

A casuistic rationale for the treatment of spastic and myocloni in a childhood neurodegenerative disease: Neuronal ceroid lipofuscinosis of the type Jansky-Bielschowsky

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Goal

The casuistic of a child suffering from late infantile neuronal ceroid lipofuscinosis (NCL) of the type Jansky-Bielschowsky aims to provide a description of possible therapeutic options for the severe spastic and the debilitating myocloni that occur within the context of this disorder. Moreover, it also should include a discussion of potential indications for the application of delta 9-Tetrahydrocannabinol (THC) (Dronabinol, Marinol) in childhood.

NCL

The four major variants of NCL (types Santavuori, Jansky-Bielschowsky, Spielmeyer-Vogt, and Kufs) are characterized by excessive ceroid and lipofuscin lysosomal storage in both neurons and astroglia as well as in muscle cells, the thyroid gland, pancreas, skin, conjunctiva, and lymphocytes. Whereas all four varieties are inherited in an autosomal recessive manner, they can be differentiated with respect to the defective gene involved, the material stored at the cellular level, their light microscopic findings, clinic, and onset of illness.

The late infantile NCL is a lysosomal storage disease that can be traced to a defect in the formation of the lysosomal pepstatin-insensitive carboxypeptidase, which results in storage of the mitochondrial ATP-synthase subunit C, a component of the internal mitochondrion membrane [1]. Storage occurs in the form of wafer-thin layers and occasionally takes on a fingerprint-like configuration. Magnetic resonance imaging reveals a generalized brain atrophy that is especially marked in the cerebellum. In PET, a rapidly progressive degeneration of the brain tissue, accompanied by cortical and subcortical (thalamic) hypometabolism, can be detected [2]. Clinically, the patients present with epileptic seizures as well as myocloni of a non-epileptic genesis originating for the most part in the cortex [3], which are capable of culminating in clonic-tonic seizures [4], loss of visual acuity and speech, ataxia, and spastic. Death occurs in late childhood.

Casuistic

The boy was presented in my praxis for the first time at the age 3 years and 4 months following an initial seizure.

His parents are first cousins. The boy's father sustained an apoplectic insult with resultant epileptic seizures. Five elder siblings, three of whom were fathered by another man, are healthy, as is the boy's younger sister who is presently 2 years and 9 months of age. With the exception of delayed speech development – the patient could speak only a few words at the age of 2 and one-half years – the other developmental milestones were reached at normal points of time (with the reservation, that they were not ascertainable in detail), but, presumably, there were developmental standstills or regressive behavior during the third year of life. In the time period following the boy's initial visit, he regressed developmentally and experienced some more epileptic seizures. The five-year old's EEG registered a generalized, continuous deceleration to a spectrum of 1–4 /sec as well as multifocal and, rarely, also generalized spikes and a photoparoxysmal reaction during a stimulus between 1–8 /sec, which could not be suppressed by a dark glasses (Dr. Boenigk, Epilepsy center, Bethel). The boy also developed an optic atrophy attended by loss of vision. Magnetic resonance imaging displayed cortical as well as subcortical diminishment of brain volume. The muscle biopsy indicated a lysosomal storage process, thereby making possible the diagnosis NCL type Jansky-Bielschowsky (Childrens Hospital Park Schönfeld, Kassel, attending physician Dr. Tegtmeyer; Department of Neuropediatrics, University of Göttingen, Professor Hanefeld).

Without going into too much detail regarding the course of the illness, it can only be said that the boy developed a severe tetraspastic symptomatic that was very trying for his caregivers, together with recurrent violent myocloni that lasted for hours and increased during sleep. These myocloni were not induced through fright or by startling the patient – exception perhaps was a cold stethoscope – they were on some occasions predominantly proximally accentuated, on others predominantly distally accentuated, and they were discharged both one-sided as well as bilaterally, sometimes presenting as myoclonic jerks (“He's working,” his mother used to say). Epileptic seizures, on the other hand, occurred seldom when treated by antiepileptic medication – oxcarbazepine proved as helpful – and under no circumstances did they constitute a therapeutic problem. The bedridden, blind, and, in the meantime, mute child receives nourishment via a percutaneous endoscopic gastrostoma (PEG), and his mother nurses him at home in a loving, tender, and genuinely devoted manner.

Spastic and myocloni are, accordingly, the intended treatment targets.

Since the oral administration of baclofen in combination with tetrazepam failed to produce any satisfactory relaxation of the spastic symptomatic, I attempted to replace both of these substances through delta

9-THC administered via PEG, in the hopes of attaining improved vigilance in addition to the drug's antispastic and analgetic effects. The regimen began with a dosage of 0.07 mg/kg body weight/d and 2 mg/m² body surface/d respectively (dispensed were Dronabinol/Marinol drops 2.5% in oil), administered in the morning and again in the evening. At the same time, the pethidine regimen that was previously in effect was terminated. No noticeable withdrawal symptoms occurred, and the child's condition improved considerably in a matter of only a few days. Whereas prior to this regimen diapering had been a tormenting procedure for both mother and child alike on account of the resistance of the adductor muscles, the mother now experienced a considerable degree of relief in this respect. The boy became generally more relaxed and alert, he laughed when spoken to, and he turned his head in the direction of his mother more purposefully. Despite emotional fluctuations, he was happier: “Sometimes he nearly laughed and cried at one and the same time.” These changes, however, did not fail to leave their mark on the interaction between mother and son: Sometimes, the boy's mother was sadder than previously owing to her awareness that the loss of her increasingly alert son was inevitable.

The myocloni were treated using 335 mg/kg body weight piracetam 3 times daily and 7 mg/kg body weight zonisamide twice daily, both administered via PEG. To determine whether the piracetam regimen is truly effective, I tried discontinuing the medication but had to resume giving it only two days later owing to the rapid increase on the part of the myocloni, with the end-result that the myocloni clearly decreased after the second day of renewed piracetam therapy. Zonisamide likewise displayed a convincing antimyoclonic effect as illustrated by the following course of events: When the medication had to be discontinued for a short period of time because of unavailability caused by import problems, violent myocloni set in after two full days. Conversely, following its reinstatement, the myocloni receded after less than three days time.

By way of additional neurotropic medications, the boy receives 1 mg/kg body weight/d clobazam 3 times daily and 0.2 mg/kg body weight melatonin in the evening. Primidone is being discontinued at this point with the intention of reducing the interactions between the various medications. The boy is not being given valproic acid, which previously even in the upper limits of the dosage range (although not combined with piracetam) had failed surprisingly to be effective in the treatment of myocloni, nor is clonazepam being administered because the patient suffers from very heavy mucous congestion. As was the case with valproic acid, DOPA had been administered only temporarily and with paradoxical results: Initially, the substance appeared to reduce the myocloni. On the other hand, its later discontinuation failed to produce any signs of increased myocloni.

Discussion

The cannabinoid derivate that is being used in this case, delta 9-THC, is a stereoisomer of the most important psychotropic ingredient of cannabis sativa L. ssp. indica. Following oral administration, resorption takes place slowly and somewhat irregularly in the gastrointestinal tract. The fact that resorption does not occur via the oral mucosa and that disintegration in the stomach appears to be possible should be emphasized in the event of administration via PEG. The drug underlies a first pass effect. Cannabinoids are lipophile and predisposed to accumulate in fatty tissues [5].

The drugs' effects are mediated by cannabinoid receptors. In the central nervous system (CNS), the CB1-receptor is pivotal: it occurs on cortical neurons and on those of the limbic system, hypothalamus, cerebellum, and basal ganglia. Delta 9-THC, however, also modulates the activity of μ - and δ -opioid receptors [6]. This fact might explain the lack of complications experienced by the child following termination of the pethidine therapy. Cannabinoids manipulate a variety of transmitter systems: acetylcholine, serotonin, GABA [7], glutamate [7], dopamine [7, 8].

The fact that endogenous cannabinoids in the basal ganglia increase GABAergic transmission and inhibit the release of glutamate [7] could be connected with the effects of cannabinoids on motor functions. Cannabinoids not only reduce spastic but also facilitate myocloni [9], an effect that did not manifest itself clearly in the case of the patient described here.

An endogenous cannabinoid system is not only an important component within motor control systems; it also is of significance for other systems, such as involving pain, appetite, and emesis.

The psychotropic effects of the cannabinoids are closely connected with influences exerted on dopaminergic projection fibers that belong to the medial forebrain bundle (i.e., rewards system!) [6]. The influence of cannabis on dopamine receptors is also clearly documented in a SPECT-study performed on schizophrenic patients [8]. In the case of one boy with a neurodegenerative disorder of unknown genesis, whom I likewise am treating with delta 9-THC (once again, applying a dosage of 0.07 mg/kg body weight/d), a reduction in autistic behavior could be observed: "He doesn't keep on trying to bite himself, like before, when someone grabs a hold of him."

Alongside of the influence on transmitter systems, changes in cerebral perfusion also presumably play a role in the effects of cannabis: thus, THC increases perfusion in the limbic system (psychotropic effects) and reduces the blood flow in the temporal neocortex (cognitive deficits) [10].

Findings regarding the effects of cannabis on epileptic seizures in patients with a known history of epilepsy are contradictory [11, 12, 13]. One observation of mine may be worth mentioning: A 12-year old girl, who perinatally had suffered from a severe case of anemia that resulted from a feto-maternal transfusion and who presented with a drastic residual spastic as well as tonic

seizures accompanied by a horizontal nystagmus, is likewise being treated with 0.07 mg/kg body weight/d delta 9-THC. Her mother reports that since the initiation of this therapeutic regimen her daughter not only is "more relaxed, gentler, completely happy and receptive in every respect," but, in addition, that she also is obviously experiencing far fewer seizures as previously during monotherapy with valproic acid. Arabic writings from the Middle Ages make mention of cannabis as a remedy for epilepsy [cited in 13]. In experiments with animals, delta 9-THC has an anticonvulsive effect in some partial epilepsy forms and in generalized convulsive forms of epilepsy, a pro-convulsive effect in other partial epilepsy forms and in absences [10]. In the EEG, cannabis (provided the patient is not intoxicated), causes a desynchronization [14]; in one male patient with a "centrencephalic epilepsy," cannabidiol caused an increase in spike wave activity [15].

Delta 9-THC possesses a neuroprotective effect: In rats injected intracerebrally with ouabain, it reduced cytotoxic edema and neuronal damage [16]. Both delta 9-THC and cannabidiol may be capable of reducing the neurotoxicity that is mediated in the rat brain by the NMDA-, AMPA-, and kainate receptors. Cannabinoids function as potent antioxidants in cultured neurons [17].

Immune-modulating effects are mediated via CB-2 receptors that are located on immune-competent cells. THC may be capable of increasing the production or release of pro-inflammatory cytokines while at the same time lessening antibody proliferation [18]. Since epileptic seizures influence cytokine secretion, and the latter, in turn, exerts influence on epileptic seizures [19, 20], the pro-convulsive and anti-convulsive effects on the part of THC possibly should be considered under these aspects as well.

Experience with regard to appropriate dosages of delta 9-THC in children is needed. At present, recommendations as to how to dose delta 9-THC in children only exist for treatment of cytostatica-induced emesis. These amounts are clearly in excess of the ones I chose. Nonetheless, even in adult patients the recommended antispastic dosages are much lower than the antiemetic ones.

Numerous medications are effective in the therapy of myocloni within the context of progressive myoclonic epilepsies [4]. The available selection, however, calls for an unambiguous pathophysiological and syndrome-related classification. By way of example, piracetam is known to be effective against cortically but not subcortically-induced myoclonus [21]; for instance, lamotrigine is helpful in the management of children with NCL but leads to worse seizures in children who suffer from severe myoclonic epilepsy of childhood (so called Doose-syndrom) [4]. On the other hand, it may not be possible to predict the effectiveness (or lack thereof) of a medication in an individual patient as can be shown here based upon the fact that, in the casuistic of the above-mentioned boy, valproic acid turned out to be ineffective – a condition, that should not have been expected according with literature.

Highly dosed (in excess of 300 mg/kg body weight/d) piracetam proved effective in the treatment of the child's myocloni. The mechanism of action is unclear and cannot be explained via the structural similarity of the substance with GABA. Among the mechanisms under discussion are influences on cholinergic transmission and an increased dopamine release [22] as well as a reduction of extracellular glutamate concentrations [23]. The observation of the effectiveness against cortical myocloni and ineffectiveness against subcortical myocloni could possibly be explained by the fact that the highest concentrations of piracetam are found at cortical sites and the lowest in the brain stem [21]. Here, the result gleaned from experimental omission as described in the casuistic as well as from reexposition is in accord with the literature [24]. It still needs to be discussed whether valproic acid would not have been capable of displaying a superior degree of therapeutic activity were it to have been administered in combination with piracetam. [25].

Similarly, zonisamide administered in a dosage of 7 mg/kg body weight/d also proved effective in the course of a strategy of withdrawal and reexposition. In the literature, dosages between 4 mg and 8 mg (up to 20 mg)/kg body weight/d [26] were recommended. Although the mechanism of action has not been elucidated definitively, a blockade of the sodium- and T-calcium canals plays a role. Disadvantages of zonisamide therapy are the possible loss of activity after many years of exposure [27] and the possibility of triggering an outbreak of malignant hyperthermia [28].

The mechanism of action of drugs effective against myocloni is unknown. At the very least, it cannot be interpreted as exclusively GABAergic, because the observations recorded in the literature suggest that vigabatrin is not helpful and because of the fact, that the effectiveness demonstrated by clonazepam is not encountered in other benzodiazepines [29]. It is possible that effects on voltage-sensitive sodium canals merit special consideration [27].

Closing Remark

I hope it has become clear that, in cases involving severe childhood neurodegenerative disorders, a nihilistic attitude with respect to the available therapeutic options for reducing tormenting symptoms is contraindicated and, furthermore, that delta 9-THC is a valuable medication in the field of pediatrics, too.

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