The effect of a large dose of intravenous immunoglobulin on general paresis of the insane

Chen Qingqing, MD1, Liu Dongliang, MD2, Sang Qingqing, MD2 and Sang Daoqian, MD2

Abstract

General paresis of the insane (GPI) remains the form of neurosyphilis most closely associated with dementia, even after the advent of penicillin. Penicillin remains the top treatment choice for syphilis, but treatment failure is not rare. Although the neurological symptoms of GPI can be alleviated by antibiotic treatment, mental symptoms may continue. A 60-year-old man was admitted to hospital due to rapidly progressive dementia. He was diagnosed as GPI. With the patient’s informed consent, we treated him with a large dose of intravenous immunoglobulin (IVIG) (0.4 g/kg/day) for 5 days, as well as penicillin (24 million units daily divided into six doses) for 14 days. A near-immediate improvement in his emotions and orientation occurred on the 17th day in hospital. The patient made an excellent recovery 6 weeks after treatment, his psychotic and mood symptoms improved significantly. Therefore, we hypothesize that patients with GPI treated with IVIG and penicillin G would have better outcomes than those treated with penicillin G alone. IVIG may be introduced as a necessary treatment for GPI.

Keywords

general paresis of the insane, intravenous immunoglobulin, dementia

Date received: 30 January 2021; accepted: 3 August 2021

Introduction

Neurosyphilis is a clinical syndrome caused by Treponema pallidum (TP) infection that affects the meninges, blood vessels, or cerebrospinal fluid (CSF) and is an important manifestation of systemic damage of late syphilis (tertiary). Spirochetes may invade the central nervous system in up to 40% of untreated patients with syphilis. General paresis of the insane (GPI) remains the form of neurosyphilis most closely associated with dementia, even after the advent of penicillin. It usually develops 10–25 years after TP infection, but can be seen earlier. Most untreated individuals die within 5 years of the onset of symptoms. Penicillin remains the top treatment choice for syphilis, but treatment failure is not rare. Although the neurological symptoms of GPI can be alleviated by antibiotic treatment, mental symptoms may continue. In addition, infection clearance with penicillin or titer improvement may not markedly ameliorate the cognitive deficit. There is currently no consensus regarding the management of the cognitive deficits of GPI.

We report a case of GPI treated with standard penicillin combined with a large dose of intravenous immunoglobulin (IVIG) whose cognitive impairment improved dramatically.

1Department of Neurology, Taihe County People’s Hospital, Fuyang, China
2Department of Neurology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, China

Corresponding author:
Daoqian Sang, Department of Neurology, The First Affiliated Hospital of Bengbu Medical College, Anhui Province Key Laboratory of Immunology in Chronic Diseases, Changhuai Road 287, Bengbu 233004, China.
Email: sangdq@sina.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Case presentation

A 60-year-old man was admitted to hospital due to rapidly progressive dementia on 10 July 2015. His soliloquy, slowness in reacting, memory loss, mental disorders, and other mental and behavioral symptoms, all without any obvious inducement, were identified by his family several months previously. His cognition and self-care ability were notably decreased such that he could not name many objects like napkins and cups and he could not dress himself. Along with impaired orientation, his memory obviously faded until he did not even know his home address. He had no history of brain trauma, broken skin, hypertension, diabetes, hepatitis, or tuberculosis. He denied a history of blood transfusion and had no tobacco and alcohol addictions. He was divorced with two sons.

On the initial examination, his arterial pressure was 130/80 mmHg. The cardiovascular, pulmonary, abdominal, and skin examinations were normal. He had a masked face, apathy, with abnormalities of orientation memory and intelligence. The shape of bilateral pupil was round whose diameter was about 3 mm, light reflex sensitive. He had normal visual field, normal sight, and normal knee reflex. Vibration and position sense was normal. His muscle strength and muscle tension were normal. The Babinski sign, Hoffman’s sign, and meningeal irritation sign were negative. His Mini-Mental State Examination (MMSE) score was 12/30 and his Montreal Cognitive Assessment (MoCA) score was 11/30, while his self-rating anxiety scale (SAS) and self-rating depression scale (SDS) scores were 61, 25, and 69, respectively.

His complete blood count, liver and kidney function, routine urine analysis, and blood coagulation function were normal. Chest X-ray showed no aortic dilatation. CSF analysis showed 174 mg/dl protein with 8 leucocytes/mm3. The CSF syphilis rapid plasma reactor test and TP particle assay were positive. Anti-NMDAR antibody, anti-LGI1 antibody, anti-CASPR2 antibody, anti-GABA receptor antibody, and anti-AMPA receptor antibody were negative in CSF. An electroencephalogram was normal. The somatosensory evoked potential showed impairment of deep sensory pathways in the cervical cord, the visual evoked potential was normal, and the left brain stem auditory evoked potential was normal, while the right was extended. Syphilis antibody and the tolulized red unheated serum test were positive (the titer of the latter was 1:16). Brain magnetic resonance imaging (MRI) revealed large symmetric areas of long T1, long T2, and high FLAIR signals adjacent to the body of the bilateral ventricles of the temporal and parietal lobes (Figure 1).

According to the United Kingdom national guidelines management of syphilis and sexually transmitted disease treatment guidelines, the standard treatment for neurosyphilis is aqueous crystalline penicillin G (24 million units per day divided into six doses) for a period of 14 days and then benzathine penicillin (2-4 million units delivered IM once per week) for 5 days. With the patient’s informed consent, we treated him with a large dose of IVIG (0-4 g/kg/day) for 5 days, as well as penicillin (24 million units daily divided into six doses) for 14 days. Penicillin and IVIG were given almost at the same time. A near-immediate improvement in his orientation occurred on the 17th day in hospital. The patient made an excellent recovery 6 weeks after treatment, his psychotic and mood symptoms improved significantly, he had a MMSE score of 20/30, and he had no focal neurological deficits. The reduced antibody titers in serum and the white blood cell count and protein content of CSF provided evidence of successful treatment with resolution of the inflammatory markers in CSF. The lesion area in the brain was decreased in his reviewed MRI on 27 May 2016 compared with the previous data (Figure 2). Furthermore, his MMSE and MoCA scores improved to 28/30 and 26/30, respectively, while his SAS and SDS scores decreased to 41, 25, and 50, respectively, with better mental processing speed and attention as well as an optimistic mood at the 10th month of follow-up. His daily life function returned to baseline.

Discussion

TP infection causes GPI 10–20 years after the initial infection, an uncommon cause of dementia affecting the brain and central nervous system. It is associated with memory loss. GPI can occur in untreated patients with latent syphilis. It was originally considered a psychiatric disorder when it was first scientifically identified around the early 19th century. By the mid-nineteenth century, the physical and mental symptoms were considered to be characteristic of GPI. A large number of patients with GPI present a progressive course and psychiatric symptoms such as depression, mania, and psychosis. TP-induced GPI is a parenchymal disease with neuronal loss in late-stage neurosyphilis. We reported a patient with GPI who substantially improved after large dose IVIG therapy combined with penicillin. Despite prompt and proper antibiotic treatment, the recovery is often incomplete, especially when tissue damage has occurred. Persistent cognitive impairment is commonly associated with GPI, despite adequate penicillin treatment. Thus, the recovery was due to effect of IVIG and penicillin. There have been no previous reports of the use of IVIG for the management of the dementia symptoms associated with GPI. Treatment of GPI with large doses of IVIG combined with penicillin achieved good effects, mechanism of which
was unknown. TP elicits antigen-specific humoral and cellular immune responses. For example, synthetic lymph nodes containing inactivated TP secrete interferon (IFN)-γ and immunoglobulin G (IgG) antibody, and showed that CD4+ lymphocytes and IFN-γ predominate in local immune responses in early experimental syphilis. The presence of low-level spirochetemia and immunophenotypic changes suggest monocyte activation. TP elicits secretion of CD4+ and CD8+ T cells, activated monocytes/macrophages, and CD11c+ monocyteid and CD11c plasmacytoid dendritic cells, and macrophages drive opsonophagocytosis in treponemal clearance. In addition, immunoglobulins have the following functions. First, to improve the efficacy of penicillin in order to promote opsonophagocytic killing of microorganisms, the antibodies enhance the resistance of patients to disease and prevent aggravation of infection. Second, neutralization of pathogenic antibodies by anti-idiotypes (neutralization of antigens). Third, inhibition of complement deposition on targets and decreased anaphylotoxin function. Fourth, regulation of Fc receptor (FcR, fragment crystallizable receptor) function, alpha 2,6-sialic acid on the variable Fab (fragment antigen-binding), and constant Fc can down-regulate proinflammatory cytokines and up-regulate anti-inflammatory factors through a variety of ways, and induce cell apoptosis. Its T cell epitope peptides, called Tregitopes, which induce Tregs to respond, leading to generation of regulatory signals. Fifth, formation of immune complexes that block phagocytosis, increased catabolism of pathogenic IgG molecules, modulation of FcR function, and acceleration of cerebral function recovery. It has been suggested that high-dose IVIG can serve as an anti-inflammatory and immunomodulatory agent in patients. IVIG also has anti-inflammatory properties that prevent the formation of and down-regulate cytokines and can thereby be efficacious even if the primary problem is a post-infectious inflammatory reaction. In summary, we hypothesize that patients with GPI treated with IVIG and penicillin G would have better outcomes than those treated with penicillin G alone. The hypothesis need being further verified by more cases treated with penicillin combined with IVIG contrast with only penicillin. To the best of our knowledge, this is the first case of GPI treated in this way. IVIG may be introduced as a necessary treatment for GPI.

Conclusion
Management with a large doses of IVIG combined with penicillin may be a choice for patient with GPI.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article:

Figure 1. MRI revealed large symmetric areas of long T1, long T2, and high FLAIR signals adjacent to the body of the bilateral ventricles of the temporal and parietal lobes.

Figure 2. MRI showed smaller areas of long T1, long T2, and high FLAIR signals adjacent to the body of the bilateral ventricles of the temporal and parietal lobes compared with the results obtained 10 months previously.
work was supported by University Natural Science Research Project of Anhui Province (CN) (KJ2013A189).

**Ethical approval**

Ethical approval to report this case was obtained from Bengbu Medical College ethics review board (2020KY097).

**Informed consent**

We have obtained written informed consent from the legally authorized presentative (sons of the patient) of the patient for the publication of this case report.

**ORCID iD**

Sang Daoqian  [https://orcid.org/0000-0003-4794-4909](https://orcid.org/0000-0003-4794-4909)

**References**

1. Workowski KA, and Berman S. and Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep* 2010; 59: 1–110.

2. Allen M, Aisenberg G, Nix B, et al. Psychosis in neurosyphilis: An association of poor prognosis. *Gen Hosp Psychiatry* 2014; 36: e5–e6.

3. Kingston M, French P, Higgins S, et al. UK national guidelines on the management of syphilis 2015. *Int J STD AIDS* 2016; 27: 421–446.

4. Workowski KA, and Bolan GA. and Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. *MMWR Recomm Rep* 2015; 64: 1–137.

5. Forest A, Barrou Z and Verny M. Neurosyphilis and cognitive disorders. *Geriatr Psychol Neuropsychiatr Vieil* 2013; 11: 423–431.

6. Rao A, Khan A, Singh K, et al. Neurosyphilis: An uncommon cause of dementia. *J Am Geriatr Soc* 2015; 63: 1710–1712.

7. Saik S, Kraus JE, McDonald A, et al. Neurosyphilis in newly admitted psychiatric patients: Three case reports. *J Clin Psychiatry* 2004; 65: 919–921.

8. Gilad R, Lampl Y, Blumstein G, et al. Neurosyphilis: The reemergence of an historical disease. *Isr Med Assoc J* 2007; 9: 117–118.

9. Bhai S and Lyons JL. Neurosyphilis update: Atypical is the new typical. *Curr Infect Dis Rep* 2015; 17: 481.

10. Hahn RC, Webster B, Weickhardt G, et al. The results of treatment in 1,086 general paralytics the majority of whom were followed for more than five years. *J chronic Dis* 1958; 7: 209–227.

11. Beauchemin P and Laforce R Jr. Neurocognitive changes in tertiary neurosyphilis: A retrospective chart review. *Can J Neurol Sci* 2014; 41: 452–458.

12. Stamm LV and Drapp RL. A synthetic lymph node containing inactivated *Treponema pallidum* cells elicits strong, antigen-specific humoral and cellular immune responses in mice. *Pathog Dis* 2014; 70: 88–94.

13. Leader BT, Godornes C, VanVoorhis WC, et al. CD4+ lymphocytes and gamma interferon predominate in local immune responses in early experimental syphilis. *Infect Immun* 2007; 75: 3021–3026.

14. Cruz AR, Ramirez LG, Zuluaga AV, et al. Immune evasion and recognition of the syphilis spirochete in blood and skin of secondary syphilis patients: Two immunologically distinct compartments. *PLoS Negl Trop Dis* 2012; 6: e1717.

15. Salazar JC, Cruz AR, Pope CD, et al. *Treponema pallidum* elicits innate and adaptive cellular immune responses in skin and blood during secondary syphilis: A flow-cytometric analysis. *J Infect Dis* 2007; 195: 879–887.

16. Berger M.. Another new mechanism of action of IVIG. *Clin Immunol* 2011; 139: 105–106.

17. Yu X, Vasiljevic S, Mitchell DA, et al. Dissecting the molecular mechanism of IVIg therapy: The interaction between serum IgG and DC-SIGN is independent of antibody glycoform or Fc domain. *J Mol Biol* 2013; 425: 1253–1258.

18. Sobolev SM, Nikolaeva TN and Pronin AV. “Non-immune” interactions of gamma-globulin in regulation of immune reactions. *Vestn Ross Akad Med Nauk* 2011; 10: 60–62.

19. Cousens LP, Tassone R, Mazer BD, et al. Tregitope update: Mechanism of action parallels IVIg. *Autoimmun Rev* 2013; 12: 436–443.