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Positron Emission Tomography in Autoimmune Disorders of the Central Nervous System

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Abstract

This chapter covers the basic knowledge on interactions between the central nervous system and immunity. It presents information about the main factors and mechanisms that refer to the traditional and new concepts on immune privilege of the brain. In addition, the immune surveillance and tolerance are discussed in context of the central nervous system homeostasis, production of autoreactive lymphocytes, and neurons vulnerability.

Certain general aspects in principles of positron emission tomography (PET) technique, radiotracer characteristics, and specificities of the cerebral glucose uptake are provided. The chapter also offers an overview of the current clinical application of (18F)-FDG PET imaging in the detection and differential diagnosis of different autoimmune disorders of the central nervous system.

This chapter reviews the autoimmune underlying mechanisms and main abnormalities in cerebral glucose metabolism in patients with multiple sclerosis, late-onset ataxias, and limbic encephalitis. Own clinical observations and results are presented in accordance to previous publications. Neuroimaging findings are discussed in context of PET sensitivity and accuracy for assessment of disease localization and characterization.

Keywords: (18F)-FDG PET/CT, autoimmunity, CNS disorders

1. Introduction

1.1. Central nervous system and immunity

Advances in scientific research and accumulated working knowledge of anatomic-functional subsystems of the central nervous system (CNS) and their relationship with the downregula-

tion of the immune system play a crucial role in the understanding of underlying mechanisms and treatment of immune-mediated neurological disorders [19, 37].

Traditionally, CNS is considered an immunologically-privileged site, meaning the brain and spinal cord can tolerate the introduction of foreign antigens without eliciting an afferent immune response [29, 34]. Immune privilege is believed to be an active process aiming to protect the brain structures from the harming effect of an inflammation. This immune privilege is thought to be due to a lack of lymphatic drainage and the integrity of blood-brain barrier (BBB) [21]. It varies throughout the different parts of the CNS, being most pointed in the white matter. Among the other factors that also contribute to the maintenance of brain immune privilege are local production of immunosuppressive cytokines, increased expression of surface molecules inhibiting complement activation, low expression of major histocompatibility complex (MHC) class Ia molecules, presence of neuropeptides, etc. [26].

Over the last two decades the concept of CNS as an immunologically-privileged site has been reevaluated. Today, experimental and clinical data show evidence suggesting the presence of resident CNS macrophages known as microglia [42]. Although the separation and isolation of CNS from the peripheral immune cells throughout the BBB, certain unique interactions exist due to the sequestration of neuronal antigens in “partially” immune-privilege sites, presence of antigen determinants shared by the nervous and immune systems, and secretion of immunoregulatory mediators by specific nerve cells [19, 29, 34]. Nowadays, it is known that activated lymphocytes are able to pass through the BBB regardless of their antigen specificity, directed by cytokines and adhesion molecules that are expressed on the brain endothelial cells (ICAM-1, VCAM-1) [2]. Normally, MHC class 1 and class 2 molecules are minimally expressed in the CNS, but in pathology the expression induced by proinflammatory cytokines IFN- γ is much higher. Immune surveillance in the CNS is under strong control and its major role is to provide constancy of the homeostasis in relation to the raised vulnerability of the neurons [26].

Immune tolerance is known to protect normal tissues from immune damage by prevention of immune response against a particular antigen to which the human organism is normally responsive. In the past, it was thought that the break of immune tolerance causes the production of autoantibodies and/or sensitized cytotoxic T-lymphocytes, attacking own tissues, the so-called autoreactive lymphocytes. Today, it is evident that these autoreactive cells normally exist in the immune system in a state of anergy and areactivity toward own antigens. Respectively, the immune tolerance is considered as a result from suppression and elimination of autoreactive T-lymphocytes [2].

It is known that autoimmunity represents an abnormal immune response directed against the cells and tissues of the organism. Autoimmune responses are considered an integral part of the immune system and present a survival self-defense mechanism. It is postulated that this aberrant immune response refers to the development of different diseases. The mechanisms of autoimmune disorders of the CNS are associated with molecular mimicry, upregulation of heat shock proteins, the release of so-called “sequestered” antigens (brain tissue antigens hidden behind the BBB), bystander activation, and production of neoantigens [13, 42]. Most commonly T- and B-cell mediated autoimmune diseases result from the elimination and inhibition of regulatory T-cells or the dysregulation of humoral immunity.

2. Positron emission tomography in neurology

In recent years, a large number of scientific reports confirm the increasing influence of nuclear medicine in the diagnosis and treatment of patients with various neurological diseases [10, 23, 25, 33, 43]. Accordingly, positron emission tomography presents a modern non-invasive technique for investigation in vivo of basic biochemical processes and physiological functions of the CNS [36]. This method provides important information about the cerebral blood flow, permeability of BBB, activity of brain enzymes, and metabolism of glucose, amine and fatty acids, as well as synthesis and metabolism of neurotransmitters, gene expression and density of neuromediators receptors.

PET has a wide clinical application in the understanding of underlying mechanisms of neurological diseases, early and correct diagnosis, monitoring of clinical course and prognosis of outcome, studying of drugs pharmacokinetics and pharmacodynamics, and assessment of therapeutic response. In addition to structural neuroimaging, PET improves the diagnostic accuracy of localization, characterization, and distribution of anatomical and functional cerebral disturbances [17, 33, 36].

PET is realized through intravenous injection of radiotracer, which is a biological marker, labeled with positron emitting isotope [7]. Carbone (^{11}C), nitrogen (^{13}N), oxygen (^{15}O), and fluorine (^{18}F) are among the most frequently used in clinical practice due to their relatively short half-life (up to 110 min) and constant body spread, without prolonged radiation exposure [40].

It is well known that the human brain presents only 2% of body weight, but utilizes about 20% of absorbed oxygen and 60% of glucose, which is a major energy source for the nerve cells. Respectively, (^{18}F)-FDG is the most appropriate radiotracer for functional study of cerebral tissue, because it reflects the level of glucose assimilation by brain neurons. ^{18}F -Fluorodeoxyglucosae - (^{18}F)FDG represents deoxyglucosae that is labeled with ^{18}F . FDG is a glucose analogue that biodistribution fully reflects the glucose consumption of different organs and tissues [44]. Its cell's influx is realized through active transport, by means of glucose transporters in mechanisms that are similar and competing with glucose. After entering the cytosol, the molecule is phosphorylated into a stable form, which has a slower metabolism and prolonged cell's retention than glucose.

The brain tissue is characterized by high glucose activity, mainly in the cortical, thalamic, cerebellar, and basal ganglia gray matter, and relatively lower in the white matter [23]. The distribution in the cerebral cortex is not homogeneous, as the highest activities are realized in the occipital lobes.

New data support the notion that PET is a useful technique for diagnosis, planning treatment, and prognosis in various neurological diseases, including autoimmune disorders of the CNS [3, 8, 24]. By measuring brain and spinal cord metabolism, FDG-PET may demonstrate extensive regions of neurologic dysfunction in patients with multiple sclerosis (MS), immune-mediated cerebellar ataxias and autoimmune limbic encephalitis [4, 10, 15, 33, 41].

3. PET in diagnosis of autoimmune neurological disorders

3.1. Multiple sclerosis

MS is an immune-mediated inflammatory, demyelinating disease of the CNS [22]. The etiology is not known, but it is supposed to involve a combination of genetic predisposition and certain triggers (e.g., various viral infections, low vitamin D levels) that cause recurrent immune attacks [28]. MS is supposed to be associated with certain genetic loci, which are known to influence the regulation of the immune system and higher susceptibility to this autoimmune disease [12]. Strong relationship exists with class II alleles (HLA-DR2, HLA-DR15), T-cell receptor gene, genes synthesizing immunoglobulins, tumor necrosis factor- α (TNF- α), and myelin basic protein (MBP).

MS is an inflammatory disease of the CNS characterized by the dissemination lesions of demyelination, called plaques, in the brain and spinal cord [32]. The main pathological changes include the degeneration of axons, astrocytes-induced gliosis, and sclerosis [22]. The stepwise lesion formation enlists the activation of myelin-reactive T cells in the periphery, breakdown of the BBB, penetration of activated inflammatory cells (lymphocytes and macrophages), and B-cell activation (generation of antibodies to MBP). Evidence exist that MS plaques are associated with expression of high levels of Interleukin (IL)-12 and B7-1, stimulating the release of proinflammatory cytokines [28]. Functionally-decreased T-lymphocytes with regulatory role (Tregs), microglia, dendritic cells, natural killer (NK) cells, and nonimmune (endothelial) cells are also involved in the mechanisms of CNS inflammation.

MS is diagnosed on the basis of clinical findings, brain magnetic resonance imaging (MRI), and cerebrospinal fluid examination (CSF) [31, 32]. Additionally, (18F)-FDG PET scans reveal the localization and distribution of cerebral hypometabolism in relation to demyelinating lesions in the white matter and their remote influence over the glucose metabolism of cortex, basal ganglia, and cerebellum [5, 10]. This method is also useful in MS patients with cognitive dysfunction for investigation of global and regional cerebral glucose metabolism in comparison to MRI findings [35]. According to Bakshi R et al. [3] and Derache N et al. [9], (18F)-FDG PET scans have clinical application as a marker for assessment of disease activity and response to immunotherapy. Although, cerebral imaging studies show variable results [6, 15, 16, 27], our (18F)-FDG PET findings in MS patients with certain cognitive impairment reveal areas of hypometabolism, corresponding to the white matter lesions and brain atrophy (Clinical case 1).

Clinical case 1. A 44-year-old male with relapsing-remitting MS and cognitive impairment. Neuroimaging findings (Fig. 1, 2, and 3).

3.2. Autoimmune cerebellar ataxia

Late-onset progressive cerebellar disorders can result from various pathologic processes, including malformations, degenerative and vascular disorders, infections, neoplasms, paraneoplastic syndromes, toxic/metabolic disorders, and demyelinating disease [1]. It is known that the immune system plays an important role in the development of paraneoplastic

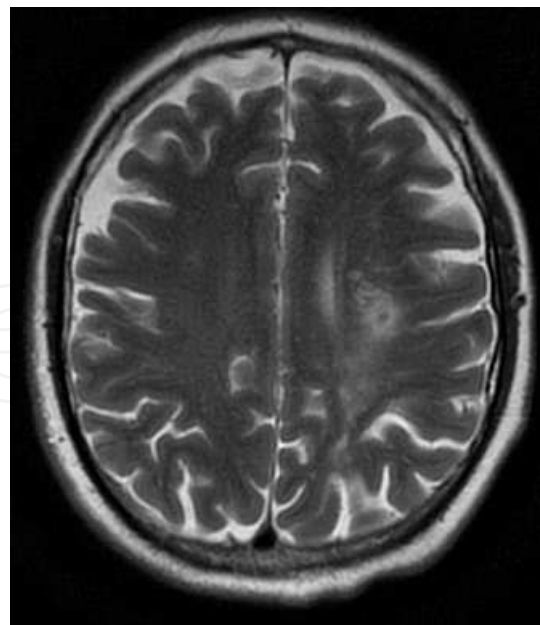


Figure 1. MRI shows MS lesions expressed in the left cerebral hemisphere.

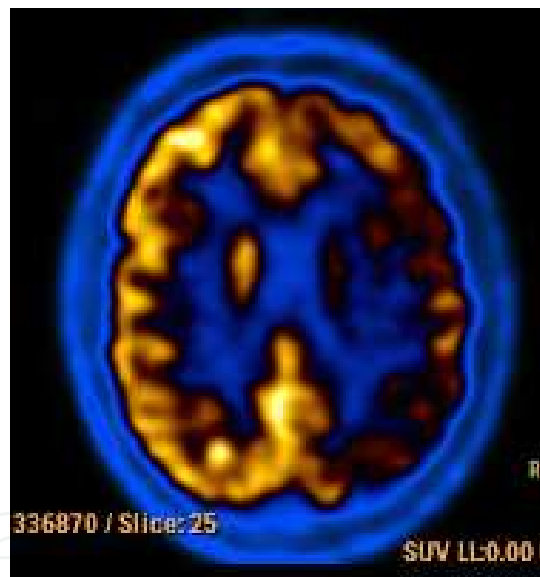


Figure 2. (18F)-FDG PET reveals areas of hypometabolism related to MS lesions and brain atrophy expressed mainly in the left cerebral hemisphere.

and nonparaneoplastic types of cerebellar ataxia [38]. Clinical data suggest that immune-mediated cerebellar ataxia may be caused by autoantibodies to various cerebellar targets [39]. Anti-voltage-gated calcium channel (VGCC), -Yo (Purkinje cell antigen), -ANNA-3, -Ri, -Hu, -Ma, -PCA-2, and -mGluR antibodies are found in patients with paraneoplastic cerebellar ataxia. In contrast, nonparaneoplastic ataxia is associated with anti-GAD, -gliadin, and -thyroid antibodies. Cross-reaction between tumor and cerebellar antigens is thought to be an underlying mechanism of autoimmune paraneoplastic ataxia [33]. The detection of circulating

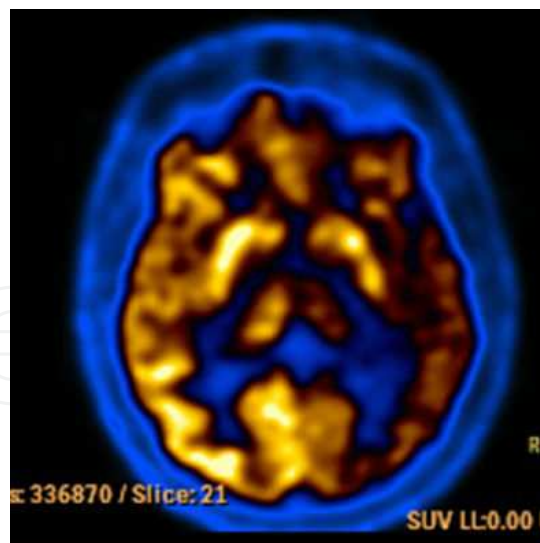


Figure 3. (18F)-FDG PET reveals areas of hypometabolism related to MS lesions and brain atrophy expressed mainly in the left cerebral hemisphere.

autoantibodies in patients with nonparaneoplastic cerebellar ataxia supports the notion that the immune system is also involved in the pathogenesis of these sporadic cases.

The diagnosis is usually suggested by the presence of atrophy of the cerebellum and brainstem on computed tomography scans (CT) and magnetic resonance imaging (MRI) [1, 38]. In addition, PET is useful in the investigation of patients with acute or chronic ataxias [33]. Functional neuroimaging with (18F)-FDG improves the detection of etiology and understanding of underlying pathophysiologic mechanisms in patients with late-onset cerebellar ataxia. Certain investigations reveal a reduction in absolute values of regional cerebral glucose metabolism in the cerebellar hemispheres and vermis, as well as in the brainstem or dentate nuclei [24, 25]. We report similar (18F)-FDG PET observations on our patient with anti-Yo antibody-positive late-onset cerebellar ataxia, associated with two different types of tumors (Clinical case 2). In contrast, Wang P et al. [41] show various patterns of cerebral glucose metabolism in patients with ataxia.

Clinical case 2. A 49-year-old female with skin melanoma and ovarian cyst in accordance with autoimmune (paraneoplastic) cerebellar ataxia. (18F)-FDG PET findings (Fig. 4 and 5).

3.3. Autoimmune limbic encephalitis

Limbic encephalitis is a severe, neuropsychiatric disorder that affects the limbic system, which is responsible for the basic autonomic functions [14]. Based on the etiology, it is divided into two clinical forms: viral and autoimmune. The inflammation in the latter is caused by the autoimmune process that involves medial temporal lobes. Autoimmune limbic encephalitis (ALE) may be either paraneoplastic, which is associated with a large number of cancers (lung, breast, testicular, thymoma, Hodgkin lymphoma) or idiopathic (non-paraneoplastic) [18, 20]. ALE can be associated with the presence of autoantibodies to two groups of antigens: intracellular neuronal and cell-surface [39]. The first group includes Hu, Mu2, Ri, glutamic acid

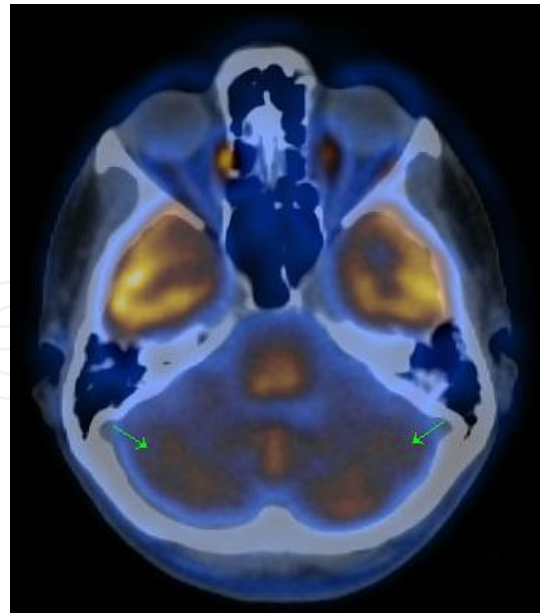


Figure 4. (18)F-FDG PET reveals strongly reduced metabolic activity in the cerebellum.

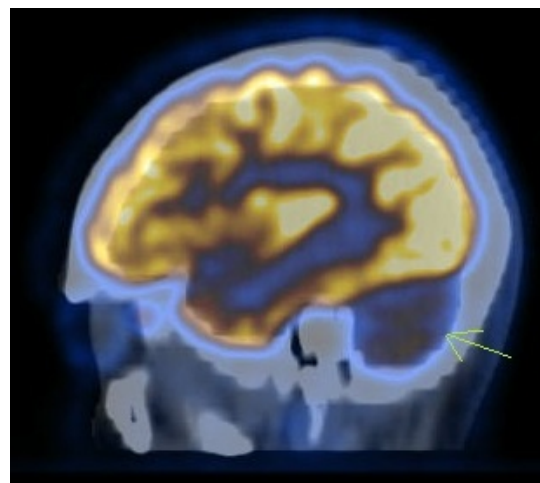


Figure 5. (18)F-FDG PET reveals strongly reduced metabolic activity in the cerebellum.

dexcarboxylase (GAD), amphiphysin, and collapsing response-mediator protein 5. Voltage-gated potassium channels (VGKC), N-methyl-d-aspartate receptor (NMDAR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMRAR) belong to the latter antigen group.

The diagnosis of ALE is based upon clinical features (memory loss, temporal lobe epilepsy, and psychiatric syndrome), MRI, electroencephalography (EEG), and cerebrospinal fluid analysis [14]. Cerebral (18F)-FDG PET studies describe different scan patterns in patients with ALE [4, 8]. According to Fisher R et al. [11], one is specific to the disease and presents a combination of pronounced occipital hypometabolism and hypermetabolism in the temporal and orbitofrontal cortex. We describe the similar findings in one patient with idiopathic ALE (Clinical case 3). The other pattern closely resembles a diffuse neurodegenerative disease. Rey

C et al. [30] report three cases with non-paraneoplastic limbic encephalitis characterized by (18F)-FDG PET bilateral striatal hypermetabolism, in contrast to diffused hypometabolism in the rest of the brain.

Clinical case 3. A 35-year-young male with idiopathic autoimmune limbic encephalitis. Neuroimaging findings (Fig. 6 and 7).



Figure 6. Coronal magnetic resonance-fluid attenuated inversion recovery (MRI-FLAIR) shows bilateral increased signal of hypothalamus and amygdala.

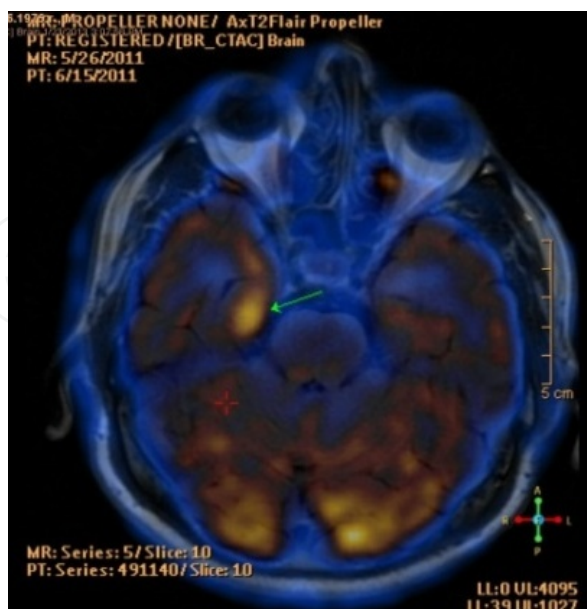


Figure 7. The (18F)-FDG PET scan reveals the nonhomogeneous distribution of cortical metabolic activity with discrete reduction in the left parietal region; hypermetabolism in both medial temporal lobes to hippocampi.

4. Summary

Although there are recent advances in molecular and cellular neurobiology, achievements of neurogenetics, and application of modern anatomical and functional neuroimaging techniques, the human brain is still an “enigma” and several immune-mediated inflammatory and neurodegenerative diseases of the CNS remain diagnosed late and unsuccessfully treated. Accordingly, a future research in basic neuroimmunology and innate mechanisms of autoimmunity is necessary to provide more precise immunodiagnostic assays and modern therapeutic approaches in patients with neurological autoimmune diseases. Furthermore, the development of new radiology methods and specific radiotracer biomarkers for the needs of neuroinflammation and degeneration imaging is another serious precondition to guarantee the early detection and adequate treatment of immune-mediated damages of the CNS. Respectively, existing clinical data support the notion that PET scanning improves the medical diagnosis, differentiation, monitoring, and prognosis of certain debilitating autoimmune diseases that affect the brain and spinal cord tissue.

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