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Peripheral neuropathies associated with antibodies directed to intracellular neural antigens

Neuropathies périphériques associées aux anticorps dirigés contre des antigènes intracellulaires neuronaux

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INFO ARTICLE

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ABSTRACT

Antibodies directed to intracellular neural antigens have been mainly described in paraneoplastic peripheral neuropathies and mostly includes anti-Hu and anti-CV2/CRMP5 antibodies. These antibodies occur with different patterns of neuropathy. With anti-Hu antibody, the most frequent manifestation is sensory neuronopathy with frequent autonomic involvement. With anti-CV2/CRMP5 the neuropathy is more frequently sensory and motor with an axonal or mixed demyelinating and axonal electrophysiological pattern. The clinical pattern of these neuropathies is in keeping with the cellular distribution of HuD and CRMP5 in the peripheral nervous system. Although present in high titer, these antibodies are probably not directly responsible for the neuropathy. Pathological and experimental studies indicate that cytotoxic T-cells are probably the main effectors of the immune response. These disorders contrast with those in which antibodies recognize a cell surface antigen and are probably responsible for the disease. The neuronal cell death and axonal degeneration which result from T-cell mediated immunity explains why treating these disorders remains challenging.

RÉSUMÉ

Des anticorps dirigés contre des antigènes intracellulaires du système nerveux périphérique ont été principalement décrits dans le cadre des syndromes neurologiques paranéoplasiques et incluent les anticorps anti-Hu et anti-CV2/CRMP5. Avec l'anticorps anti-Hu la neuropathie sensitive est la plus fréquente des manifestations cliniques. Elle est fréquemment associée à une atteinte du système nerveux autonome. Avec l'anticorps anti-CV2/CRMP5 la neuropathie est fréquemment sensitivomotrice avec un profil électrophysiologique axonal ou axono-myélinique. Les manifestions cliniques de ces neuropathies sont conformes à la distribution cellulaire dans le système nerveux périphérique d'HuD et de CRMP5. Bien que présents en titre élevé, ces anticorps ne sont probablement pas directement responsables de la neuropathie. Des études anatomopathologies et expérimentales

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indiquent que les cellules T cytotoxiques sont probablement les principaux effecteurs de la réponse immune. Ces maladies s'opposent donc à celles au cours desquelles des anticorps reconnaissant des antigènes de la surface cellulaire provoquent probablement le processus pathologique. La mort neuronale et la dégénérescence axonale qui résultent de l'activation de l'immunité cellulaire médiée par les cellules T expliquent que le traitement de ces neuropathies reste difficile.

1. Introduction

Recent developments have identify a series of antibodies directed toward cell surface antigens such as ion channels, neurotransmitter receptors or proteins associated with them leading to the characterization of new clinical entities. The most fascinating aspect of these developments is that there is an increasing number of evidences demonstrating that these antibodies play a crucial role in the pathophysiology of these disorders [1]. Antibodies directed toward cell surface antigens have long ago been identified in diseases of the neuromuscular junction (anti-Acetylcholine receptors antibodies in myasthenia gravis or anti-voltage gated calcium channel antibodies in the Lambert-Eaton myasthenic syndrome) and in several forms of dysimmune peripheral neuropathies [2]. Such is the case of monoclonal IgM directed to the myelin associated glycoprotein (MAG) or IgG or IgM antibodies reacting with gangliosides. All these antigens are located on myelin or axonal membranes and can be accessible to auto-antibodies. Animal models have similarly demonstrated that for both the neuromuscular junction and the peripheral nerve, these antibodies are responsible for the disorder. More recently antibodies reacting with surface proteins of the nodal and paranodal regions have been identified in variants of chronic of inflammatory demyelinating polyneuropathies but it is not known whether these antibodies are pathogenic or not [3].

In opposition with cell surface-antibodies there exist another category of antibodies, which recognize intracellular antigens. These antibodies have been described in the context of paraneoplastic neurological syndromes (PNS). In contrast with the previous category, more than 90% of patients harboring these antibodies have a tumor, mostly a small cell lung cancer (SCLC), while cancer is inconstant or absent with the previous group. Another striking difference is that it was not possible to demonstrate that these antibodies are pathogenic living open the question as to whether they are only biomarkers of the underlying tumor. Two main antibodies reacting with intracellular antigens are associated with peripheral nervous system disorders, namely the anti-Hu and anti-CV2/CRMP5 antibodies.

2. Sensory neuronopathy and other peripheral nervous system disorders associated with anti-Hu antibodies

Anti-Hu antibodies react with HuD a neuronal specific mRNA binding protein, which is expressed in all categories of neurons in the central and peripheral nervous system [4], and in autonomic structures including the digestive tract. In sensory neurons HuD is located in the nucleus and in the cytoplasm in mitochondria and the Golgi apparatus where it may enable mRNA interactions with sub-cellular organelles and regulate their cellular localization [5]. It also interacts with SMN in motor neurons, which may facilitate the localization of mRNAs into motor axons [6]. HuD is expressed by most of small cell lung cancers in a normal non-mutated form [7] and it is commonly admitted that it is the recognition of the protein by the immune system in a tumor context that leads to the development of the neurological syndrome. This may be facilitated by an expression of the protein at the cell surface both in tumors and neurons as it has at least been showed in vitro [8]. However, HuD although belonging to the repertory of antigens normally recognized by circulating T-cells [9] shows a high degree of immune tolerance [10] which probably explains that only a very few patients with SCLC develop a PNS and that autoimmune disorders directed against HuD are extremely rare in patients, mainly children, who never develop cancer even after several years of follow-up [11].

Patients with anti-Hu antibodies show a wide spectrum of neurological disorders involving the central, peripheral and autonomic nervous systems [12] but the most frequent manifestation occurring in more than half of the patients is sensory neuronopathy (SNN) (Graus et al., 2001). This disorder depends on the destruction of sensory neurons in dorsal root ganglia [13]. SNN was first identified and recognized as a PNS by Denny-Brown in 1948 [14] but a paraneoplastic origin is only one of the etiologies of SNN which may depend on autoimmune diseases, viral infections, toxic or genetic causes [13,15]. In our series, paraneoplastic SNN represent 11% of all SN cases but 17.5% of patients with an acute or subacute form (Antoine et al., to be published). However, in the PNSEuro network database, SN occurs in 24% of patients making it one of the most frequent PNS [16].

Paraneoplastic SNN has a highly suggestive clinical presentation [17]. The onset is usually subacute or rapidly progressive with paraesthesia and pain. Sensory loss is frequently multifocal or asymmetrical, and the upper limbs are almost invariably involved [12,18]. The face, the chest, or the abdomen may also be concerned. Pain is frequent and sensory loss, affecting especially deep sensation often leads to severe sensory ataxia in the four limbs. Although usually present in most patients with an equal intensity, small or large sensory fiber involvement may predominate in some cases [19]. If diagnosed late in the evolution, SSN can be a very disabling disorder, but in the PNSEuro network database patients are frequently only mildly disabled with a mean