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Therapeutic approaches in antibody-associated central nervous system pathologies

Approches thérapeutiques dans les pathologies du système nerveux central associées aux anticorps

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ABSTRACT

Initially, antibodies targeting intracellular compounds were described in patients with paraneoplastic neurological syndromes (PNS) such as anti-Hu, anti-Yo, anti-Ri or anti-CV2/CRMP5 antibodies. As more than 90% of patients with these antibodies suffer from an associated cancer, these antibodies were used as biomarkers of an underlying tumour. Recently, autoantibodies targeting cell-surface synaptic antigens have been described in patients with neurological symptoms suggesting PNS. These autoantibodies being less frequently associated with a tumour, they completely changed the concept of PNS. They lead to a new classification, not based on clinical symptoms or oncological status but on the location of the targeted antigens. Three groups of autoantibodies can be delineated according to the neuronal localization of the targeted antigen: Group 1: cytoplasmic neuronal antigens (CNA) (anti-Hu, Yo, CV2/CRMP5, Ri, Ma1/2, Sox, Zic4). Group 2: cell-surface neuronal antigens (CSNA) (anti-NMDAR, Lgi1, CASPR2, VGCC, AMPAr, GlyR, DNER, GABABR, GABAAR, IgLONS, mGluR1 and mGluR5). Group 3: intracellular synaptic antigens (ISA) (anti-GAD65 and anti-amphiphysin). More than being solely a classification of patients, these three groups are related to profound differences in the pathophysiology and in the pathogenic role of the associated autoantibody. According to the type of associated autoantibody, the age and sex of patients, physicians are now able to predict the presence or absence of tumour, the clinical evolution and prognostic and also the response to immunomodulator treatments that differ fundamentally from one group to the others.

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RÉSUMÉ

Initialement, des anticorps ciblant des protéines neuronales intra-cellulaires ont été décrits chez des patients atteints de syndromes neurologiques paranéoplasiques (SNP), tels que les anti-Hu, anti-Yo, anti-Ri ou anti-CV2/CRMP5. Étant donné que plus de 90 % des patients présentant de tels auto-anticorps développent également un cancer, ces anticorps ont été utilisés comme biomarqueurs des SNP. Récemment, d'autres auto-anticorps ciblant des antigènes neuronaux membranaires ont été décrits chez des patients présentant des symptômes neurologiques suggérant un SNP, mais la fréquence des cancers associés est moindre et variable suivant les auto-anticorps, ce qui a complètement modifié le concept de SNP. De ce fait, une nouvelle classification a été proposée reposant non pas sur les symptômes cliniques ou le statut oncologique, mais sur le type d'auto-anticorps associés. Trois groupes peuvent être identifiés selon la localisation neuronale de l'antigène ciblé : Groupe 1 : antigènes cytoplasmiques neuronales (CNA) (anti-Hu, Yo, CV2/CRMP5, Ri, Ma1/2, Sox, Zic4). Groupe 2 : antigène membranaire neuronal ou synaptique (CSNA) (anti-NMDAR, LGI1, CASPR2, VGCC, Ampar, GlyR, DNER, GABABR, GABAAR, IgLONS, mGluR1 et mGluR5). Groupe 3 : antigène intracellulaire synaptique (ISA) (anti-GAD65 et anti-amphiphysine). Il existe des différences profondes entre ces trois groupes sur le rôle pathogène de l'auto-anticorps associé et les mécanismes physiopathologiques. De ce fait, le clinicien est maintenant capable de prédire, en fonction de l'auto-anticorps associé, de l'âge et du sexe des patients, la présence ou l'absence d'une tumeur associée, le pronostic et l'évolution du patient, ainsi que la réponse aux traitements immuno-modulateurs.

1. Introduction

Paraneoplastic neurological syndromes (PNS) are defined as immune mediated disorders potentially affecting the whole nervous system, from its central part to the neuromuscular junction [1]. Some clinical patterns are highly frequent in these syndromes such as Cerebellar Degeneration (PCD), Limbic Encephalitis (LE), Subacute Sensory Neuronopathy (NSS) and Lambert-Eaton myasteniform syndrome (LEMS) [1]. In the 1980's, antibodies, targeting intracellular neuronal proteins were described as biomarkers of PNS [1]. The presence of these antibodies was a strong argument advocating for an underlying tumour with more than 90% of patients with such antibodies suffering from an associated cancer. Recently, other autoantibodies targeting cell-surface synaptic antigens have been described in patients with similar clinical presentation than PNS, but these autoantibodies are less frequently associated with a tumour and completely changed the concept of PNS [2].

The new PNS classification is not now based on clinical symptoms or oncological status but on the location of the targeted antigen. Three groups of autoantibodies can be delineated according to the neuronal localization of the antibodies-targeted antigen. Group1: antibodies to cytoplasmic neuronal antigens (CAN-Abs). Group2: antibodies to cell-surface neuronal antigens (CSNA-Abs). Group 3: antibodies to intracellular synaptic antigens (ISA-Abs). Interestingly, each group are related to profound differences in the pathophysiology and the pathogenic role of the considered antibodies. Presence or absence of a tumour, prognostic and treatment responses also differ fundamentally from one group to the other.

2. Group 1: antibodies with cytoplasmic neuronal antigens (CNA-Abs)

Diseases associated with CAN-Abs are rare: a European study conducted during 8 years was able to compile less than 1000 cases of PNS [3] and incidence is estimated being about 0.01% of all cancers. CNA-Abs targeting intracellular antigens, such as HuD [4], Ri [5], Yo [6], Ma1/2 [7], CV2/CRMP5 [8], Sox1 [9], Zic4 [10], are strongly associated to a tumour that can be extrapolated from the antibody itself. Anti-Hu and anti-Yo antibodies are the most frequent, and are heavily related to small cell lung carcinoma (SCLC) and gynaecological tumours (breast and ovarian carcinomas), respectively [3]. The pathophysiological function of CNA-Abs is still under debate and they seem to play no role and could be only a marker of a cytotoxic T-cell immune response directed towards neurones. Indeed, cerebral biopsies and autopsies of patients with such autoantibodies have shown the presence of cytotoxic T-cells in parenchyma, associated to a profound loss of neurones [11]. Experiments, by the injection of antibodies [12,13] or the immunisation of murine model with purified Yo or HuD antigens [12,13], or activated T-cells injections (especially in the case of anti-Hu and anti-Yo antibodies [13] failed to create an animal model of PNS. None of these procedures have permitted to recreate the neuronal loss observed in patients. A profound neuronal death is responsible of the neurological symptoms explaining why patients may not improve. Thereby, cure is not reachable and the therapeutic main purpose is to stabilise the neurological symptoms. The relative rarity of these disorders, together with the heterogeneity of clinical patterns, are the main reasons explaining the absence of consequent clinical trials in the field of PNS with CNA-Abs.

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