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Peripheral nervous system neuroimmunology seen by a neuro-pathologist

L'immunologie du système nerveux périphérique discutée par un neuropathologiste

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ABSTRACT

In most dysimmune neuropathies, historically the microscopical lesions were described prior to immunological studies. The latter along with neuropathological studies have found some immune, albeit incomplete, explanations of the mechanisms of these lesions which we will describe in two main syndromes: the primitive auto-immune inflammatory peripheral polyneuropathies (GBS and CIDP) and polyneuropathies induced by a monoclonal dysglobulinemia. In some patients who have to be discussed case by case pathology (nerve biopsy) will confirm the diagnosis, may help to delineate the molecular anomalies and identify lesional mechanisms. We will review the high variability of nerve lesions which is characteristic of dysimmune neuropathies. Pathological studies confirm that both humoral and cellular immune reactions against Schwann cell and/or axonal antigens are implicated in primitive dysimmune neuropathies due to a dysfunction or failure of immune tolerance mechanisms. In case of a polyneuropathy associated to a monoclonal dysglobulinemia, pathological and immunological studies have shown that in many patients, the dysglobulinemia did harm the peripheral nerve; knowledge of the pathological lesions and their mechanisms is of major interest for orienting specific treatments.

RÉSUMÉ

Au cours de la plupart des neuropathies dysimmunes, chronologiquement les lésions pathologiques ont été décrites avant les études immunologiques. Les examens microscopiques expliquent néanmoins incomplètement les mécanismes lésionnels que nous décrivons dans deux syndromes : les neuropathies inflammatoires primitives auto-immunes (SGB et PIDC) et les neuropathies induites par une dysglobulinémie monoclonale. Chez quelques malades chez lesquels a été réalisée une biopsie nerveuse, l'étude microscopique peut contribuer à préciser les anomalies moléculaires et identifier les mécanismes lésionnels qui dans ce contexte d'auto-immunité sont très variés. Des réactions immunes humorales et cellulaires contre des antigènes des cellules de Schwann ou axonaux sont

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impliquées dans ces neuropathies dues à un dysfonctionnement des mécanismes de tolérance immunitaire. Dans les cas d'association à une gammapathie monoclonale, les constatations microscopiques montrent que l'immunoglobuline sérique anormale est bien responsable directement des lésions nerveuses ; la mise en évidence de ces lésions ainsi que leurs mécanismes lésionnels sont d'un grand intérêt pour discuter de la stratégie thérapeutique au cas par cas.

The aim of this presentation is to describe the different types of microscopic nerve lesions in dysimmune neuropathies, which may help to delineate the molecular anomalies induced by what is thought to be an auto-immune process. Historically, the pathological lesions were described prior to immunological studies. The latter along with neuropathological studies have found some immune, albeit incomplete, explanations of the mechanisms of these microscopic lesions.

Better details from such studies could guide more accurate treatment options. The neuro-pathologist may also diagnose mechanisms not related to the dysimmune processes such as the adverse effects of chemotherapy or other coincidental causes.

At present, microscopic studies in these indications encounter unavoidable difficulties. Nerve biopsy of a distal sensory nerve is the only technique which can be used; the indications in humans have to be on a case by case basis and need to take the therapeutic possibilities into account. In the ''primary'' dysimmune neuropathies, the lesions are multifocal, randomly distributed, mainly involve nerve roots, so that they would be better studied at autopsy; fortunately only a few patients die of these disorders. Otherwise, for the neuropathologist, it is quite difficult to establish links between morphological lesions which are static and the more dynamic mechanisms of immune system disorders. As in multiple sclerosis, several types of lesions exist depending not only upon their location, but also on the age and the stage of the disease along with inter-individual differences [1]. This high variability of nerve lesions is also characteristic of dysimmune neuropathies.

In practice, the rather complex immunological mechanisms give rise to a variety of phenotypes such as Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory neuropathy (AMSAN); subacute inflammatory demyelinating polyneuropathy (SIDP), chronic inflammatory demyelinating polyneuropathy (CIDP) which can be presented as typical and atypical forms: distal involvement (DADS), pure motor and pure sensory forms, multifocal distribution (Lewis-Sumner syndrome). As there are few pathological data, we will not discuss acute (e.g. Fisher's syndrome and acute sensory ataxia) and chronic sensory ataxic neuropathies with disialosyl antibodies.

In the second part, we will present the different nerve lesions induced by a particular immune process, linked to a monoclonal dysglobulinemia.

We will not discuss here the lesions induced by necrotizing vasculitis.

1. "Primitive" auto-immune inflammatory demyelinating peripheral polyneuropathies

Whether they are of acute (GBS) and/or chronic course (CIDP), the initial inflammatory and demyelinating processes of these primitive dysimmune neuropathies are identical. As we shall describe, during such dysimmune processes, it is possible to discriminate different stages in the progression of the lesions. It should be noted that such discrimination may be rather theoretical due to the temporal overlap of the various types of lesion which include areas of active tissue damage, reactive changes, remyelination and repair.

It is also important to stress the variability of the pathological lesions among patients suffering from the same disease: GBS or CIDP probably due to the complexity of the immune processes. It has to be viewed in the light of the clinical, electrophysiological phenotypes and the biological data, especially serum antibodies. It is not always easy to determine logical links between all these data in any given patient. The discovery of new antibodies should be completed by a detailed pathological study of the nerve to try to understand the molecular anomalies. No consistent antigen has been shown to be associated with these diseases. Nevertheless, a few studies have shown that some CIDP cases might be linked to antibodies against target proteins of the peripheral nerve; no pathological studies have been presented [2,3].

1.1. *Common initial phase of demyelinating forms « acute inflammatory demyelinating polyneuropathy (GBS) and CIDP*

1.1.1. *Inflammatory phase*

Considering the humoral immune response, it has been shown that there is an increase of systemic concentrations of tumor necrotic factors (TNF), interleukin 2 in line with activation of T cells. Some GBS cases are in relation to an acute demyelination without immune cell invasion and are probably primarily humorally mediated. In most cases, the humoral immune responses are thought to predominate at early stages of GBS and then at later stages, additional cellular mechanisms mediated by cytotoxic T cells contribute to myelin damage via granzyme release [4]. Deposits of complement have been shown on the abaxonal surface of Schwann cells in GBS and it has been demonstrated that nodes of Ranvier and paranodes are the targets of the immune attacks in GBS and CIDP. Devaux et al., 2012 showed that in CIDP and GBS patients IgG colocalized with Nav channels at nodes and with Caspr at the paranodal septate-like junctions; these