Neuropsychiatric Symptoms Related to Interferon Therapy

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Abstract: The severity and duration of side effects of interferon (IFN) therapy vary considerably. The neuropsychiatric symptoms induced IFN therapy are the most frequent reason for discontinuing it. The incidence of neuropsychiatric symptoms is as high as 30 to 40% when mild neuropsychiatric alterations are included. Among various neuropsychiatric symptoms, affective disorders such as depression are predominant, followed by cognitive disorders such as delirium. Others include insomnia, anxiety, irritability, mania, delusion, hallucination, and change to aggressive personality. Neuropsychiatric symptoms occur at a wide range of times during IFN therapy. Characteristics of patients at risk of experiencing neuropsychiatric symptoms during IFN therapy include high age, high dosage of IFN, severe comorbid physical disorders, a history of psychiatric illness, neurotic premorbid personality, organic brain disease, family history of psychiatric illness, severe depression/somatic anxiety/sleep disturbance before treatment, and low degree of informed consent to IFN therapy. In general, dosage reduction or discontinuation of IFN is recommended in cases of IFN neurotoxicity. If necessary, psychotropic agents are to be administered. We should make carefully and early intervention in any case where there is evidence of possible suicidal tendencies.

Key words: Interferon; Depression; Suicide; Delirium; Side effect; Neurotoxicity

Introduction

Among various side effects of interferon (IFN), neuropsychiatric side effects are frequently observed and most likely to prohibit the continuation of the therapy. Suicide attempts related to IFN therapy are a particularly serious concern. Therefore, IFN should be used under careful monitoring.

Diagnosis of Drug-Induced Mental Disorders

It is important to clarify the time relationship
resses to liver cirrhosis and hepatic cell carcinoma if it is not treated promptly, and IFN is effective in only about 30% of chronic hepatitis patients. IFN is being used for the treatment of different malignancies, such as multiple myeloma, and chronic myelogenous leukemia. It is therefore important to note that the psychological factors of patients with the indications for IFN are far from normal.

Neuropsychiatric Symptoms Related to IFN Therapy\(^1-6\) (Table 1)

1. Incidence of neuropsychiatric symptoms
To summarize the previous reports, approximately 10% of patients with chronic hepatitis C develop neuropsychiatric complications requiring treatment with psychiatric drugs or discontinuation of IFN therapy. About 30–40% of patients experience mild psychiatric complications.

2. Classification of neuropsychiatric symptoms
Although neuropsychiatric symptoms vary, affective disorders such as depression are most frequent, followed by cognitive disorders including delirium. Others include insomnia, anxiety, irritability, mania, delusion, hallucination, and change to aggressive personality.

3. Onset and duration
Influenza-like symptoms such as fever, headache, fatigue, anorexia, nausea, vomiting, and insomnia develop within one week after the start of IFN therapy. Since these primary symptoms cause both physical and neuropsychiatric discomfort, the failure to appropriately treat them leads to persistent insomnia and anxiety, which form a basis for secondary neuropsychiatric symptoms.

During the intermediate stage of IFN therapy (from weeks 1 to 8), the following symptoms may occur: insomnia, anxiety, irritability, depression, mania, delusion, hallucination, and change to aggressive personality, delirium, and...

**Table 1 Characteristics of Neuropsychiatric Symptoms Related to Interferon**

1. Most of the neuropsychiatric symptoms of IFN are depression, and the remainder are forms of delirium.
2. Depression often develops as psychomotor retardation or anxiety/irritability with aggressiveness.
3. Insomnia often precedes depression. Sometimes severe depression occurs suddenly and the patient becomes suicidal.
4. Approximately 10% of patients with chronic hepatitis C develop neuropsychiatric complications requiring treatment with psychiatric drugs or discontinuation of IFN therapy. About 30–40% of patients experience mild psychiatric complications.
5. Neuropsychiatric symptoms occurred at a wide range of times during IFN therapy.
6. Most neuropsychiatric symptoms disappear within several days to 2 weeks after discontinuation of IFN therapy, but some may persist.
7. In some patients who have no clouding of consciousness, EEG abnormalities such as slowing of background activities is also observed.


Psychological Factors of Patients with Indications of IFN Therapy

It has been pointed out that important psychological factors affect chronic hepatitis C patients treated with IFN. The patients know that in most cases chronic hepatitis C prog...
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During the last stage of treatment (2 months and later), patients often experience insomnia, continued fatigue, and depression. High-dose IFN therapy may cause IFN cerebroPATHY in patients with malignant tumors. It is characterized by somnolence, delirium, confusion, mental and motor slowing, difficulty in concentrating, memory impairment, and seizures, and it is associated with electroencephalogram (EEG) abnormality such as slowing of background activities.7)

4. Risk factors1,2,6) (Table 2)

The risk factors of neuropsychiatric symptoms are classified into drug and patient factors. Drug factors include dosage (high dosage), application form (intracerebroventricular > intravenous > intramuscular > subcutaneous), and schedule of IFN therapy (everyday > intermittingly), while patient factors include the type and severity of underlying disease (malignancy > hepatitis), comorbid chronic physical disorders, premorbid personality (neurotic or typus melancholicus), history of psychiatric illness and organic brain disease (brain injury, atrophy, trauma, metastasis), family history of psychiatric illness, (low) degree of informed consent to IFN therapy, and age (high age).

Table 2 Possible Risk Factors for Neuropsychiatric Symptoms of IFN

1. High dosage (One day dosage)
2. High age
3. Organic brain injury or dysfunction (atrophy, trauma, metastatics, etc.)
4. Current or previous psychiatric diagnosis
5. Drug and alcohol abuse
6. Depressive state before the start of IFN therapy
7. Sleep disturbance before the start of IFN therapy
8. Strong anxiety for somatic disorders (HCV, RCC, CML, etc.)
9. HIV infection
10. Premorbid personality (neurotic, typus melancholicus)
11. Personality disorder

Depression, Suicidal Ideation, and Suicide Attempts as the Most Serious and Life-Threatening Adverse Reactions Requiring Full Attention

The investigation by the Ministry of Health and Welfare5) into 32 patients who attempted suicide (including 12 who died by suicide) showed that about 80% of them attempted suicide within three months from the start of IFN therapy, and that 20% had a history of depression or psychiatric disorders. Typical cases impulsively and suddenly attempted suicide in a negligent, impatient, and desperate mood after they expected insomnia, anxiety, and irritability for more than two weeks persistently. It should be noted that they attempted suicide with no clear forewarning.

Our prospective study led by Otsubo5) showed that 37.3% of 85 patients with hepatitis C had depression during IFN therapy, and that the following factors could indicate a depressive state: neurotic premorbid personality, severe depression, insomnia and anxiety about disease before IFN therapy. Typical symptoms associated with depressive states include being easily tired, loss of ambition, and loss of thought or concentration. Most patients experience insomnia before entering a depressive state, but sometimes severe depression occurs suddenly in one or two days and the patients become suicidal.

Putative Mechanisms Underlying IFN-Induced Neuropsychiatric Symptoms1–6)

(1) IFN is indicated for serious disease with relatively poor prognosis, such as chronic active hepatitis C, renal cell carcinoma, multiple myeloma, and chronic myelogenous leukemia. Since the patients have obtained substantial medical knowledge from the mass media, many patients tend to be pessimistic. Such diseases restrict the social activities of the patients, and the patients encounter economic difficulties and a poorer
quality of life. Under these situations, the patients readily feel hypochondriac, desperate, and depressed and have only pessimistic views of their future. It is inevitable that this may lead to suicidal ideation and thence to suicide attempts.

(2) The direct cytokine effect of IFN on the central nervous system (CNS) or the neurotoxicity of cytokines induced by IFN may also influence the CNS. IFN stimulates the activation of neurons, induces convulsions, and increases slow waves in EEG. However, these phenomena have not been fully explained because IFN is hardly able to cross the blood-brain barrier (BBB) and has a short half-life. Nevertheless, IFN enter the brain via the circumventricular organs associated with the hypothalamus, where is no BBB. This enables it to directly influence the brain.

(3) IFN is known to induce production of secondary cytokines, such as IL-1 and tumor necrosis factor (TNF), which may be neurotoxic. IL-1 induces fever, sleep associated with slow EEG activity, and loss of appetite, and stimulates the hypothalamic-pituitary-adrenal (HPA)-axis. IFN is structurally and functionally similar to neuroendocrine hormones, such as ACTH, and the plasma cortisol level has been reported to increase during IFN therapy. It has been suggested that the HPA-axis stimulation caused by IFN is related to the occurrence of depression or suicide.

(4) IFN has also been shown to have opiate-like neurotransmitter activity, and IFN may reduce the activities of noradrenaline in the locus ceruleus mediated by opiate receptors.

(5) It is also possible that the malignant tumors or hepatitis virus for which IFN is indicated may be directly involved in neuropsychiatric symptoms.

Treatment of Neuropsychiatric Symptoms Associated with IFN

(1) If neuropsychiatric symptoms occur with IFN therapy, dosage reduction is often recommended, and if serious suicidal ideation occurs, IFN is usually discontinued and the patient hospitalized.

(2) Appropriate psychotropic drugs should be administered if psychiatric symptoms persist after IFN is discontinued. Anxiolytic drugs should be administered for anxiety, irritability, and insomnia. Unlike other benzodiazepine anxiolytic drugs, lorazepam (Wypax) is directly glucuronate-conjugated and quickly excreted, and this metabolic pathway is maintained even in patients with advanced hepatic disease. Lormetazepam (Evamyl/Loramet) is recommended as a hypnotic for insomnia because of its one-step metabolic pathway.

Previously, depression, suicidal ideation, and suicide attempts were treated with tricyclic antidepressants such as amitriptyline (Tryptanol), which have both antidepressant and sedative effects, although they may cause dry mouth, dysuria, constipation, or eye modulation disorder. Some selective serotonin reuptake inhibitors (SSRIs) with almost no such anticholinergic effects have recently became available in Japan: they include fluvoxamine (Depromel/Luvox) and paroxetine (Paxil). Although they are useful and have fewer adverse reactions, they often cause digestive disorder. Milnacipran (Toledomin), a serotonin and noradrenaline reuptake inhibitor (SNRI), is safe due to its lack of interaction with other drugs.

For psychotic symptoms including hallucination/delusion and excitement, antipsychotics, such as haloperidol (Serenace), are often selected, although they caused extrapyramidal symptoms (EPS) at high incidences. Recently, antipsychotics with fewer EPSs and little effect on the cardiac circulation system have been increasingly used: such drugs include risperidone (Rispadal), olanzapine (Zyprexa), quetiapine (Seroquel), and perospirone (Lullan).

(3) There are various IFN preparations, and it has not been determined which preparation is likely to cause psychiatric symptoms. It is worth trying to switch from one IFN preparation to another.

Incidentally, the treatment of chronic hepato-
titis C, which had almost reached its limit with conventional IFN therapies, has entered a new paradigm with new therapeutic techniques from Western countries. They include therapy with consensus interferon (cIFN) obtained by the molecular-biological synthesis of parts common to many of 13 subtypes of IFN-α and the use of Peg-IFN, which extends the drug’s activities for a long period due to the combination with polyethylene glycol. Further, the combination therapy of IFN and ribavirin has become a standard therapy for chronic hepatitis C in Western countries because it has a markedly increased complete response rate. Ribavirin is a quanosine derivative that acts widely on DNA and RNA viruses. Maddrey, who investigated the adverse reactions of combination therapy in 2,089 patients, noted that suicide was attempted by 24 patients, including 14 who had a history of suicide attempts. However, he considered that the psychiatric symptoms were mainly attributable to IFN and not worsened by ribavirin.

Prevention of Neuropsychiatric Symptoms Induced by IFN

1) It is necessary to carefully examine whether the target disease responds to IFN or not and strictly decide whether IFN is indicated for it or not. For chronic hepatitis C, viral type and amount, progression, and the balance of benefit and risk should be considered in deciding the type, dosage, and administration method and period of an IFN preparation to be used.

2) In principle, IFN should not be used for patients with a history of psychiatric disorder. IFN should be administered under strict control in patients who have a family history of psychiatric disorder. IFN should be immediately discontinued if any psychiatric symptom occurs.

It is necessary to inquire into the history of depression or depressive state in detail: the main symptoms, clinical course, and treatment given in medical institutions are important items of information. Since depression is associated with high familial aggregation, it is necessary to inquire as to whether there is any family history of psychiatric disorders. The following questions are typically asked: “Have you ever felt depressed or miserable without specific reason?”, “Have you ever felt any loss of energy or difficulties in continuing your work?”, “Have you ever experienced loss of interest in your favorite TV programs or books?”, and “Have any of your family members committed suicide?” If a patient clearly has a history of depression, it is necessary to discuss with the patient whether IFN should be ruled out, or started only under strict monitoring. It is also important to inform the patient’s family members that psychiatric symptoms may occur, and that they have to carefully observe the patient and keep communicating with the medical professionals concerned.

3) Patients and their families must be informed of what chronic hepatitis C is, what IFN therapy is, and possible side effects of IFN therapy. Furthermore, physicians should remember to inform them that IFN therapy is not the only choice for treatment of chronic hepatitis C, if the therapy is discontinued because of side effects. Psychotherapy, such as supportive psychotherapy, may be effective for treating IFN-induced depression.

4) Psychiatrists can advise physicians specializing in other fields of medicine on how to diagnose, treat, and handle the psychiatric state and behavior of patients. This function is called consultation. Psychiatrists can organize medical teams based on continuous cooperative relationships with physicians specializing in other fields of medicine, nurses, and caseworkers to help handle, and give instructions on, psychiatric issues in other departments. This function is called liaison. Putting consultation-liaison psychiatry into practice will help prevent adverse reactions to IFN.

5) It is necessary for medical professionals who handle any IFN preparation to carefully read its attached papers and fully understand it.

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All IFN preparations have a warning about suicide attempts, and the adverse events requiring closest observation, at the top of each attached paper.

Conclusions

Psychiatric symptoms induced by IFN prevent patients from continuously receiving effective care and, in the worst-case scenario, cause suicide. It is necessary to carefully decide whether IFN is indicated or not for each patient, obtain informed consent based on full explanation, and administer IFN carefully.

Each patient and his/her family members should be asked whether they have any history of psychiatric symptoms before starting IFN. If any psychiatric symptom develops, it should be appropriately handled and carefully observed. It is necessary to inform family members of possible psychiatric symptoms in advance. It is useful to put consultation-liaison psychiatry with psychiatrists into clinical practice to prevent the progress of psychiatric symptoms and ensure appropriate action by medical teams.

REFERENCES