Case Report
https://doi.org/10.9758/cpn.2020.18.3.463 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2020;18(3):463-466

Immune Activation and Deficit in Neurotransmitters Synthesis in Treatment Resistant Depression: About a Case of Hashimoto Encephalopathy

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We report a case of Hashimoto encephalopathy initially presented as a drug-resistant depression with predominant apathy and asthenia, successfully treated with cyclophosphamide. We suspected that the psychiatric symptoms were due to a deficit in neurotransmitter synthesis related to immune activation. We hypothesized that the immunomodulatory treatment helped to restore the neurotransmitter synthesis and thus decreased the patient's depressive symptoms. In this case report we propose an innovative model in which immunity might disturbs neurotransmitters synthesis leading to depressive symptoms.

KEY WORDS: Psychiatry; Depression; Immunity; Neurotransmitter agent.

INTRODUCTION

Hashimoto encephalopathy (HE) also known as steroid-responsive encephalopathy associated with auto-immune thyroiditis has an estimated prevalence of 2/100,000 [1]. It has pleiotropic clinical presentation associated with positive serum antithyroid-peroxidase autoantibodies [2]. Psychiatric symptoms are common in HE including psychosis, major depressive disorders (MDD), mania and tics [3-5]. MDD is one of the most common psychiatric features described in HE [6]. The diagnosis of MDD is challenging in case of HE considering that isolated psychiatric presentation represents around 10% of cases [7].

It is now well established that a subgroup a major depressive episode is driven by immunity [8-10]. Even if the exact mechanism is not known, it has been suggested that the pathophysiology of those MDD can be related to both a serotonin and dopamine deficit caused by the inflammatory environment [11]. So far, the link between immunity, neurotransmitters and depression have been only reported in animal models (for review see [12,13]). It is hypothesized that in response to immune activation, the increase of indolamine 2,3 dioxygenase (IDO) level observed in MDD leads to 5-HT synthesis inhibition and thus decreased of 5-HT brain availability [14]. The immune activation also inhibits a biopterin key-enzyme (tetrahydrobiopterin or BH4) responsible for dopamine synthesis, thus leading to a decrease brain availability of dopamine [15]. Treatment resistant depression is a severe and heterogeneous condition affecting more than 30% of patients [16]. It has been demonstrated that treatment resistant depression is more associated with immune activation [17,18].

CASE

A 51-year-old man, with Hashimoto thyroiditis diagnosed two years ago, underwent a major depressive

Received: March 15, 2019 / **Revised:** June 5, 2019
Accepted: June 10, 2019
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episode. He started paroxetine 40 mg/day for 12 weeks then escitalopram 20 mg/day for 8 weeks, without efficacy. He was then admitted to our psychiatric department with a diagnosis of treatment-resistant depression. At the admission, his Montgomery Asberg Depression Rating Scale (MADRS) was 21 and the Beck Depression Inventory (BDI) was 20.

We prescribed venlafaxine 300 mg/day with Mirtazapine 30 mg/day without any clinical effect after 6 weeks, both MADRS and BDI score were the same. The patient presented mainly an intense asthenia, apathy and avolition with depressive mood, hypersomnia and loss of weight but without suicidal ideation. We thus confirm, according to the Diagnostic and Statistical Manual-5 Criteria, the MDD diagnosis. This symptomatology associated to treatment resistance led us to investigate on a potential neurological cause of his major depressive episode. The results of blood serum screening found normal thyroid hormones, normal anti-thyroglobulin (TG) antibodies but elevated thyroperoxydase (TPO) antibodies (389 UI/ml, N < 34). C-reactive protein ultrasensitive (CRPus) was 1.7 mg/L. Magnetic resonance imaging (MRI) was normal but electroencephalography (EEG) found bilateral temporal theta waves. Considering those results, we conducted a lumbar puncture that found elevated protein (0.65 g/L, N < 0.15−0.45), elevated albumin (481 mg/L, N < 200), and elevated immunoglobulin G (IgG) (52 mg/L, N < 35) without intrathecal synthesis indicating a failure of the blood brain barrier function. Cerebrospinal fluid (CSF) antibodies assessment (including TPO, TG, and neuropil) were negative, no pleiocytosis was found. Neurotransmitters screening in the CSF found important decrease of both homovanillic acid (HVA) (55 nmol/L, N = 156−410) and 5-Hydroxyindolacetic acid (5HIAA) (22 nmol/L, N = 63−185), combined with decreased biopterin (13 nmol/L, N = 14−36). It is important to note that no precursor deficit (5-hydroxytryptophane and tyrosine levels were normal) were found, indicating a synthesis defect in both dopamine and serotonin. The association between treatment resistant depression, Hashimoto thyroiditis with elevated blood anti-TPO antibodies, slow wave at the EEG led us diagnosed HE [19]. Thus, an immunosuppressive treatment with IV cyclophosphamide (1 g/d during 3 days a month) was initiated and lasted 6 months. Without any change in the psychotropic treatment, he presented a dramatic improvement with MADRS measured at 11 and BDI at 12 after the 6th administration of cyclophosphamide. To note, Thyroid Stimulating Hormone was normal before cyclophosphamide initiation (1.01 mUI/L) and after treatment (3.23 mUI/L). CSF proteins (0.85 g/L), albumin (650 mg/L), IgG (79 mg/L) and plasmatic anti TPO antibodies (346 UI/L) were still elevated indicating the persistence of the blood-brain barrier defect. Post-treatment CRPus was 1.10 mg/L. At the contrary, 5HIAA were normalized, HVA underwent a twofold increased and EEG was normalized. After 6 months of follow-up no relapse has occurred.

The patient has been informed of the publication and gave his consent.

DISCUSSION

The diagnosis of HE is difficult, especially when psychiatric symptoms are isolated [2]. The diagnosis of HE is underpinned by (i) encephalitis criteria (based on CSF analysis, MRI, EEG) (ii) presence of serum thyroid antibodies and (iii) exclusion of other differential diagnosis of encephalitis [19]. To note, no pleocytosis or CSF thyroid autoantibodies are required [19]. Historically, response to steroid was expected to confirm the diagnosis but since then several other treatments have proved their efficacy. Especially, even if the exact mechanism is not known, some case reports have reported the efficacy of cyclophosphamide on psychiatric symptoms related to autoimmune disorders [20-22]. The pathophysiology of depressive episodes in HE is still unclear but the two raised hypotheses are either a direct action of antibodies within the brain or brain vasculitis [7]. In our case, considering the absence of correlation between the clinical improvement of the depression and the remaining elevated biological markers (IgG in the CSF, anti TPO in the serum) the main mechanism of psychiatric symptoms is in favour of the latter hypothesis. This is reinforced by the fact that lymphocyte infiltration has been found in patients and that plasmatic exchanges are not effective in HE [2].

The inflammatory hypothesis of MDD is based on the fact that stress, a major risk factor of MDD, is associated with the activation of the hypothalamic-pituitary-adrenal axis, leading to the release of catecholamine [15]. Catecholamine seems to act on the pathophysiology of MDD through damage-associated molecular patterns, which eventually activate the NOD-like receptor family, pyrin domain–containing protein 3 inflammasome [15], a

Table 1. Pre and post treatment evolution of clinical parameters and paraclinical data

Time of assessment	Clinical/paraclinical features							
	MADRS	BDI	CSF protein	CSF IgG	Anti TPO serum	CSF albumin	CSF HVA (nmol/L)	CSF 5HIAA (nmol/L)
Pre-treatment	22	20	0.65	52.8	389	481	55	22
Post-treatment	11	12	0.85	79	346	650	105	64

MADRS, Montgomery Asberg Depression Rating Scale; BDI, Beck Depression Inventory; CSF, cerebrospinal fluid; IgG, immunoglobulin G; TPO, thyroperoxidase; HVA, homovanillic acid; 5HIAA, 5-Hydroxyindolacetic acid.

pro-inflammatory multiprotein complex activated by pathogenic microorganisms and by sterile stressors (for example adenosine triphosphate, oxidative stress). The inflammasome is responsible for the secretion of cytokines which in turn could drive the inflammatory response associated with MDD. Indeed, cytokines inhibit the enzyme tetrahydrobiopterin, which is essential for the synthesis of dopamine, therefore decreasing the availability of this neurotransmitter [15]. Activation of IDO, leading to a decrease of the neurotransmitter serotonin (5-HT) and an increase in *N*-methyl-*D*-aspartate signaling (metabotropic glutamate receptor) is also observed [11].

Our report also highlights the need for immune investigation in treatment resistant patient, including lumbar puncture if encephalopathy is suspected (for precise guideline about this prescription see [19]). More, lumbar puncture allowed the screening of neurotransmitters pathways, which, according to our report, may be an interesting biomarker for treatment resistant depression. Indeed, we hypothesized that in our patient, the focal immune activation related to brain infiltration of HE decreased the biopterin leading to the deficit of brain dopamine, as described in animal models. In absence of routine test, we can only assume that this immune activation might have inhibited the IDO as showed by the serotonin deficit found (Table 1). Their normalization and the concomitant depressive symptoms reduction trend to confirm the hypothesis that this deficit in neurotransmitter synthesis might be responsible for the clinical depression observed and draw a direct link between immunity, neurotransmitter deficit and depression. We hypothesized that our case illustrates, for the first time in a patient, a holistic approach of the immune theory of depression.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Pierre Ellul, Matthieu Gasnier. Redaction: Pierre Ellul, Matthieu Gasnier, Vincent Trebossen and Raphaël Gaillard. Pierre Ellul & Matthieu Gasnier contributed equally to this work as first co-authors.

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