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Psychotic disorders as a complication of interferon-α treatment of hepatitis C

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Summary

Low-dose long-term interferon-α is a standard therapy for hepatitis C and is often associated with neuropsychiatric side effects, most frequently depression, mild cognitive impairment and fatigue which disappear with cessation of such treatment. Psychotic disorders are a rare complication of the treatment and usually resolve with its termination. In this paper, a review of the literature on interferon-α-induced psychotic disorders in hepatitis C patients has been performed. Epidemiology, predisposing factors, clinical picture, treatment and mechanisms of this serious neuropsychiatric complication have been discussed. Also, an own case of chronic schizophreniform psychosis and dementia following such treatment is described.

interferon-α / psychotic disorders / clinical factors / treatment / mechanisms

Hepatitis C virus (HCV) changes brain metabolism and replicates in brain tissue [1, 2]. The treatment of choice for chronic hepatitis C (CHC) is six or twelve month therapy with interferon-α (IFN-α) plus ribavirin which is effective in a substantial proportion of patients (40–88%) [3, 4]. IFN-α significantly modulates function of cytokine system and enhances antiviral immunological response [5]. Ribavirin does not induce neuropsychiatric side effects directly though it may disturb thyroid function and in this way influence brain function [6]. Low-dose IFN-α therapy is often associated with neuropsychiatric side effects, most frequently depression, mild cognitive impairment and fatigue which disappear with cessation of interferon-α in almost all patients [7, 8]. Psychotic disturbances as the adverse neuropsychiatric side effects of interferon-α therapy have been observed infrequently [9, 10, 11]. In this paper, we attempted to review the cases of interferon-α –induced psychotic disorders, their epidemiology, predisposing factors, clinical picture, treatment and to discuss their possible pathophysiological mechanisms.

The analysis of serious adverse events in a group of 11 241 CHC patients treated with IFN-α revealed that psychotic episodes were identified in 10 patients (aged 25–62, males to females ratio 7/3) with no previous apparent psychiatric symptoms or substance abuse [12]. In another study, psychotic episodes occurred for the first time in 4 out of 943 CHC patients [13]. Therefore the combined ratio of psychotic episodes elicited with IFN-α therapy is 0.001 %.

In some cases psychosis occurred during first months of IFN-α therapy, usually in persons with psychotic episode(s) in the past [14, 15, 16]. However, there are observations on IFN-α-induced psychotic episodes that appeared for the first time in patients' lives [12, 13]. The clinical picture consisted of auditory hallucinations, persecutory delusions, and delusions of guilt or grandeur, anxiety, insomnia and attention disturbanc-

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es. Mood symptoms frequently accompanied the psychotic symptoms.

The time frame for emergence of psychotic symptoms associated with IFN-α therapy was 6–46 weeks and on average- third month of the therapy [12, 13]. Although psychotic symptoms usually appear later during IFN-α therapy than depressive symptoms, one report describes a case of a healthy 21-year-old woman from a family multiply affected by psychotic disorders in whom acute psychosis developed within 10 days after the first pegylated-α interferon injection and did not resolve within several weeks in spite of IFN termination and neuroleptic treatment [23].

Nevertheless, consent exists across published reports that stopping IFN-α and institution of neuroleptic treatment are sufficient for dissolving psychosis [12, 13, 14, 18, 19]. In 3 out of 10 patients observed by Fattovich et al. psychotic symptoms disappeared spontaneously after cessation of IFN-α and in the remaining 7 patients the symptoms resolved under neuroleptic treatment [12]. Institution of a butyrophenon or a butyrophenon plus a normothymic brought about full remission within 4–12 weeks in all four patients described in Hosoda et al. study [13].

Psychotic episodes associated with interferon-α therapy are reported more frequently in CHC patients with a history of illicit drug abuse and/or HIV co-infection [19, 20, 21, 22]. The known risk factors for mental disorders associated with IFN-α therapy are age over 40 years, presence of brain abnormalities, a history of psychiatric and neurological disorders, familial psychiatric history, substance or alcohol abuse in the past, being HIV-positive, simultaneous treatment with other cytokines or receiving high doses of IFN-α [8, 13, 20, 23].

There are also reports on psychotic maniacal or psychotic depressive episodes induced with the IFN-α therapy in high-risk patients [10, 19, 20, 21, 24]. The majority of these disturbances disappear with cessation of IFN-α, however in some subjects serious affective or psychotic symptoms may continue for many months despite adequate therapy [17, 24, 25, 26].

Pathogenesis of interferon-α-induced psychotic disturbances is not clear [5, 8, 15]. Data from both experimental and clinical studies indicate that influence of the cytokines' system on the brain may be responsible for a plethora of neuropsychiatric consequences, including psychosis [7, 27]. IFN-α can enter the brain through the blood-brain barrier during inflammation or even in the absence of inflammation in the periaqueductal area of hypothalamus or spinal cord [8, 28, 29]. IFN-α receptors were found in microglial cells [30]. IFN-α stimulates peripheral production of proinflammatory cytokines IL–1, IL–2, IL–6 and tumour necrosis factor alpha (TNF-α) which may intrude brain and modify local production of prostaglandins or other cytokines which may evoke significant changes in neuronal function. Cytokines may also modulate the activity of vagal nerve and in this way influence brain function [5, 8]. IFN-α acts directly as a neuromodulatory compound or indirectly modifies function of main the neurotransmitter systems through other cytokines [23, 27, 31].

Initially IFN-α stimulates dopaminergic neurons but on chronic administration, induction of dopaminergic blockade and down-regulation of dopaminergic receptors was demonstrated [32]. IFN-α binds to brain opioid receptors and through this modulates the dopaminergic activity of frontal-subcortical pathways [33]. Dopamine dysregulation in limbic and prefrontal pathways is associated with impairment of executive functions, working memory, positive and negative psychotic symptoms [34, 35]. Dopaminergic dysfunction (either IFN-α-induced or endogenous) might play an important role in initiation and course of psychotic disturbances.

HCV patients have lower serum tryptophan (serotonine precursor) levels than healthy control subjects [36]. Interferon-α stimulates indoleamine 2,3-dioxigenase and this results in tryptophan depletion and simultaneously in the increase of kinurenine neurotoxic metabolites [37, 38]. Neurotoxic influence of IFN-α via NMDA may impair processes of synaptogenesis and neuroplasticity [39, 40]. Chronic administration of IFN-α may induce hypercortisolemia, HPA axis dysregulation and central corticoliberin increase. These changes may result in damage to hippocampal neurones and neuroplasticity impairment [41, 42]. IFN-α increases the time of inhibition in the forced swimming test which indicates a depressiogenic effect [43]. In humans IFN-α can induce reduction of brain metabolism in the prefrontal cortex (hipofrontality) which

may predispose to both cognitive and psychotic disturbances [35, 44, 45].

Studies on relationships between interferon and schizophrenia has been inconclusive. There was no sign of cytokine disturbances in cerebrospinal fluid of schizophrenic patients. On the other hand, in a part of the patients non-specific abnormalities in regulation of endogenous interferons were confirmed [9]. Schizophrenic patients who recently had an acute psychotic episode, tended to have a higher endogenous interferon level in the serum [46]. In relation to the viral theory of schizophrenia attempts were made to augment neuroleptic treatment with interferon. In the placebo-controlled trial long-term add-on interferon therapy induced a significant improvement in part of schizophrenic patients [47].

The cases of psychotic disturbances described in the literature and data from preclinical studies indicate the possibility of IFN-α-induced psychosis in susceptible patients. The underlying cause of the susceptibility is yet to be determined, however dopaminergic, opioid, serotoninergic and glutaminergic pathways as well as HPA axis hypersensitivity might be supposed. Overlap influence of biological vulnerability and the cytokine's action on the brain can induce burdensome consequences.

We have recently reported the case of a patient without personal and familial psychiatric history and good premorbid functioning in whom a serious psychotic disorder and cognitive decline developed after seven months of therapy with pegylated interferon-α plus ribavirin due to hepatitis C [48]. Patient J-D male, aged 44, without perinatal complications, without head trauma, worked for 25 years in the same firm as an electrician. He has been married for 20 years. In his wife's opinion the patient never abused alcohol and always looked for some kind of occupation after he returned from work. He was always vigorous and expressed his emotions readily but did not reveal impulsiveness or dysphoric mood. He slept well. In 1981 the patient underwent appendectomy and peritonitis occurred as a complication. Oedema of lower extremities and feeling unwell urged the patient in 1998 to perform some examinations and the HCV antigen was detected. In 2002 the patient was granted a disability pension due to hepatitis C.

He was qualified for treatment with interferon-α and ribavirin after formal routine psychiatric assessment with brief examination of some cognitive functions which excluded the presence of any significant mental abnormality. The patient's wife observed increased tension and irritability while on the therapy but the patient was not referred for psychiatric examination. After seven months treatment the patient became increasingly agitated and upset. Then suddenly acute psychotic symptoms appeared. The patient experienced religious delusions and for several hours demanded from his family an absolute obedience with performance of some bizarre and magical activities. Consequently the patient was referred to a psychiatric hospital for compulsory in-patient stay. There IFN-α plus ribavirin therapy was stopped.

The diagnosis of an acute psychotic episode, paranoid type, was established and the patient was treated with chlorpromazine. The hospitalisation lasted for two weeks. On discharge the patient was relatively free of hallucinations and religious delusions but distinct extrapyramidal signs were apparent. In spite of consecutive changes of neuroleptic drugs parkinsonian side-effects did not allow the patient to walk or perform everyday activities. He became apathetic and dereistic, he needed assistance even in maintaining self-hygiene. Moreover he claimed suicidal thoughts and impulses. Hallucinations and delusions were reduced but still existed. Cognitive impairment reached the level of mild dementia. Subsequently, treatment with low doses of clozapine and clonazepam was instituted. Slow, gradual improvement of psychiatric and neurologic state was observed. However, dereism, lack of criticism, slight delusions, negativism and cognitive decline persisted in spite of withdrawal from IFN-α plus ribavirin therapy and intensive treatment with different neuroleptics including 18-month treatment with clozapine. Altogether, serious and chronic disturbances resulted in enduring deterioration of the patient's functioning. The patient still needs everyday assistance.

Taking into consideration good premorbid psychosocial functioning, no addiction in the past and lack of familial psychiatric burden in the presented patient, we can hypothesise that a relationship exists between IFN-α therapy and in-

cidence of both psychotic disturbances and cognitive deterioration. Though it is not possible to delineate an ultimate explanation of the symptoms we may suppose that the influence of IFN-α and HCV virus on the brain were not the only reasons of chronic illness in the patient. Probably equally important might be an individual predisposition, presumably resulted from sensitivity to long-term influence of IFN-α on crucial neurotransmitter and neuromodulatory systems.

It may be suggested that early identification of psychosis and adequate psychopharmacologic treatment might prevent subsequent development of serious debilitating symptoms. Considering all these details, the necessity of regular psychiatric consultations not only for the patients who have risk factors to develop neuropsychiatric side effects but rather for all patients undergoing long-term treatment with IFN-α can be postulated.

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