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Review

Spasticity in multiple sclerosis: Contribution of inflammation, autoimmune mediated neuronal damage and therapeutic interventions

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ABSTRACT

In contrast to other diseases that go along with spasticity (e.g. spinal cord injury), spasticity in chronic autoimmune diseases involving the CNS is complicated by the ongoing damage of neuronal networks that leads to permanent changes in the clinical picture of spasticity.
Multiple sclerosis (MS) is the most frequent autoimmune disease of the central nervous system (CNS) and spasticity is one of the most disabling symptoms. It occurs in more than 80% MS patients at some point of the disease and is associated with impaired ambulation, pain and the development of contractures.
Besides causing cumulative structural damage, neuroinflammation occurring in MS leads to dynamic changes in motor circuit function and muscle tone that are caused by cytokines, prostaglandins, reactive oxygen species and stress hormones that affect neuronal circuits and thereby spasticity.
The situation is complicated further by the fact that therapeutics used for the immunotherapy of MS may worsen spasticity and drugs used for the symptomatic treatment of spasticity have been shown to have the potential to alter immune cell function and CNS autoimmunity itself. This review summarizes the current knowledge on the immunologic pathways that are involved in the development, maintenance, dynamic changes and pharmacological modulation of spasticity in MS.

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1. Pathogenesis of spasticity in immune-mediated diseases of the central nervous system (CNS)

Chronic autoimmune mediated CNS-inflammation may occur with diseases as distinct as paraneoplastic encephalitis, infectious meningoencephalitis or "classic" autoimmune diseases as rheumatoid arthritis, lupus erythematodes or multiple sclerosis (MS). Demyelination, astrogliosis, axonal damage, loss of synapses, neurodegeneration and neuroplasticity are key features of immune mediated lesions of brain and spinal cord, irrespective of the underlying disease entity [1]. Functional deficits resulting from these pathological processes are either direct consequences of tissue damage or develop from adaptation processes on the cerebral and spinal level and give rise to sensory, motor, autonomic or cognitive-behavioral symptoms [2–4]. Among the highly variable clinical signs and symptoms threatening ambulation and self-sufficiency, the "upper motor neuron syndrome", which is composed of muscular weakness, ataxia and spasticity, is of outstanding importance [5].

Multiple Sclerosis (MS) is the most frequent and best characterized autoimmune disease of the CNS. The anatomical distribution of MS lesions is highly variable with involvement of cerebrum, cerebellum, brain stem and spinal cord [2]. Even more than the damage associated with acute inflammatory lesions, it is the subsequent neurodegeneration that is associated with the progressively developing sustained disability in MS, to which spasticity gives a major contribution [6–8].

Spasticity originates from a disinhibition of physiological proprioceptive reflexes on the spinal level due to shifts in the highly complex balance between excitatory and inhibitory inputs to the α motor neuron (MN [9]. This balance shift is either caused by lesions affecting the ascending and descending tract systems anywhere along the trajectory through brain stem and spinal cord or by lesions damaging the local network of spinal interneurons in close vicinity to the clinically affected segment. Subcortical lesions may lead to prolonged spasticity without relevant paralysis observed in some patients, whereas isolated damage to the primary motor cortex (M1 or Brodmann's area 4) typically results in flaccid paralysis without spasticity [10,11]. A correlative analysis of MRI data and clinical parameters revealed that spasticity is correlated with lesion number in brainstem, callosal radiation and pyramidal tracts [12]. Fig. 1 provides a simplified illustration of the key components of structural damage and dynamic processes that set the stage for spastic movement disorders in subjects suffering from MS.

Since the primary causes for the development of spasticity are to be found always and exclusively in the CNS, it has traditionally been in the focus of spasticity research. However, spasticity induced secondary changes to the affected muscles gain increasing attention. These changes include alterations in the contractile apparatus, metabolism, the extracellular matrix and the cytoskeleton with differing effects on type I and type II - muscle fibers [13–17].

2. Clinical presentation of spasticity: reflecting past and presence of individual CNS autoimmune disease courses

In some patients, spasticity-related impairment clearly dominates functional deficits caused by other symptoms and gives a relevant contribution to the individual and socio-economic burden of MS [18,19]. Depending on the individual course and duration of the disease, spasticity can occur simultaneously or sequentially in one or more of the following manifestations [20–23].

- increased muscle tone during active movements
- increased muscle tone during passive stretching
- unprovoked, persistent increase of muscle tone
- transient, painful, paroxysmal muscle spasms

For each patient, the pattern of manifestations can be related to the individual disease history and lesion distribution. Spasticity may be limited to single extremities (segmental spasticity), or present as monolateral (hemispasticity) or bilateral syndrome (paraspasticity, tetraspasticity). Unlike many other underlying diseases that cause spastic symptoms (e.g. traumatic myelopathy), the cause of disease in MS and other autoimmune diseases affecting the CNS is highly dynamic, interindividually different and still not readily predictable for the individual patient. The intraindividual phenomenology and functional relevance can change drastically over time and disease course: Occasional paroxysmal spasms in the calf muscles during early stages of disease may worsen to permanent paraspasticity with marked involvement of adductors and extensors years later. Even within hours, the severity of spasticity may vary over a wide range. This, of course, does not reflect rapidly occurring and vanishing CNS lesions. In fact, these highly dynamic changes in spasticity are caused by changes in the balance of excitation and inhibition of spinal MN.

As paralysis progresses, an initially disturbing mild paraspasticity of the legs may prove essential to maintain transfer, standing and walking ability. Hence, continual joint reevaluation of therapeutic approaches by therapists and patients in context of the individual prevailing symptom constellation is essential to improve quality of life, mobility and daily living [24]. The occurrence of stiffness, spasms, pain and clonus in arms and legs was studied in the 2016 NARCOMS – study. Considering symptoms irrespective of their severity, they were reported to be almost twice as frequent in the lower as in the upper extremities. When considering severe symptoms only, the difference was even more striking. For instance, severe stiffness of one or both arms was reported by only 3.2%, whereas 18.8% of patients reported severe stiffness of one or both legs.

3. Prevalence of spasticity in multiple sclerosis

The involuntary increase in muscle tone can occur in diverse qualitatively and quantitatively distinct manifestations [22,25]. It is of critical importance to recognize that both static damage (cumulative CNS lesion load leading to altered wiring of motor spinal circuits) and dynamic functional variability add up to give the clinical picture of spasticity in MS. Understanding the epidemiology and details of the clinical presentation of spasticity at different disease stages thus offers important insights to the relative contribution of the various pathophysiological mechanisms contributing to MS spasticity.

Data of the largest German MS register consistently show a symptom prevalence of more than 50% [20,26,27]. Available data, albeit limited, imply that not all types of MS comprise the same risk of developing spasticity. The largest studies addressing the epidemiology of MS

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