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Botulinum toxin in patients with multiple sclerosis

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Abstract Nearly all patients with multiple sclerosis (MS) will develop spasticity in the course of their disease. This symptom accounts for most of the handicap and impairment in the quality of life. Treatment with botulinum toxin will enable an efficient and safe alleviation of spasticity and the problems involved, given a realistic definition of the therapeutic target and a graded multimodal approach. Treatment may fail for a great number of reasons that require diligent analysis. Compared with other disorders resulting in spasticity as well, MS does not constitute a monophasic disorder but is influenced by many factors. Treatment of spasticity in MS must therefore be guided by its particular aspects.

Key words multiple sclerosis · spasticity · botulinum toxin · treatment

Introduction

Application of botulinum toxin A in patients with multiple sclerosis (MS) is presently focused on three areas: spasticity, neurogenic bladder dysfunction and pain therapy. Most experience has been gathered by neurologic users in the field of spasticity. The act of botulinum toxin on the various forms of tremor in MS has not been overly satisfying.

Nearly all patients with multiple sclerosis will develop *spasticity* in the course of their illness. At least 25 % of the patients want of antispastic management tailored to their needs. From concurring experience of neurologic users under both outpatient and inpatient conditions and neurologic rehabilitation, this can only be warranted by a *multimodal approach*. An appropriate concerted combination of physiotherapeutic training, serial casting, ergotherapy, and the introduction of ortheses, kinesitherapy trainers and functional electrostimulation on demand is most important for the individual patient, and often it is botulinum toxin that opens the therapeutic window first.

Despite the highly variable course of disease, spasticity-induced *"standard situations"* are in a manageable proportion and specifically involve the legs: adductor spasticity, hip flexor spasticity, hip extensor spasticity, spastic talipes equinus and striatal toe. Only about 7 % of the patients receive treatment of the upper extremity: Mostly due to severe adductor spasticity of the shoulder joint.

Therapeutic objectives of antispastic management

It is indispensable to define a realistic *therapeutic target* including any relevant information that can be elicited from the patient and his family, on the one hand, and from the multiprofessional team, on the other.

Two levels must principally be distinguished from another:

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- Improvement of "active" function, e. g., symmetry or gait or "passive" function, e. g., transfer or
- Improvement of the care-taking situation, alleviation of pain and prevention of complications.

There is no universal measuring tool to evaluate the goal of treatment, and possibly – owing to tenor – there never will be.

Best results of botulinum toxin in MS are obtained for *focal spasticity*. The possibilities of regional antispastic therapy (e. g., with a baclofen pump) should always be discussed in patients with paraspasticity, either as an alternative or in combination. Good results for patients with predominantly spinal MS lesions have been documented after intrathecal triamcinolone treatment, which has not yet been approved in Germany. Botulinum toxin showed good effects in regional spasticity, when an *action-triggered expansion of spasticity* has been successfully *blocked*, for instance from the muscles of the lower limb toward the proximal thigh and trunk muscles by treating "trigger muscles".

Practical approach: Which are the important decisions to make?

Initiation of an efficient antispastic management should not be delayed, given the fact that MS is a progressing disease, in which – analogous to parkinsonism – we must not waste "golden years". The *maximum dose* required for one therapeutic session may only be exceeded in well-founded individual cases, while observing safety standards closely. A focal change of dose distribution in serial therapies will frequently enable a regional reduction of tonus in paraspasticity, thus, reaching a "steady state" after 3 to 4 sessions. Even in the presence of quite favorable current data regarding the incidence of secondary failure due to formation of neutralizing antibodies, a *minimal therapeutic interval* of 10 to 12 weeks should be observed. The question of a *therapeutic endpoint* is iteratively raised: The diagnosis "fixed contracture" should be challenged in any particular case. When the involved joint is not completely contracted, it may be helpful to search for treatable areas in the muscle via EMG or ultrasound, as experience has shown that soft tissue transformation in the transverse section is not taking place synchronously in the large muscles (adductor muscles, flexor muscles of knee). EMG-monitoring can prevent a botulinum toxin injection into the "silent regions" within a muscle, thereby enhancing the efficacy of treatment. Botulinum toxin is thus capable of opening the therapeutic window in bedridden patients for treatments that reduce tonus and stimulate blood supply, aided by a kinesitherapy device. In the intermediate term, this will interrupt the vicious circle of spasticity, faulty posture, decubital ulcer and pain.

What are the causes of failure?

After all, it is the patient who decides on whether he is sufficiently benefiting from antispastic treatment. The causes of *therapeutic failure* are manifold. Disappointment will set in when the therapeutic objective is overestimated by large margins, i. e., functional improvement is an unrealistic goal. We must always inquire whether the patient can avail him- or herself of adequate resources on the cognitive and motivational plane to make use of the potential kinetic liberties.

When functional improvement is the intention, the therapist may overrate the therapeutic window with the result of temporary functional impairment by excessive weakening of the muscular system (e. g., by simultaneous treatment of the synergists). The same will happen when choosing the wrong target muscle, or when failing to localize it properly, or with maldosing. Formation of neutralizing antibodies does not play a substantial role in therapeutic failure.

Owing to the complexity of their illness, patients with MS are frequently being treated by several doctors at the same time, with the undesired result that their antispastic regimen (oral antispastic agents, physiotherapy) is changed by third parties, thus feigning inefficiency of botulinum toxin.

What to keep in mind when treating spasticity in MS?

The *specific problems of spasticity in MS* as compared to other disorders associated with spasticity have to be kept in mind when evaluating this treatment:

MS is no monophasic disease: "MS never sleeps!"

- Purely motor-centered relapses may be faking side effects of botulinum toxin.
- The intensity of spasticity is subject to considerable diurnal and seasonal fluctuations and is influenced by numerous factors unrelated to treatment.
- Our instruments to measure spasticity are inadequate. The widely used Ashworth-Scale should – for instance – be documented in analogy to the ON- and OFF-periods of spasticity in Parkinson's disease.
- Patients with paraparesis do often present with a number of concomitantly existing spasticity patterns; their relevance in everyday life ought to be analyzed carefully and jointly with the patient and his relatives in every single case.
- In the course of disease, the pattern of spasticity may either change very rapidly owing to relapses, or changes may go almost unnoted owing to slow and chronic progression. The therapeutic regimen must be adapted accordingly.
- Steroid pulse therapies will transitorily change spasticity.

- Various immunomodulating therapies (e. g., interferons) may interfere with botulinum toxin by having an impact on spasticity.
- Some immunosuppressive treatments might counteract antibody formation, which would render intervals in the lower therapeutic window (10 weeks) less cumbersome. Adequate data are not available, however.
- In view of the slow progression of disease and cognitive deficits, patients with advanced MS may, at times, perceive the gradual general aggravation of spasticity and paralysis as an increasing failure of botulinum toxin. This differentiation may be difficult even for the therapists. The documentation of findings (EDSS among others) should take this into account.

By defining a realistic goal and designing a graded multimodal approach, we are able to induce efficient and safe alleviation of spasticity in many MS patients. Randomized controlled studies are urgently needed concerning the primary objectives of treatment and the close to everyday life evaluation.