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Cortical, subcortical and spinal alterations in neuroimmunological diseases

Abstract Inflammatory and immune mediated diseases of the nervous system are reflected by a broad spectrum of different clinical deficits. The reason for this is that inflammation may affect any part of the nervous system. Nevertheless, certain regions in the brain and spinal cord are more frequently affected than others. The topographical distribution of inflammatory lesions in the nervous system depends upon a large variety of different factors, which are different in the various infectious and autoimmune diseases. Aim of this short review is to discuss the main factors determining lesional topography in brain inflammation and to illustrate these patterns of tissue injury with clinical examples.

Key words brain inflammation · autoimmunity · infection · lesion topography

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Introduction

The nervous system is affected in a variety of different neuroimmunological diseases. These include classical infectious diseases as well as autoimmune disorders. Mechanistically, inflammatory lesions can be induced either by T-lymphocytes, by B-cells and autoantibodies as well as by cells from the innate immune system. Depending upon the mechanisms of immune mediated damage, different parts of the nervous system are dominantly affected. This is reflected by a clinical disease manifestation, which is at least in part characteristic for a given neuroimmunological disease.

Infectious diseases

The major factor determining the topography of lesions in infectious diseases is the local presence of the infectious agent [4]. This is in part determined by the cellular tropism of the infectious agent, determining what cell type or what particular subpopulation of cells are infected. Yet, not only the cellular tropism of infection is important, but also the efficacy of clearance. In Theiler's virus induced encephalitis, infection of the brain first results in a global infection of neurones and glia leading to an acute phase of panencephalitis. With chronicity, however, the infection is cleared from nerve cells and grey matter, but persists in glia cells of the white matter. As a consequence, infected animals later develop a subacute demyelinating encephalomyelitis, mainly affecting the spinal cord [2].

Another important factor, determining lesional topography in infectious diseases, is the route of entry of the virus into the central nervous system (CNS). Infections that reach the nervous system via retrograde axonal transport obviously reveal a different pattern of lesion distribution compared to those that are entering the brain through blood vessels.

T-cell mediated brain inflammation

Initial lesions in T-cell mediated brain inflammation arise around small veins. This is reflected by the perivenous orientation of demyelinated lesions in multiple sclerosis [3, 23] and experimental autoimmune encephalomyelitis [26]. Hence, in T-cell mediated inflammatory diseases of the CNS lesions may appear in any lo-

cation, but the chance of finding them in areas with high anatomical density of veins is much higher. This explains the preferred localisation of demyelinated plaques in certain anatomic sites, such as the periventricular white matter, the subcortical white matter, the optic nerves, the cerebellar peduncles and certain areas of the spinal cord [5, 13, 20].

In addition to this perivenous distribution of lesions, their topography also reflects the presence of the respective CNS antigen, recognised by encephalitogenic T-cells. Thus, characteristic differences in lesion distribution are found in models of autoimmune encephalomyelitis, depending upon the target antigen recognised by the encephalitogenic T-cells [1]. Autoimmunity against myelin antigens mainly affects the white matter, while T-cells directed against astrocytic of neuronal antigens predominantly target grey matter areas [1, 6, 10, 21].

A third aspect, which determines lesion topography in T-cell mediated autoimmune encephalomyelitis, relates to the conditions of the target tissue. Preferential homing of inflammatory lesions to sites of traumatic tissue injury has been shown in many models of autoimmune encephalomyelitis [8, 17]. Whether a genetically determined metabolic injury of certain brain components may determine lesional topography is currently not resolved. Yet, multiple sclerosis patients with mitochondrial gene defects develop lesions preferentially within the optic nerve, presenting clinically with severe bilateral optic neuritis [7].

Antibody or immune complex mediated disease

Direct antibody mediated damage in the CNS is rare, since the intact blood brain barrier restricts serum proteins from reaching the CNS in sufficient concentrations. Thus, antibody mediated autoimmune diseases mainly affect peripheral nerves and the neuromuscular junction. Within the CNS leaky blood vessel endothelia are present in the choroid plexus and the circumventricular organs. Circulating immune complexes can pass this barrier and may become deposited in the basement membrane of such vessels. Such a mechanism of brain damage is suggested to play a role in immune complex diseases and systemic lupus [9, 22].

Autoantibodies, however, can massively augment disease and tissue injury, when present together with a T-cell mediated inflammatory process [18]. When autoimmune encephalomyelitis is induced by T-cells in the presence of a demyelinating antibody response, the shape of the lesions and their distribution depends upon the balance between the T-cell and antibody reaction. A massive T-cell reaction with no or only a minor demyelinating antibody response results in perivenous demyelination, ubiquitously distributed within the CNS. This closely resembles the pathology of acute disseminated leukoencephalitis. In case the antibody response is more severe, focal demyelinated plaques are formed, which occur in random distribution throughout the CNS [14]. Yet, when the T-cell response is low but the antibody response is pronounced, lesions are concentrated mainly in the optic nerves and the spinal cord [25]. The reason for this peculiar affection of optic nerve and spinal cord is not clear, but differences in the blood brain barrier properties within different brain and spinal cord regions may be one pathogenic factor.

These results may be relevant for Devic's type of neuromyelitis optica. In these patients a profound antibody response against the astrocytic water channel aquaporin 4 has recently been identified [15, 16]. Despite the ubiquitous presence of aquaporin 4 in the entire CNS, the lesions in Devic's disease are mainly present in the optic nerves and the spinal cord [19].

Compartmentalised inflammation in the central nervous system

In chronic inflammatory diseases of the CNS such as multiple sclerosis, inflammation may become trapped behind a closed or repaired blood brain barrier. This is reflected by the appearance of lymphatic like tissue within the meninges or the perivascular spaces [24]. Tissue damage is then induced by soluble factors (cytokines or antibodies), derived from T- and B-cells, which exert their toxicity either directly or indirectly through microglia activation. Such a mechanism appears to be important in the formation of cortical lesions and diffuse white matter injury in the progressive stage of multiple sclerosis [11]. It is important to realise that compartmentalisation of T- and B-cells in the CNS is restricted to the connective tissue spaces, such as the meninges and the Virchow Robin spaces. The consequence for lesional topography is that such lesions are dominantly located at the inner and outer surface of the brain and spinal cord, due to the anatomical location of meninges and perivascular connective tissue spaces. Furthermore, cortical demyelination in multiple sclerosis is most extensive in deep indentations of the brain surface, such as the insular or cingulated cortex, as well as in sulci of the cortical ribbon [12]. The reason for this peculiar distribution appears to be that in such meningeal areas the circulation of the cerebrospinal fluid is low.

Conclusions

Although inflammatory processes may affect all parts of the nervous system, certain areas are more likely to be affected than others, depending on disease related im-

munological mechanisms. This may explain at least in part the differences, observed in the clinical manifestation of distinct autoimmune or infections diseases of the nervous system.

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