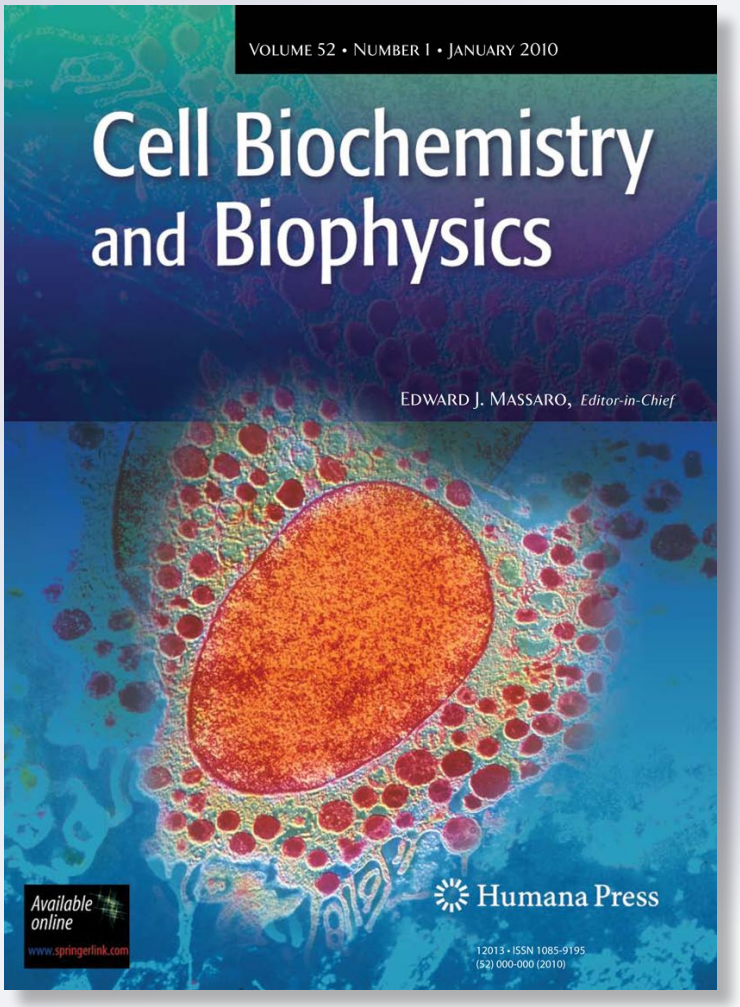
Drug-Indiced Aseptic Meningitis: Development of Subacute Sclerosing Panencephalitis Following Repeated Intraventricular Infusion Therapy with Interferon Alpha/Beta

George Imataka, Eiji Nakagawa, Hideo Yamanouchi & Osamu Arisaka

Cell Biochemistry and Biophysics

ISSN 1085-9195
Volume 61
Number 3

Cell Biochem Biophys (2011) 61:699-701
DOI 10.1007/s12013-011-9228-y



Springer

Cell Biochem Biophys (2011) 61:699–701
DOI 10.1007/s12013-011-9228-y

TRANSLATIONAL BIOMEDICAL RESEARCH

Drug-Indiced Aseptic Meningitis: Development of Subacute Sclerosing Panencephalitis Following Repeated Intraventricular Infusion Therapy with Interferon Alpha/Beta

George Imataka · Eiji Nakagawa · Hideo Yamanouchi · Osamu Arisaka

Published online: 12 July 2011

Abstract Interferon (IFN)-α was reported to be effective in longterm intrathecal treatment of subacute sclerosing panencephalitis (SSPE). However, the side effects related with longterm use of IFN-α/β are unclear. We evaluated the therapeutic effects of IFN-α/β in a 13-years-old patient with SSPE. The cerebrospinal fluid (CSF) measles antibody titer was 64 × NT/128×HI, IgG-index was 4.5, and the SSPE diagnosis was based on electroencephalography (Jabbour-stage II on admission). With Inosiplex (INP) given orally, IFN-α (3×10^6 units) was infused intraventricularly twice-a-week for 1-year. Resultantly, CSF cell count was elevated (2502/3), total protein and glucose levels were normal; however, DIAM occurred repeatedly. Consequently, reduced IFN-α (5×10^5 units) with hydrocorton was administered at 2-months interval for 19 months, during which, DIAM occurred four times. Therefore, IFN-β (3×10^6 units; twice-a-week) therapy was started and continued for 3 years. Although the symptoms were improved considerably, DIAM recurred after 15-months therapy and CSF cell counts were also elevated (2121/3). Since SSPE progressed to Jabbour-stage IV, indicated by irreversible consciousness disorder, IFN therapy was discontinued and INP monotherapy was followed for another 3 years. We, therefore, concluded that the longterm intraventricular IFN-α/β infusion therapy of SSPE involved the potential risk of DIAM with serious irreversible neurological sequelae and should be monitored carefully.

G. Imataka (✉) · O. Arisaka
Department of Pediatrics, Dokkyo Medical University School of Medicine, Kitakobayashi 880, Mibu, Tochigi 321-0293, Japan
e-mail: geo@dokkyomed.ac.jp

E. Nakagawa
Department of Pediatric Neurology, National Center of Neurology and Psychiatry, Musashi Hospital, Kodaira, Japan

H. Yamanouchi
Department of Pediatrics, Saitama Medical University School of Medicine, Saitama, Japan

Introduction

Miyazaki et al. have reported a successful long-term intrathecal treatment of subacute sclerosing panencephalitis (SSPE) with interferon (IFN) alpha [1]. As those authors suggested, this drug may be effective and safe for SSPE. The clinical course in which IFN prolonged survival will give hope to many patients with SSPE.

We also performed intraventricular infusion therapy with IFN in with SSPE. Short-term follow-up confirmed improvement in the clinical symptoms. However, drug-induced aseptic meningitis (DIAM) repeatedly occurred even after 1 year since the start of this therapy, thereby rapidly deteriorating the neurological symptoms. In this article is reported the first case in which intraventricular infusion therapy with IFN alpha/beta caused repeated DIAM and this agent remained a serious neurological sequela. We describe the clinical course and discuss this serious adverse effect with DIAM due to intraventricular infusion therapy with IFN alpha/beta.

Case Report

The patient developed measles at 11 months of age. At 12 years and 10 months of age, failure of memory, personality changes, and myoclonic seizure appeared. The cerebrospinal fluid (CSF) measles antibody titer was 64× in the NT method and 128× in the HI method. The CSF

measles antibody titer was 16× in the two methods. When ELISA was employed, the anti-IgG antibody titer was 640.0 (cutoff value: 2.0). The patient was positive for CSF oligoclonal IgG band. The IgG index was 4.5. Electroencephalography revealed periodic synchronous discharge, suggesting SSPE (Fig. 1). On admission, the stage was evaluated as Jabbour II. Inosiplex (INP) was orally administered, and intraspinal injection therapy with natural human lymphoblast IFN-α (Sumiferon®) at 3,000,000 units was performed twice a week. After 1.5 months, Ommaya reservoir was inserted to the ventricle, and intraventricular infusion was started. After 1 year of treatment, DIAM repeatedly occurred; fever was observed 12 h after IFN administration. CSF from ventricular tap showed elevated cell counts of 2,502/3. The total protein level was slightly increased. The glucose level was normal. Meningeal sings improved in a few days. Subsequently, the dose of IFN-α was decreased to 500,000 units, and combination therapy with IFN-α and hydrocorton was administered at 2-month intervals. However, DIAM recurred four times. After 1 year and 7 months of treatment, the regimen was switched to IFN-β (Betaferon®) at 3,000,000 units, which was administered twice a week, because of recurrent DIAM. After that, DIAM did not recur for 1 year and 3 months. After 3 years of treatment, improvement in the symptoms facilitated drawing a picture (Fig. 2), reading characters, and sitting. However, 3 years and 4 months after onset, IFN-β-related DIAM developed, with elevated cell counts of 2,121/3 in CSF. Irreversible consciousness disorder rapidly occurred, suggesting Jabbour stage IV. Then, IFN therapy was discontinued, and single therapy with INP was continued for 3 years and now, the stage remains Jabbour IV.

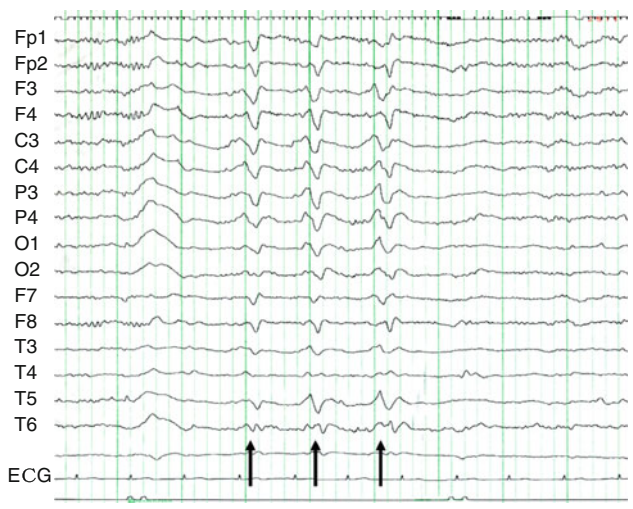


Fig. 1 Electroencephalography of the patient showed typical type of periodic synchronous discharge (arrows:↑)

Fig. 2 She drawing the beautiful picture with word, number, human, animals, and flower with full of colors

Discussion

In 1978, Widener and Littman [2] indicated the development of DIAM after administration of ibuprofen to patients with systemic lupus erythematosus. Since then, DIAM has been reported to as a side effect in patients with autoimmune disease. Non-steroidal anti-inflammatory agents, antibiotics, vaccine, agents for intraspinal administration, and various other agents caused DIAM [3]. Recently, massive dose of immunoglobulin therapy has been administered to treat primary immunodeficiency, Kawasaki disease, Guillain–Barre syndrome, and idiopathic thrombocytopenic purpura, and the incidence of immunoglobulin-related DIAM has increased [4]. The pathogenesis of DIAM remains to be clarified; however, drug administration rapidly caused DIAM, but DIAM improved immediately after discontinuation. Therefore, the pathogenesis may involve hypersensitivity reaction related to the direct reactions of drugs and type III allergic hypersensitivity response via the immune mechanism. DIAM does not cause any specific symptoms other than meningeal signs. However, DIAM develops within 48 h after drug administration, and improves immediately after discontinuation. For continuous administration, the interval until the symptom appears is shortened with the frequency of dosing. For diagnosis, diagnosis by exclusion is performed. Many studies have reported a good prognosis; the symptom improves immediately after discontinuation, without sequelae.

However, in our patient, DIAM repeatedly occurred, resulting in severe sequelae, although we switched from IFN-α to IFN-β. In the present patient, IFN was directly administered into the ventricular pulp cavity via a reservoir placed in the ventricle, suggesting that a direct stimulus to the meninges induced DIAM. However, the immune

mechanism in the onset of DIAM remains to be clarified. While administering long-term intraventricular infusion therapy with IFN to patients with SSPE, the risk of DIAM, which may lead to serious irreversible neurological sequelae as demonstrated in our patient, should be considered.

References

1. Miyazaki, M., Nishimura, M., Toda, Y., Saijo, T., Mori, K., & Kuroda, Y. (2005). Long-term follow-up of a patient with subacute sclerosing panencephalitis successfully treated with intrathecal infection alpha. *Brain and Development, 27*, 301–303.
2. Widener, H. L., & Littman, B. H. (1978). Ibuprofen-induced aseptic meningitis in systemic lupus erythematosus. *JAMA, 239*, 1062–1064.
3. Jolles, S., Sewell, W. A., & Leighton, C. (2000). Drug-induced aseptic meningitis: Diagnosis and management. *Drug Safety, 22*, 215–226.
4. Sekul, E. A., Cupler, E. J., & Dalakas, M. C. (1994). Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: Frequency and risk factors. *Annals of Internal Medicine, 121*, 259–262.