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Cannabinoid agonists in the treatment of blepharospasm – A case report study

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Abstract

The benign essential blepharospasm is a subliminal form of primary torsion dystonia with still uncertain aetiology. It is characterized by involuntary convulsive muscle contractions of the M. orbicularis occuli, accompanied by unbearable pain of the cornea, eye bulb and the muscle itself. It has been suggested that blepharospasm is neurobiologically based on a dysfunction of the basal ganglia and an impairment of the dopamine neurotransmitter system. Therefore, therapy of blepharospasm contains administration of anticholinergic- and tranquillizing drugs as well as botulinum toxin as neuromuscular blocking agent. However serious side effects can be observed as well as failure of therapy.
In the brain a dense co-localisation of cannabinoid (CB1) and dopamine (D2)-receptor was identified which had been associated with the influence of cannabinoids on the dopaminergic reward system. Additionally, it has been demonstrated that cannabinoids may have an impact on the central GABAergic and glutaminergic transmitter system and thus might be involved in the influence of movement control. In the present case we administered the cannabinoid receptor agonist Dronabinol® (Delta-9-Tetrahydrocannabinol) to a woman suffering from severe blepharospasm. Multiple treatments with botulinum toxin did not reveal a long-lasting beneficial effect. By contrast, treatment with 25 mg Dronabinol® for several weeks improved the patients' social life and attenuated pain perception remarkably. This case study demonstrates that the therapy with a cannabinoid agonist may provide a novel tool in the treatment of blepharospasm and maybe of other multifactorial related movement disorders.

CASE STUDY

Abbreviations
BEB – benign essential blepharospasmus;
BOTOX – Botulinum Toxin ;
GABA – Gamma-Amino-Butyric-Acid

Introduction

In contrast to a symptomatic form the benign essential blepharospasm (BEB) is a common form of primary torsion dystonia. The incidence of BEB is 1 /200 000 and occurs preferably in middle-aged women rather than in men. However, the aetiology of BEB is still unclear. An autosomal-dominant inheritance is postulated [1, 2], but apart from the idiopathic form environmental conditions or medication have been assumed to be critical factors for the maintenance of BEB (narcoleptics, dopaminagonists, metabolic, vascular, degenerative or inflammatory brain disorders). In general, Hallet suggested a dysfunction of the basal ganglia and a disturbance of the dopamine neurotransmitter system as a neurobiological correlate [1].

BEB and all subtypes of blepharospasm can be augmented by affection. If an underlying conflict is diagnosed and a history of relevant events is found in close relationship, a psychosomatic disorder may be considered and a combination of drug therapy and psychotherapeutic treatment should be employed. As an effective but rather symptomatical treatment botulinum toxin has emerged, although anticholinergics and benzodiazepines provided being beneficial therapeutics as well [1, 3]. For instance, psychogenous derived movement disorders associated with behavioural alterations provided a good response to psychomimetic drugs such as benzodiazepines. However, regardless the medication, psychogenous derived blepharospasm requires excellent diagnostic expertise of the physician and experienced psychiatrists for treatment. The observation that some patients display a lack of insight in the pathophysiology and psychology of their disease often demands a symptomatical medicinal treatment rather than a causal one. Since symptomatical medication is often accompanied by a narrow therapeutic band and the likelihood of side effects, one may consider an alternative approach for therapy. Given the wide array of cannabinergic drugs, their successful use in the treatment of e.g. multiple sclerosis [4, 5], but also the distinct co-localization and inter-action of Cannabinoid and Dopamine receptors [6, 7], may provide cannabinoids – the pharmacologicl active compounds of the plant *Cannabis sativa L.* – as putative candidates for the treatment of psychosomatic motor disturbances.

For medical use, Dronabinol® (delta-9-tetrahydrocannabinol, delta-9-thc) has been established as cannabinergic drug and was successfully used in the treatment of chronic pain [8, 9], dystrophy [10, 11] and combat withdrawal symptoms [12].

In the following case we report the administration of Dronabinol® to a woman who was diagnosed with severe blepharospasm. Finally, repeated treatment with botulinum toxin did not show a long-lasting beneficial effect, probably due to the psychogenous origin of the blepharospasm. Thus, medication was changed to the cannabinergic drug Dronabinol®, in order to affect simultaneously cognitive signal processing, involuntary muscle movement and pain.

Case Report

A 56-year-old woman was presented in our center of pain therapy and diagnosed with severe blepharospasm. Symptoms persisted daytimes and increased during evening hours. The patient already had been admitted to the neurology department to receive a treatment with botulinum toxin. Relief of symptoms was reported subsequent to the first two injections and lasted about 5–8 weeks, although weakness of the facial nerve occurred. The last injection – about 4 months ago – evoked only little improvement for 3 weeks, for which the patient was transferred to the local pain department.

The medical history revealed no further obvious somatic or psychiatric disorders. Primary headache did not appear, holocephalic headache occurred only sometimes during blepharospasm attacks. No allergies were reported and no mimical impairment or muscular weakness could be observed. A sympathic participance was excluded by sympathic test blockade. Imaging tests revealed only a small asymptomatic meningeoma, which did not contribute to the blepharospasm symptoms because of localisation. The current medication was just vitamin C. The Body-Mass-Index was 25.2 kg/m.

The patient is married to a recently retired 64-year-old man. Further inquiries revealed that the patients' symptoms started shortly after the husband's retirement. Additionally, the patient stated that she had to take care of her elderly mother at the same time, which was regarded as emotional burden. Social contacts, daily work and leisure activities (shopping, watching TV etc.) were considerably impaired. Severity of symptoms was rated by the patient on a numerical rating scale with the endpoints 0 (no pain/symptoms) to 10 (maximal pain/symptoms imaginable) at the maximum of 10.

Since botulinum toxin therapy failed to evoke long-lasting improvement of the symptoms, and the blepharospasm may be originated in a disturbed dopaminergic signal transmission, a therapy regimen with delta-9-tetrahydrocannabinol (Dronabinol®) was started in order to augment the neuronal central inhibition pathway. At a daily dose of 10 mg Dronabinol® over two weeks no alleviation of the symptoms, but at least no severe side effect either, was observed. Thus, dosage was increased to a maximum of 30 mg per day, which lead to a mild but impaired vertigo. Therefore, daily doses were administered in the paradigm 10–5–15 mg and dizziness was reduced. After 5 weeks of medication a clinical stable state was achieved. The intensity and number of attacks decreased and the patient reported that she had experienced whole days without any attacks. The bodyweight index remained

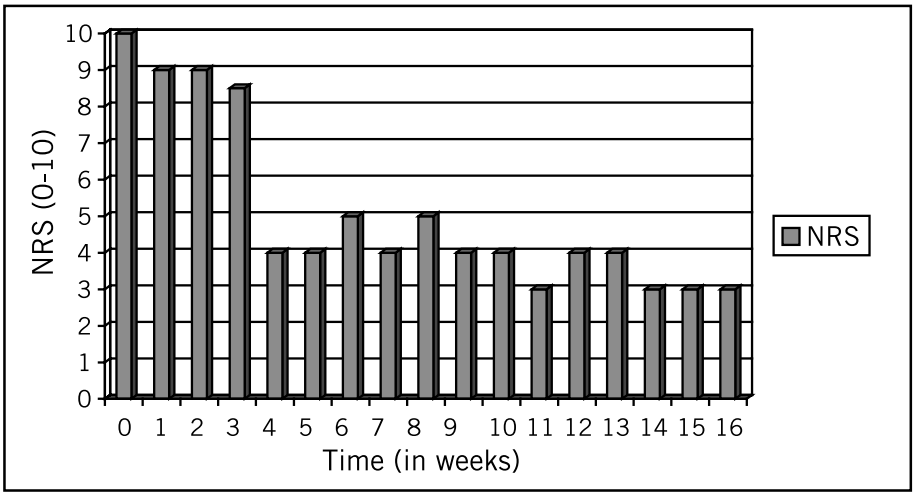

Fig. 1. Symptomscore. Numerical Rating Scale (NRS0-10), Intensity of the symptoms over 16 weeks starting with intake of medication at week 1.

stable throughout the Dronabinol® medication over a 16 week period.

Social contacts, reading and working in front of a screen improved and the mood of the patient cleared up. Compulsive crying had disappeared and dry eye symptoms decreased as well. Thus, application of an artificial lachrymal fluid was no longer required. On the numeric scale the intensity of symptoms declined from 10 to 8 after week 2 to 4 of medication, and further decreased to a level of 4 during week 5. From week 10 onwards, the patient rated her symptoms at a score-level of 3.

Discussion

Benign essential blepharospasm (BEB) is a movement disorder of uncertain origin. Despite reports of increased familiar incidence [1, 2], the development of BEB may be triggered by contributing factors such as gender, age, environmental conditions, medication etc. However, BEB is clinically characterized by involuntary convulsive muscle contractions of the M. orbicularis occuli, and therefore has been classified as a subliminal form of dystonia. The word dystonia is defined as an involuntary body movement that may be generalized or might affect particular limbs and body sites. The origin of dystonia can be genetic or idiopathic, although structural, metabolic and neurodegenerative alterations are abundant and occur frequently. Cortical hyperactivity, particularly of the visual cortex, thalamus, cerebellum and basal ganglia, has been demonstrated to be involved in dystonic movement disorders [13, 14]. An impaired central inhibition, probably due to a decreased Dopamine-(D2)-receptor activity [1, 15], was suggested to maintain dystonia. Thus, for a "causal" therapy of dystonia, deep brain stimulation of the internal segment of the globus pallidus [16], administration of anticholinergics and benzodiazepines [1, 3], and neurofunctional surgery [17, 18] have been considered for treatment. However, a "symptomatic" therapy by intramuscular injections of Botulinum toxin (Botox), a presynaptic neuromuscular blocking agent, seems to be first choice in the therapy of dystonia [19, 20]. In patients suffering blepharospasm, injections of Botox into the M. orbicularis occuli alleviates the symptoms, even up to years, but only as long as the injections are given [3, 19, 21]. However, weakening of the orbicularis occuli muscle due to Botox may trigger BEB, although this phenomenon apparently does not aggravate the conditions [1]. Regardless the putative efficacy of such therapy, other cardinal symptoms such as dry eye and exaggerated corneal pain are not affected significantly by Botox [1, 3]. Thus, an alternative approach to Botox for the therapy of BEB is needed, which ideally should address both the causal therapy by modulation of the central dopaminergic pathway and the symptomatical treatment by attenuation of muscle spasm and pain.

In human and rodent brain co-localisation of CB1- and Dopamine-(D2)-receptors has been identified on the same neurons [6, 7, 22]. Since both receptor sub-types are membrane bound G-protein coupled receptors, dopamine-associated signal transduction has been suggested to be influenced by selective Cannabinoid receptor agonists [12, 22, 23]. Moreover, CB1-receptor expression was analysed in the output nuclei of the basal ganglia, the cerebellum, hippocampus and hypothalamus (for an overview see [24]). These findings were linked to a cannabinergic influence of motor activity, learning, memory and appetite, probably caused by inhibition of a neurotransmitter release in cerebral cortex, hippocampus, amygdale and cerebellum [9, 24, 25]. Suggestions have been made that the endogenous cannabinoid anandamide also modulates the signal transduction of other cortical transmitter systems, i.e. [9, 26–28].

In several studies investigating movement disorders the therapeutic utility of cannabinoids was reported. In patients suffering multiple sclerosis an improvement of the symptoms was observed following cannabinoid treatment [9] and a therapeutic profit has been demonstrated in other movement disorders, for instance the Tourette syndrome [29, 30] or the levadopa-induced dyskinesia in Parkinson`s disease [25]. In the present study we have demonstrated – although only in one patient – that BEB-symptoms can be alleviated through adequate intake of the cannabinoid Dronabinol®. Social obstacles as a symptom of BEB were reduced and exaggerated pain was significantly alleviated to a well-tolerated level. Both effects in-

creased the patients' quality of life considerably. It should be noted that no acute side effects of the drug, for instance sedation, anxiety, short-term memory impairment and stimulation of appetite, was observed. This is in correspondence to the long term Delta-(9)-THC therapy of Tourette patients that demonstrated no impact of the cannabinoid agonist on the neuropsychological performance [31].

Provided that cannabinoids may have an influence on the dopaminergic system [7, 22] and probably interacts with acetylcholine [32, 33] and GABA [34], the amelioration of the patients' symptoms could be related to a central mode of action of Dronabinol®. Likewise, a central effect of the cannabinoid may have affected the perception of pain as well, as it was demonstrated for instance in the treatment of multiple sclerosis [35, 36]. However, despite the promising result of the present case report, further clinical investigations are required to thoroughly identify cannabinoids as novel therapeutic in the treatment of blepharospasm.

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