravenous immunoglobulin (IVIG) therapy (40 mg/kg everyday for 5 days) and albendazole (0.6 g bid for 7 days) at the same time, and his mental status recovered gradually. When he discharged on day 18 after admission, he was able to have a simple communication with us and his EEG became normal, even though his reaction and language was still slow. In the follow-up 1 month after discharge, the patient could communicate with us normally and had no neurological symptoms or signs. Because of an unsuccessful lumbar puncture, we just screened the serous parasite antibodies again which had been showed above.

Discussion

Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis is a recently described severe, treatable and potentially reversible disorder with prominent neuropsychiatric symptoms, such as amnesia, seizures, dyskinesias, loss of consciousness, central hypoventilation, and autonomic

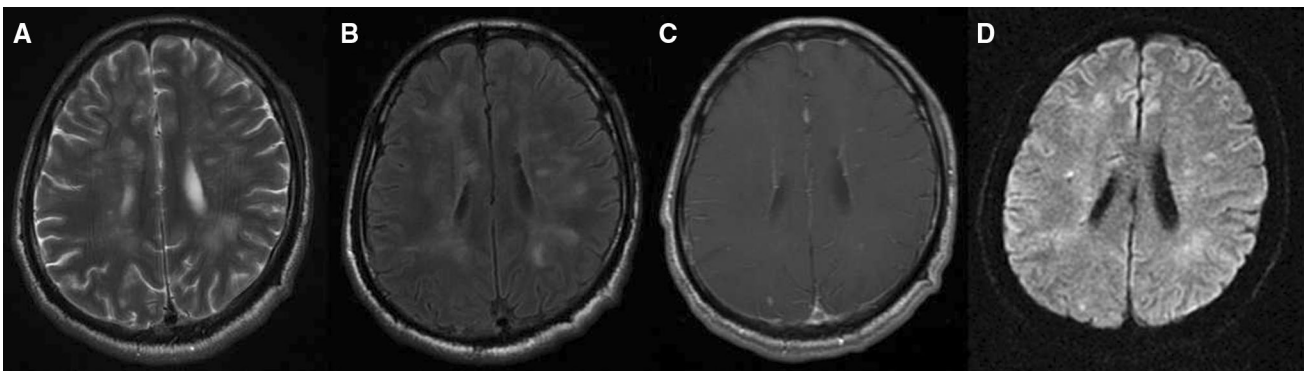

Fig. 1 The MRI of brain shows multiple patchy lesions in bilateral cerebral white matters which looked like demyelinating diseases such as multiple sclerosis. **a** T2-weighted image. The lesions were hyperintense on the T2-weighted image, which distributed in the white matters around bilateral ventricle. **b** Fluid-attenuated inversion recovery image. The lesions also were hyperintense on the fluid-attenuated inversion recovery images. **c** Gadolinium-enhanced T1-weighted image. It shows several enhanced spots within the lesions. **d** Diffusion weighted image. The lesions also manifested spotty hyperintense on DWI

dysfunction [1, 2]. Accumulating evidences suggest that these neuropsychiatric symptoms were the direct pathogenic role of anti-NMDAR antibodies binding with NMDA receptors [3, 4]. Therefore, the presence of anti-NMDAR antibodies in serum or CSF is the most important evidence for the diagnosis of NMDA receptor encephalitis. We detected anti-NMDAR antibodies both in serum and CSF using a commercially available transfected HEK293 cell-based kit from EUROIMMUN®, which is one of the most extensive techniques employed for detecting anti-NMDAR antibodies [4]. Immunohistochemistry using rodent hippocampus revealed these antibodies in serum and CSF all bind to antigens on neural membrane. These clinic presentation and laboratory findings made us diagnose the patient as NMDA receptor encephalitis.

The NMDA receptor encephalitis was first described as a paraneoplastic syndrome in women with ovarian teratoma [5, 6]. However, more and more literature described this disease without teratoma in men and children [7, 8], with one series finding up to 80 % of patients had non-paraneoplastic NMDA receptor encephalitis [9]. In addition to tumors, infections are also considered as a trigger for NMDA receptor encephalitis. Since 2012, there has been several reports of NMDA receptor encephalitis triggered by infectious etiologies including herpes simplex viral encephalitis (HSE), mycoplasma pneumonia, *H. influenza*, HHV6, mumps, and enterovirus [4, 10, 11]. But NMDA receptor encephalitis associated with *A. cantonensis* or other parasites has not been reported.

Angiostrongylus cantonensis, the most common cause of eosinophilic meningitis, was first described by Chen [12] in 1935 in rat lungs, in Canton, China. The infection of this parasite mainly outbroke in Southeast Asia, and patients presented with severe headache, neck stiffness, nausea, and vomiting [13]. The definitive diagnosis of *A. cantonensis* depends on finding larvae in CSF of the patient, but it is rarely achieved. Therefore, the diagnosis of human *A. cantonensis* is based on clinical features as well as laboratory findings [14]. The most important diagnostic finding is marked eosinophilia in CSF. The ratio of eosinophil to WBC in CSF could range form 0 to 50 % as the literature reviewed [15]. Over the past decades, ELISA for IgG antibodies of *A. cantonensis* has been widely applied to support the clinical diagnosis [16, 17], and has a sensitivity approach 100 %. ELISA with crude antigen may have many cross reactions, but the titers of antibody are useful to distinguish the reaction positive or false positive. In the recent years, ELISA with various purified antigens, such as 29-, 31-, and 32-kD antigens, have been developed for detecting *A. cantonensis* antibody, attaining a specificity approach 100 % [18, 19], but it is not an economic and simple field test. Though it was a pity that we neither found larvae in CSF, nor applied ELISA with purified antigen to confirm the pathogenic agent further more, we still thought the patient as *A. cantonensis* probably for the following reasons: (1) the patient had a typical presentation of eosinophilic meningitis, especially the elevated eosinophils as high as 25 % in CSF. (2) The patient came from the epidemic area and his skin ulcers had a direct exposure to snails just before the onset. Snails are the definite intermediate host of *A. cantonensis*, and there have been many reports of *A. cantonensis* associated with snails [20]. (3) The results of ELISA should be analysed with its concentration or optical density. We used the conventional technique of ELISA with crude antigen and detected IgG antibody of *A. cantonensis* twice in serum, and its optical density reduced about 60 % off after treatment. Though we also detected other parasite antibodies that might confuse the diagnosis of pathogenic agent at the first time, but these antibodies disappeared after treatment. Therefore, they probably were false positive because of the cross reactions with the antibody of *A. cantonensis*.

There are several hypotheses about the mechanisms of NMDA receptor encephalitis after infection [4, 10, 21]. One possibility is molecular mimicry, whereby the pathogen's protein sequence triggers an immune response that is misdirected against a structurally similar epitope present in the NMDAR. This mechanism is more appropriate for the relationship between teratoma and NMDA receptor encephalitis, because teratoma expressing epitopes mimic to NMDAR has been reported and removal of the NMDA expressing tumor could decrease the level of pathologic auto-antibodies in serum and CSF [22]. However, to date, there are no reports of a shared epitope sequence between NMDAR and *A. cantonensis* or HSV or other pathogen. Alternatively, the infectious inflammatory destroys the limbic structures, and then releases and presents abundantly expressed local NMDAR epitopes to the immunological system, and then initiates an autoimmune response. We think that this hypothesis is more appropriate for the post-infection NMDA receptor encephalitis. It was supported by the difference of antibodies between classic NMDA receptor encephalitis and post-infection NMDA receptor encephalitis [4]. Pruss et al. [10] reported that patients of post-HSE anti-NMDAR encephalitis may display a broader antigenic repertoire than the classic syndrome. As this reason, we predict that there will be more and more anti-NMDAR encephalitis after infection reported in the future.

Compliance with ethical standards

Conflict of interest None.

References

1. Dalmau J, Gleichman A, Hughes EG et al (2008) Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 7:1091–1098
2. Hung TY, Foo NH, Lai MC (2011) Anti-*N*-methyl-D-aspartate receptor encephalitis. Pediatr Neonatol 52(6):361–364
3. Waxman EA, Lynch DR (2005) *N*-methyl-D-aspartate receptor subtypes: multiple roles in excitotoxicity and neurological disease. Neuroscientist 11:37–49
4. Venkatesan A, Benavides DR (2015) Autoimmune Encephalitis and Its Relation to Infection. Curr Neurol Neurosci Rep 15(3):3
5. Dalmau J, Tuzun E, Wu HY et al (2007) Paraneoplastic anti-*N*-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 61:25–36
6. Sansing LH, Tuzun E, Ko MW, Baccon J, Lynch DR, Dalmau J (2007) A patient with encephalitis associated with NMDA receptor antibodies. Nat Clin Pract Neurol 3:291–296
7. Florance NR, Davis RL, Lam C et al (2009) Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 66:11–18
8. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 10:63–74
9. Irani SR, Bera K, Waters P et al (2010) *N*-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 133:1655–1667
10. Pruss H, Finke C, Holtje M et al (2012) *N*-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol 72:902–911
11. Gable MS, Gavali S, Radner A, Tilley DH, Lee B, Dyner L et al (2009) Anti-NMDA receptor encephalitis: report of ten cases and comparison with viral encephalitis. Eur J Clin Microbiol Infect Dis 28:1421–1429
12. Chen HT (1935) Un nouveau nematode pulmonaire: *Pulmonema cantonensis* n.g., n. sp. des rats de Canton. Ann Parasitol Hum Comp 13:312–317
13. Pien FD, Pien BC (1999) *Angiostrongylus cantonensis* eosinophilic meningitis. Int J Infect Dis 3(3):161–163
14. Eamsobhana P, Yong HS (2009) Immunological diagnosis of human angiostrongyliasis due to *Angiostrongylus cantonensis* (Nematoda: Angiostrongylidae). Int J Infect Dis 13(4):425–431
15. Tsai HC, Liu YC, Yen CM (2001) Eosinophilic meningitis caused by *Angiostrongylus cantonensis*: report of 17 cases. Am J Med 111(2):109–114
16. Intapan PM, Maleewong W, Polsan Y, Sawanyawisuth K, Chotmongkol V (2002) Specific IgG antibody subclasses to *Angiostrongylus cantonensis* in patients with angiostrongyliasis. Asian Pac J Allergy Immunol 20:235–240
17. Dorta-Contreras AJ, Noris-Garcia E, Escobar-Perez X, Duenas-Flores A, Mena-Lopez R (2003) IgG subclasses intrathecal synthesis patterns in eosinophilic meningoencephalitis due to *Angiostrongylus cantonensis*. Rev Neurol 36:506–509
18. Eamsobhana P, Yoolek A, Kreethapon N (2003) Blinded multilaboratory evaluation of an in-house dot-blot ELISA kit for diagnosing human parastrongyliasis. Southeast Asian J Trop Med Public Health 34:1–6
19. Eamsobhana P, Yoolek A, Suvouttho S, Suvuttho S (2001) Purification of a specific immunodiagnostic *Parastrongylus cantonensis* antigen by electroelution from SDS-polyacrylamide gels. Southeast Asian J Trop Med Public Health 32:308–313
20. Tsai HC, Liu YC, Kunin CM, Lai PH, Lee SS, Chen YS et al (2003) Eosinophilic meningitis caused by *Angiostrongylus cantonensis* associated with eating raw snails: correlation of brain magnetic resonance imaging scans with clinical findings. Am J Trop Med Hyg 68:281–285
21. Höftberger R, Armangue T, Dalmau J et al (2013) Clinical Neuropathology practice guide 4-2013: post-herpes simplex encephalitis: *N*-methyl-D-aspartate receptor antibodies are part of the problem. Clin Neuropathol 32(4):251–254
22. Seki M, Suzuki S, Lizuka T et al (2008) Neurological response to early removal of ovarian teratoma in anti-NMDAR encephalitis. J Neurol Neurosurg Psychiatry 79:324–326