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FUNCTION TESTING AND THERAPEUTIC FOLLOW-UP

Circulating antibodies to conjugated tryptophan derivatives of the IDO pathway in amyotrophic lateral sclerosis, Alzheimer's, Parkinson's and multiple sclerosis patients

Détection d'anticorps circulants dirigés contre les dérivés du tryptophane provenant de la voie IDO dans les sérums de patients atteints de sclérose latérale amyotrophique, de maladie d'Alzheimer, de maladie de Parkinson et de sclérose en plaques

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Summary Tryptophan—kynurenine pathway is known to be involved in neurodegenerative disorders, such as amyotrophic lateral sclerosis, as well as Alzheimer's and Parkinson's disease. The activation of indoleamine 2,3-dioxygenase, an inducible enzyme, is able to increase the production of neurotoxic metabolites, such as quinolinic acid and 3OH-kynurenine. This report describes how isotype G, M, and A circulating immunoglobulins recognize a pattern of conjugated tryptophan metabolites from the IDO pathway in each pathology. Isotype A immunoglobulins were mainly found in amyotrophic lateral sclerosis and Alzheimer's disease. Conversely, isotype G, M, and A immunoglobulins increased in multiple sclerosis. In Parkinson's disease, statistically high antibody levels were obtained, but not a high percentage of positive patients. These data indirectly confirm the implication of tryptophan derivatives in the pathogenic processes of amyotrophic lateral sclerosis, Alzheimer's disease and multiple

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sclerosis. Further studies are required to evaluate the interest of these specific patterns in monitoring of each disease.

MOTS CLÉS
Sclérose latérale amyotrophique ;
Maladie d'Alzheimer ;
Maladie de Parkinson ;
Sclérose en plaques ;
Dérivés du tryptophane

Résumé L'activation de la voie de l'indolamine 2,3-dioxygénase est connue pour être présente dans un grand nombre de maladies neurodégénératives, telles que la sclérose latérale amyotrophique, les maladies d'Alzheimer et de Parkinson, la sclérose en plaques. Cette enzyme inductible est à l'origine de la production de métabolites neurotoxiques. Dans notre étude, nous rapportons l'élévation de titres en anticorps circulants, dirigés contre certains composés conjugués, dans les sérums de malades atteints des affections citées. Pour cela, nous avons utilisé une méthodologie éprouvée : (1) synthèse de conjugués protéiques, (2) utilisation de tests immunoenzymatiques permettant la quantification des anticorps sériques circulants, spécifiques. Nous avons trouvé des profils immunologiques spécifiques pour chaque affection où prédominent des immunoglobulines A dans la sclérose latérale amyotrophique et la maladie d'Alzheimer, les isotypes G, M et A dans les différentes formes de sclérose en plaques. En revanche, on note une élévation significative d'immunoglobulines anti-dérivés du tryptophane conjugué dans la maladie de Parkinson, mais, le pourcentage de malades positifs sur les antigènes est faible. Les résultats présentés permettent : (1) de confirmer indirectement la production excessive de ces composés dans ces affections neurodégénératives ; (2) de proposer un profil biologique spécifique en vue du suivi biologique de chaque maladie.

Introduction

The pathogenic mechanisms of several neurological diseases, including amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), include some common inflammatory reactions. Moreover, many studies have established variable differences between selective vulnerability to neurodegeneration and tissue necrosis in the central nervous system (CNS). For example, the dopaminergic neurons in the substantia nigra are selectively destroyed in PD, whereas loss of motor neurons in the spinal cord occurs in ALS, and cholinergic neurons in the CNS are selectively destroyed in AD. In MS, myelin, oligodendrocytes, and neuronal axons are destroyed. Unfortunately, the etiology and physiopathology of these diseases are unclear.

Tryptophan is an essential amino-acid for cell growth and metabolism. Two pivotal biochemical pathways metabolize tryptophan in the central nervous system [1], with different affinities for this substrate. The first, tryptophan hydroxylase (THO), a rate limiting enzyme, participates in serotonin and melatonin synthesis, via enzymatic systems. In the other pathway, tryptophan is degraded by indoleamine 2,3-dioxygenase (IDO), an enzyme found in many tissues. IDO catalyses tryptophan to kynurenine, an intermediate for several biochemical compounds. The major tryptophan metabolites via IDO activation are: kynurenine (Kyn), 3-OH kynurenine (3-OHKyn), kynurenic acid (Kyna), quinolinic acid (Quina), quinaldic acid (Quinald), 3-OH anthranilic acid (3-OHAnthra), anthranilic acid (Anthra), xanthurenic acid (Xantha), and picolinic acid (Pico). The enzymatic systems and tryptophan derivatives of the IDO pathway are represented in Fig. 1. More, IDO is an inducible enzyme, activated by pathogens, pro-inflammatory cytokines [35,2,3], and chemokines.

The etiopathogenesis of ALS, AD, PD and MS are linked to associated pro-inflammatory cytokines and chemokines, activated glial cells (astrocytes and microglial cells), and lymphocyte infiltration. The expression of IDO and other enzymes associated with tryptophan pathways at inflammation sites are stimulated by pro-inflammatory cytokine IFN-γ [4,38]; IL-12 and IL-18 [5], lipopolysaccharides, and superantigens [6], dominantly mediated by an IFN-γ-independent pathway [7]. Neuroinflammation in the CNS may be a major factor in these diseases, as a consequence of cytotoxic tryptophan metabolite production by specific neuronal and glial cells [8].

In this study, the up-regulation of tryptophan derivative components or kynurenines was indirectly assayed by identifying the circulating antibodies. We first detect the presence of isotype G, M, and A antibodies directed against these conjugated compounds in sera from ALS, AD, PD, and MS patients, then describe their specific patterns.

Materials and methods

Biological materials

All sera were obtained with informed consent. In this study, the age and sex ratios of the healthy control populations were matched with those of the patients diagnosed with the diseases concerned.

For ALS, sera were taken from a population of 34 patients (mean age: 55, range 34—62, female: male patient ratio = 2:1). All patients suffered from sporadic ALS and none from the familial disease. These patients were affected by various onsets of ALS and treated with riluzole. Each blood sample was obtained at least six months after diagnosis. For comparative studies, 18 healthy controls were assayed (mean age: 47, range 43—57).

For AD, sera were taken from a population of 48 patients (age range: 65—85). AD states associated with dementia syndrome were segregated. Twenty sera were obtained from healthy controls (mean age: 70, range: 64—82).