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DEPRESSION AND IMMUNITY: THE HCV MODEL

Emanuela Apicella

Clinic for Eating Disorders "Villa Miralago", Cuasso al Monte (Va), Italy

SUMMARY

Available research shows that only some individuals will develop a specific psychiatric disorder in the presence of the same life events. Different regulation scales are used to define the events that can be considered as stressful and to value their psychological burden. A personal illness, especially if chronic, is certainly an event characterized by great emotional and psychological impact. Moreover, symptoms such as mood changes and anxiety, which are commonly observed in patients affected by HCV, can be related to the awareness of suffering from a chronic progressive disease and to the past or current substance abuse. It is well known that the assumption of interferon α (IFN α) is associated with the onset of depressive symptoms, similar to those observed in major depression, in fact, from 30% to 50% of patients receiving IFN develop depression during treatment.Many data in literature show the very important role of pro-inflammatory cytokines in the onset of the Depression.

Key words: *immunity – depression - HCV*

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The role of stressful psychosocial events or "life events" in the unleashing of psychic pathology is generally accepted by most clinicians. As a matter of fact, it is difficult to document a causal link between life events and mental illness and it is hard to think of a real direct causality between these two factors. Some authors have proposed a model based on a circular relationship between the event and the psychopathological manifestation, rather than a model based on a linear cause-effect relationship (Lteif 1995). Available researches, moreover, show that only some individuals will develop a specific psychiatric disorder at the presence of the same life events (Kessler 1989).

Different regulation scales are used to define the events that can be considered as stressful and to value their psychological burden. A personal illness, especially if chronic, is certainly an event characterized by great emotional and psychological impact (Paykel 1997). Moreover, symptoms such as mood changes and anxiety, which are commonly observed in patients affected by HCV, can be related to the awareness of suffering from a chronic progressive disease and to the past or current substance abuse (Carta 2007).

It is well known that the assumption of interferon α (IFN α) is associated with the onset of depressive symptoms, similar to those observed in major depression (Dieperink 2000), in fact, from 30% to 50% of patients receiving IFN develop depression during treatment (Lotrivh 2007). Many data in the literature show the very important role of pro-inflammatory cytokines in the onset of the Depression (Licinio 1993, Loftis 2004, Raison 2006, Schiepers 2005). Since the 90s, several studies have highlighted that in certain cases the alterations of the immune system can contribute to the development of depressive symptoms, favouring the acquisition of new knowledge about the so-called Psychoneuroimmunology (Andreoli 1993).

The Neuro- Endocrine System (SNE) and the Immune System (SI) are part of a totally integrated biological circuit, in fact, the same biochemical signals are used both for the exchange of information between the components of the same system and for communications between the two systems. Numerous studies, in fact, have shown that the SI is able to modify its responses, either through automatic mechanisms of regulation by signals coming from the Central Nervous System (CNS) and endocrine system (SE). In turn, the cells of the SI, sending signals to the central nervous system and to the SE, trigger specific neuroendocrine and behavioural responses. Pro-inflammatory cytokines are some of the main messengers employed by SI to communicate directly with the SNE, in particular, they stimulate the activity of the locus coeruleus (LC) and the hypothalamic secretion of Corticotrophin-Releasing Factor (CRF) (Leonard 2009).

The immune cells communicate with the SNE also by means of several neuropeptides and neuro-hormones, such as the CRF, adrenocorticotropic hormone (ACTH), the Growth Hormone (GH), the Thyrotropin-Releasing Hormone (TRH), prolactin, β-endorphin, etc. Immune cells, in fact, possess specific membrane receptors, both for these mediators and for neurotransmitters such as adrenaline, serotonin, histamine, GABA (Turnbull 1999).

The relationship between the nervous system, endocrine system and immune system has been highlighted by several studies. The baseline concentration of soluble receptors for TNF and IL-6 were linked with the development of depression during therapy with IFN α (Friebe 1997). Moreover it was found that patients suffering from cancer and depression showed higher levels of interleukin 6 (IL6) compared to patients affected by cancer but without depression (Musselman 2001). In patients suffering from HCV, concentrations of receptors for IL-2, IL-6 and IL-10 are significantly higher in patients who develop a depressive symptomatology during therapy with IFN, compared to patients who did not develop it. Therefore, a greater activation

of the immune system may be predictive of the development of depression during IFN therapy (Wichers 2006, Morasco 2007).

Let us look now at the way by which pro-inflammatory cytokines, in particular IFN α, act in the genesis of psychiatric interest symptoms. It is well known that serotonergic and dopaminergic neuro-transmitter systems are involved in depressive disorders and anxiety disorders. In clinical practice, drugs that act on the neurotransmitter systems are commonly used. The role of IFNα in the development of depression and anxiety may be partly due to its action on serotonin metabolism. The administration of selective serotonin reuptake inhibitors (SSRIs), in fact, inhibits the development of depression in patients treated with IFN α (Morasco 2007). The administration of paroxetine (SSRI) reduces to approximately 4 times the risk of onset of depression during therapy with IFN α (Musselman 2001). The IFNα and cytokines in general, would contribute to the alteration of serotonin metabolism through the activation of an enzyme called indoleamine 2-3 deoxigenase (IDO), which converts tryptophan, an amino acid precursor of serotonin, into kynurenine (Dantzer 2008), leading to a reduction in the synthesis of serotonin. In fact, it has been demonstrated that, patients treated with IFN α, who develop de-pression, have lower blood concentrations of tryptophan (Capuron 2002, Maes 2001). Patients who develop major depression during IFN-α therapy, compared with patients who did not develop it, show significantly reduced level of tryptophan and increased levels of kynurenine in the peripheral blood (Miller 2009). These data would support the hypothesis according to which the reduction of levels of tryptophan and, consequently the reduction of the synthesis of serotonin, are consequent to activation of the IDO.

Another mechanism involved in the reduction of levels of serotonin induced by cytokines is the acti-vation of a protein kinase, called MAPK, by themselves. The IFNα is a potent inducer of p38 MAPK; the activation of this protein kinase increases the expression and synthesis of serotonin transporters (Zhu 2005, Zhu 2006), thus resulting in the increase of serotonin reuptake, with consequent reduction of the neurotrans-mitter in the synaptic cleft. Recent studies have linked the increased function of serotonin transporters with seasonal affective disorder (Willeit 2008). In addition to the reduction of serotonin, alterations in metabolism of dopamine (DA), would also contribute to the onset of symptoms such as psychomotor retardation and fatigue. In fact, the IFN and, more generally, pro-inflammatory cytokines, act on the metabolism of DA, especially at the level of the basal ganglia, causing a sympto-matology characterized by neuro-vegetative symptoms, anhedonia, psychomotor retardation, fatigue (Majer 2008, Horikawa 1999, Kamata 2000).

Dopamine is involved in different circuits in mood, reward and motivation, motor activity, sleep-wake rhythm and cognitive processes (Salamone 2005, Schultz 2007). It has been shown that IFN α induces motor slowing and this slowing down is correlated, significantly, to the development of depression and fatigue (Majer 2008).

The mechanisms by which the IFN would act resulting in a reduction of DA in the synaptic cleft are manifold; primarily cytokines, and therefore the IFN α as well, induce an increase of nitric oxide (NO), which causes a reduction of tetrahydrobiopterin (BH4) that is a co-enzyme for tyrosine hydroxylase, which converts tyrosine to L-DOPA, this causes a reduction in the synthesis of DA. It has also been shown that the action of IFN on BH4 is mediated by nitric oxide, in fact, treatments that inhibit the synthesis of NO, block the inhibitory effect mediated by IFN on the concentration, at the level of the central nervous system, of tetra-hydrobiopterin (BH4) and DA (Capuron 2003). It has also been demonstrated that the IL6 (whose blood concentrations increase after administration of IFN α), reduces the tetrahydrobiopterin at the neuronal level (Wu 2007).

Another mechanism by which the IFN α works reducing the levels of DA in the synaptic cleft involves the Kynurenic acid (KA). As we have already said, with regard to the effect of cytokines on the metabolism of serotonin, the IFN determines an activation of the enzyme indoleamine 2,3 dioxygenase (IDO), which cleaves the tryptophan into kynurenic acid (KA). KA reduces the release of glutamate. The glutamate, as well known, stimulates the release of dopamine (Moron 2003, Capuron 2005, Reichenberg 2001). The final effect is, in this case as well, a reduction of the levels of DA in the synaptic cleft. Finally, the IFN α, as we mentioned above, can activate some protein kinase, the MAPK pathway, which results in the increase in the expression of those genes coding for transporters of DA, this causes an increased DA reuptake with consequent reduction of the available levels of DA in the synaptic cleft (Ursu 2003).

In recent years it has been also supposed that psychiatric disorders that occur in patients affected by HCV are due to a direct effect of the virus. In particular, it has been suggested that there is no link between the onset of depressive disorders in patients with HCV infection and the IFN α- therapy (Grassi 2002). An interesting study using magnetic resonance spectro-scopy (MRS), a non-invasive technique that allows us to get localized biochemical information from tissues and organs, has pointed out several alterations of cerebral metabolites in patients with HCV infection (Carta 2007, Forton 2001). These alterations are very similar to those caused by the HIV virus which can be found in the central nervous system during the overt disease (Chang 2002, Chang 2004). These studies support the hypo-thesis according to which, even the HCV would be able to infect cells of the central nervous system, causing changes in the brain (Thomas 1999). According to this hypothesis, the virus after infecting monocytes in circulation, is introduced into the CNS thanks to a

mechanism known as "Trojan Horse," resulting in neuronal dysfunction. This hypothesis is supported by recent studies that have demonstrated the presence of HCV gene sequences in post-mortem examined brain tissue (Radkowski 2002). Another important aspect that rises from data in the literature is that different viral genotypes correlate with a different response to the antiviral therapy with IFN-α. Up to now, according to differences in nucleotide sequence, 7 different genotypes of HCV (in turn subdivided into several subtypes) have been identified, with a different geographical prevalence. The most common genotypes in Europe are 1a, 1b, 2a, 2b and 3 while in the USA is genotype 1a. Many people believe that the genetic heterogeneity of the virus strains is the basis of the differences in the development of disease and in the responsiveness to treatment. It is well known, in fact, that the genotypes 1, 5 and 6 have a lower response to antiviral treatment. In particular, the virus 1b leads to a more rapid progression to cirrhosis. In contrast, viral genotypes 2 and 3 have a better response to antiviral treatment (Shepherd 2004). The management of patients with HCV, candidates for therapy with interferon-α, is a vexed question, considering the prevalence of hepatitis C, the likely presence of problems related to substance abuse, the psychological question that the impact of the diagnosis of a disease with poor prognosis determines and multisystemic side effects that the therapy itself may cause. Many studies have shown, in fact, that the impairment of quality of life in these patients is both linked to the severity of the disease (Forton 2001) and to the previous substance abuse and side effects of treatment (Hussain 2001, Spiegel 2005). On the other hand, it is also true that interferon therapy, slowing down and, in some cases, arresting the progression of the disease, could improve the quality of life of patients suffering from hepatitis C virus (Kamal 2011). Psychiatric disorders more frequently found in HCV patients treated with interferon α include: sleep disorders, fatigue, irritability, anxiety disorders, cognitive disorders with impairment of concentration and memory, depressive episodes (mild, moderate or severe), confusion, delirium, psychotic disorder, mania, craving (alcohol, drugs). It is worth stressing that Depression does not just mean deflection of mood; this clinical picture, in fact, is characterized by a collection of disorders, involving emotional, cognitive and neuro-vegetative changes, which may occur in several combinations but usually tend to occur all together, resulting in the so-called depressive spectrum. Some studies have highlighted that depression related to interferon therapy is significantly different from Major Depression itself. The differences would mainly involve the ideational sphere. Patients on interferon therapy, in fact, do not present depressive ideations of guilt and ruin, ideas of inadequacy and worthlessness (Pasquini 2008), typically experienced by patients with major depression. The hypothesis might be that depression occurring during interferon therapy should be included in the diagnostic category of "Mood Disorder due to a general medical condition" or "According to the DSM IV TR, in fact, a Mood Disorder due to a general medical condition, is "a significant and persistent alteration in mood that is believed to be due to direct physiological effects of a general medical condition", including degenerative neurological diseases, metabolic conditions, viral infections or other infections as well. With regards to "Substances-Induced Mood Disorder", this is a condition that can be induced not only by drugs of abuse but also by medication or toxins. These conditions are not only characterized by a purely depressive symptomatology but also include symptoms such as high, expansive or irritable mood.substance-induced disorder", according to the classification in the DSM IV TR (Gregory 2006). According to the DSM IV TR, in fact, a Mood Disorder due to a general medical condition, is "a significant and persistent alteration in mood that is believed to be due to direct physiological effects of a general medical condition", including degenerative neurological diseases, metabolic conditions, viral infections or other infections as well. With regards to "Substances-Induced Mood Disorder", this is a condition that can be induced not only by drugs of abuse but also by medication or toxins. These conditions are not only characterized by a purely depressive symptomatology but also include symptoms such as high, expansive or irritable mood.

In the guidelines of the EASL (European association for the study of the liver 2011) it states that depression is the leading cause of discontinuation of antiviral treatment with interferon α. According to these guidelines, patients with a documented story of depression should be evaluated by a psychiatrist before the start of antiviral therapy, so that the presence of possible psychiatric contraindications could be assessed. These patients should be followed throughout the treatment to find out the onset of depression immediately and then, must be treated with antidepressant-based pharmacotherapy, when depressive symptoms are recognized. Some studies have evaluated the possible use of antidepressants, in particular SSRIs, for "preventative" purposes, showing actually a reduction in the incidence of depression during treatment with interferon-α (Bezemer 2008). SSRIs are the first choice for depressive disorders, especially paroxetine, sertraline, citalopram, that is, those with the best tolerability profile, the fewer interactions,and the best demonstrated efficiency. If the severity of depressive condition is mild or moderate, antiviral treatment can be continued. Even in this case psychotherapeutic support interventions are suggested. If depressive symptoms persist and therapy does not work (by 2-4 weeks), the use of another antidepressant with a different mechanism of action should be considered, or the reduction or discontinuation of IFN treatment; this decision could be made jointly by the infectious disease specialist, the consultant psychiatrist, the patient and a familiy member at least. If psychotic symptoms occurred, IFN

therapy should be discontinued and, if necessary, started again, only after the patient has been properly treated with antipsychotic drugs.

Depression induced by IFN α responds well to treatment with SSRIs, as it would be mainly due to alterations involving the serotonergic circuits, while the so-called Neuro-vegetative Syndrome induced by IFN, characterized by fatigue, anorexia, pain and psychomotor retardation, which is often found in association with depressive symptoms, would benefit from drugs such as SNRIs (venlafaxine) and Bupropion (Charles 2005).

Finally, we must not forget that interferon therapy may increase the risk of suicide although studies in this field are still few and results do not appear unique (Sockalingam 2011, Debien 2001). It is clear that the prognosis of viral disease itself, which, as is well known, can result in cirrhosis and hepatocellular carcinoma, may cause psychological reactions of despair that can lead to depression and suicidal ideation. It is worth noting that, according to the DSM IV TR "Mood Disorder due to a general medical condition increases the risk of suicide attempts and suicide" (DSM IV TR 2000). Even in the case of suicide then, we must consider several risk factors, ranging from psychological consequences of diagnosis and prognosis to depression caused by the therapy.

In view of these considerations, it is understandable that the management of patients with HCV treated or not with IFN α, requires several specialized figures that can deal with the many aspects that this condition brings with it. The guidelines and literature recommend the presence of a multidisciplinary team, in which the psychiatrist plays a key role because of the great incidence of psychiatric disorders in these patients.

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Correspondence:
Emanuela Apicella, M.D.
Clinic for Eating Disorders "Villa Miralago"
Via Casa Mora 19, 21050 Cuasso al Monte (Va), Italy
E-mail: manu.apicella@gmail.com