PSYCHIATRIC SIDE EFFECTS OF INTERFERON

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Introduction

Interferon (IFN), a cell-derivative chemical mediating protein (cytokine), was first found in 1950s as a virus migration inhibition factor. Other functions of IFN, such as cell migration inhibition and immune-adjusting functions, were found later, and IFN was used for therapeutic drug for hematopoietic tumors, renal cell carcinoma, type-B hepatitis, and so on. In Japan, the usage of IFN as a therapeutic drug for type-C hepatitis has occurred more frequently since it came to be covered by Japanese health insurance.

The number of reports of side effects with IFN is increasing. Initial side effects include influenza-like symptoms, such as fever, fatigue, headache, joint pain, muscle pain, and back pain. These are followed by general symptoms such as fever, fatigue, and body weight loss, digestive symptoms such as appetite loss, nausea, and diarrhea, and cutaneous symptoms such as skin eruption. Long-term side effects include alopecia and autoimmune disorders. Also, interstitial pneumonia, thyroid dysfunction, cardiomyopathy, retinopathy are recently reported.

Psychiatric symptoms are another, and probably the most troublesome, side effects which internal medical doctors encounter. Suicides and suicidal attempts due to depressive state during IFN treatment were reported by the Ministry of Health on March, 1994.

In this report, we explain IFN treatment briefly and two current cases which showing psychiatric symptoms during their treatment. Also, we demonstrate the characteristics of the psychiatric symptoms found in Japan and discuss whether they are predictable or not.

1. IFN Treatment

In Japan, IFN such as α (natural type), α-2a (gene transplant type), α-2b (gene transplant type), and β (natural type) are used for treatment of chronic type-C hepatitis. For this purpose, IFN α is usually used daily for 2 to 4 weeks, followed by 22 to 24 weeks of administration 3 times a week. IFN β is used daily for 6 weeks. No significant differences among IFN types are reported. Treatment is effective for 30–40% of the cases, although the type of IFN is determined according to the administrative route (muscular injection for α types and intravenous injection for β types), other differences include appearance of antibodies (transplant types have higher percentages of making antibody production than natural types), and cost (the cost for natural types is higher than for transplant types).

Factors determining the effectiveness of treatment are various, including the quantity of HCV-RNA and types of HCV gene, and the best method is not yet determined.

2. Case reports (Yokoyama et al., 1984)

1) A case with depressive state, 38-year-old, female, school teacher

She divorced three months previous to the IFN treatment, and got treatment for insomnia by hypnotics at a nearby hospital for one month.

In July 1992, type-C hepatitis was indicated
at a physical checkup. She stayed in the hospital from August, and was diagnosed as having chronic, active hepatitis by biopsy. She was discharged after 2 weeks of continuous IFN α-2a (9MU) treatment, and administration 3 times a week. She developed anxiety, chills, appetite loss, headache, face flushing, and gastric discomfort, which were improved by digestive medicine.

She got back to work from September 1, but became depressive by the end of September. She continued to work, but was not working efficiently, and felt that she was bothering students and other teachers, and saw a psychiatrist on October 4. Upon visiting, she mentioned depressive mood, fatigue, insomnia, appetite loss, psychomotor retardation, and self-accusation. No remarkable findings were noted in her brain CT scan and electroencephalogram.

Because she wanted to continue IFN treatment but was unwilling to be admitted to a hospital, we started anti-depressants while continuing IFN. After one week, no significant improvement was found, so we recommended her suspension from duty. One week later, her depressive state got better and the antidepressants was stopped.

She got back to work from the beginning of November, and IFN was continued until February, 1993 with no psychiatric side effects.

Summary: Depressive state occurred after 2 months of IFN treatment and continued for 3 weeks. Psychiatric symptoms improved by the medication and suspension from duty, although the IFN treatment was continued.

In this case, however, psychological factors such as divorce and her struggle for getting back to work cannot be excluded for the reason for her psychiatric symptoms.

2) A case with delirious state, 57-year-old housewife

In November 1991, she visited a nearby hospital for upper abdominal pain, and was diagnosed as having type-C hepatitis. The IFN treatment started from May, 1992. After 2 weeks of continuous IFN α-2b administration, administration was continued at a nearby hospital 3 times a week.

Appetite loss and body weight loss appeared from November 1992, and from December 21, total insomnia appeared. On December 24, she complained of agitation and restlessness, and said “My daughter is coming. She is hiding”. On December 26, she was admitted to a mental hospital. She was is confused state, showing delirium, but hallucination was not appeared.

One week after admission, a low-grade fever of 37°C appeared, followed by delirium-like hallucinatory-paranoid state. While her consciousness was quite clear, abnormal experiences were strong, sensitive, and negative. Neuroleptics were used for these symptoms, which improved by February 15.

Summary: In this case, the psychiatric symptoms followed by fever appeared 6 months after IFN treatment, which lasted for nearly 2 months. The symptoms were delirium which included hallucination and delusion.

3. Characteristics of Psychiatric Side Effects

1) Sex, age

There is no remarkable difference based on either sex or age.

2) Symptoms

More than 2/3 of the symptoms are depressive state. Other symptoms such as hallucinatory-paranoia, confusion, delirium, anxiety, agitation, and insomnia are also reported.

3) Types of IFN

Psychiatric symptoms appear with all types of IFN, including α, α-2a, α-2b, and β types.

4) Total Dose of IFN

There is individual variation, from 30 MU to 300 MU. High dose of IFN tend to correspond with severe symptoms, such as hallucination, delusion, delirium, convulsion, and coma.

5) Interval between IFN treatment and onset of psychiatric symptoms

While symptoms can occur any time during the IFN treatment, 20% occur within 1 week after starting the treatment, 40% within 2 weeks, 60% within 1 month, 90% within 3 months.

6) Past History of Psychiatric Treatment

Nearly 30% of the cases had a past history of depression, alcohol dependency, and schizophrenia, although in some cases, the patient did not tell the exact truth about his/her past and family history. A case in which IFN was used for a schizophrenic patient who did not show any psychiatric side effects is also reported (Ogawa et al., 1993).
7) IFN treatment after the appearance of psychiatric symptoms

IFN treatment was stopped in 2/3 of the cases, while in some cases, IFN was continued regardless of psychiatric symptoms, such as depression and anxiety.

8) Prognosis of psychiatric symptoms

In cases in which the depressive state appeared and IFN treatment was stopped, 1/2 of the cases were remitted within 2 weeks, and almost all of the cases within 1 month. As for hallucinatory-paranoid and/or delirious states, most of the cases were remitted within 1 month, but in some cases, the symptoms lasted for awhile after stopping the treatment.

9) Frequency of psychiatric symptoms

According to the clinical trial reports, the frequency of psychiatric symptoms was 1.6%. However, cases which required psychiatric treatment and/or interruption of IFN treatment were seen on 8.5% of the time, and cases which had symptoms although psychiatrists did not become involved were seen 20 to 30% of the time.

10) Laboratory finding

Diffuse slow waves in the electroencephalogram, especially in the frontal areas, are often reported. In most of the cases, this is reversible, and such waves decreased in 3 to 14 days after stopping IFN. Abnormal electroencephalogram also appear on asymptomatic cases, though.

No abnormalities were reported in brain CT scan and CSF.

4. Pathological mechanism

Many factors may be involved in the onset of psychiatric symptom, although the mechanism in still unknown.

1) Direct and indirect action of IFN on the nervous system

IFN has a high molecular weight and does not normally pass through the blood-brain barrier, but with high doses of IFN, a few percent can pass through the barrier. It acts on the nervous system by permeation through areas such as organs without the barrier.

In animal experiments, fever, appetite loss, and slow wave sleep followed by IFN administration, suggesting directly on the nervous system. Morphine-like analgesia and catalepsy appeared in mouse experiments (De Sarro et al., 1990).

IFN also has nervous action, and some report that IFN suppresses dopamine transmission causing parkinsonism and akathisia (Sasano and Watanabe, 1993).

Recent reports also state that cytokine forms a complex network for transmission and regulation of the immune, nervous, and endocrine systems via endocrine hormones and neurotransmission. In addition to direct action on the central nervous system, IFN administration is involved in the secondary reactions as well.

Secondary functions of IFN which may be involved in the appearance of psychiatric symptoms are (1) activation of other cytokines (the depressive state often appears in influenza psychosis), (2) changes in the nervous-endocrine system, especially a rise in cortisol concentration, as IFN is similar in structure and function to ACTH (the depressive state often appears in Cushing’s syndrome), and (3) IFN promotes the activation of the opioid receptor (it supresses the release of noradrenaline) (Meyers et al., 1991).

2) Individual factors

Liver dysfunction: Patients with chronic hepatitis are likely to be sensitive to stress and fatigue.

Past history, Hereditary factors: Past history of psychiatric disorders and autoimmune disorders are among the points needing careful consideration regarding IFN treatment, and many reports support this. In autoimmune diseases, there is a possibility of not only worsening the original disorders but also inducing psychiatric symptoms via the nervous-immune-endocrine system.

Abnormalities in brain imaging are reported as a risk factor in IFN neurotoxicity (Adams et al., 1988).

Personality trend: Extroverted character is reported to be a risk factor for depression caused by IFN (Otsubo et al., 1994). Melancholic character, featuring high responsibility and methodical, is also reported as a risk factor. In our study via the DRP questionnaire, the group that became depressive tended to have a depressive affinity character compared to the control group (Aoki et al., 1995).

Psycho-social stress: There is much stress and anxiety in IFN treatment, including factors of as being in the prime of life, risk of liver cirrhosis.
and hepatic cell cancer, lack of possible treatment of hepatitis C, long time required for treatment, flu-like side effects, and so on. Such stress and anxiety factors may lead to a stressful state that is likely to effect the appearance of psychiatric symptoms. Other stress items, such as divorce, broken heart, transference, distrust of hospital, and so on, could be involved during the IFN treatment, although this obviously depends upon the individual case.

Results—Are psychiatric symptoms predictable?
As we have discussed above, many factors are involved in the appearance of psychiatric symptoms, and it is difficult to predict them. Therefore, it is essential to know the patient’s past and present history of nervous-immune-endocrine disorders, hereditary factors, and personality trends. Exams such as electroencephalogram, brain CT scan, brain MRI, and psychological exams are essential as well. During the treatment, the dose amount, body weight, and general condition are important, and it is also necessary to examine, and in some cases adjust, the psycho-social factors involved in the treatment.

References


