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REVIEW ARTICLE

Aminopyridines and Acetyl-DL-leucine: New Therapies in Cerebellar Disorders

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Abstract: Cerebellar ataxia is a frequent and often disabling syndrome severely impairing motor functioning and quality of life. Patients suffer from reduced mobility, and restricted autonomy, experiencing an even lower quality of life than, *e.g*., stroke survivors. Aminopyridines have been demonstrated viable for the symptomatic treatment of certain forms of cerebellar ataxia. This article will give an outline of the present pharmacotherapy of different cerebellar disorders. As a current key-therapy for the treatment of downbeat nystagmus 4-aminopyridine (4-AP) is suggested for the treatment of downbeat nystagmus (5–10 mg Twice a day [TID]), a frequent type of persisting nystagmus, due to a compromise of the vestibulo-cerebellum. Studies with animals have demonstrated, that a nonselective blockage of voltage-gated potassium channels (mainly Kv1.5) increases Purkinje-cell (PC) excitability. In episodic ataxia type 2 (EA2), which is frequently caused by mutations of the PQ-calcium channel, the efficacy of 4-AP (5–10 mg TID) has been shown in a randomized controlled trial (RCT). 4-AP was well tolerated in the recommended dosages. 4-AP was also effective in elevating symptoms in cerebellar gait ataxia of different etiologies (2 case series).

A new treatment option for cerebellar disease is the amino-acid acetyl-DL-leucine, which has significantly improved cerebellar symptoms in three case series. There are on-going randomized controlled trials for cerebellar ataxia (acetyl-DL-leucine *vs* placebo; ALCAT), cerebellar gait disorders (SR-form of 4-AP vs placebo; FACEG) and EA2 (sustained-release/SR-form of 4-AP *vs* acetazolamide *vs* placebo; EAT2TREAT), which will provide new insights into the pharmacological treatment of cerebellar disorders.

Keywords: Cerebellar ataxia, central vestibular disorders, aminopyridines, 4-aminopyridine, episodic ataxia type 2, downbeat nystagmus, acetyl-DL-leucine.

1. INTRODUCTION

Cerebellar ataxia is an often disabling syndrome that impairs motor performance and quality of life [1]. A Japanese survey found a prevalence of all types of cerebellar ataxia of 18.5:100,000 [2]. In southeast Norway, the prevalence of hereditary ataxias was 6.5:100,000 [3]. A population-based study performed in south east Wales found a prevalence of late-onset, non-hereditary ataxia of 8.4:100,000 [4]. The studies suggest that the overall prevalence of cerebellar ataxia in Europe is like that in Japan with about 20:100,000. Patients suffer from reduced mobility, restricted autonomy and social participation. They experience lower quality of life than, *e.g*., stroke survivors, and costs for the health system and society are higher [5]. This reflects the high socioeconomic burden of the disease [6].

The leading clinical symptoms of cerebellar ataxia are disturbances of stance/gait (> 85%) with repetitive falls, ataxia of the limbs with severe functional impairment of hand and arm movements, dysarthrophonia with impaired oral communication abilities and dysfunction of the ocular system with impaired vision [1]. In a European multi-center study patient-reported health status was severely compromised (mean EQ-5D visual analogue scale 61.5). In particular, issues were reported for self-care (38.2%), depression/anxiety (46.4%), pain/discomfort (49.4%), usual activities (68%), and mobility (86.9%). A multivariate analysis revealed 3 independent predictors of subjective health status: ataxia severity, extent of non-cerebellar involvement, and the presence of depressive syndrome [7]. Further, most sorts of cerebellar ataxia are progressive and along these lines turn out to be all the more debilitating over the span of the disease, seriously impairing functioning and the quality of life

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[1]. In addition to functional impairment, cerebellar ataxia also affects cognitive and psychosocial abilities and limits the ability to perform tasks of daily life. It is thus a severely disabling condition with a major impact on quality of life, progressively restricting autonomy and social participation. With progressing disease QoL decreases and utilization of health resources increases [5]. Symptom control should lead to a decreased burden of disease for patients and caregivers. An improvement in cerebellar ataxia also results in less impaired patients who can better participate in social and working environments for a longer period of time.

According to a recent CONSENSUS paper by some of the leading experts on cerebellar ataxia, no drug has yet been demonstrated compelling for the symptomatic or even causative treatment of degenerative cerebellar ataxia [8]. Effects of varenicline and riluzole have been reported. However, according to the CONSENSUS paper, the experience of many ataxia clinics is less promising and the findings need to be confirmed in further placebo-controlled trials [8]. Even more importantly, the trial on varenicline had an overall dropout rate of 40%, which is most likely due to the considerable side-effects of varenicline. Ultimately, the preplanned cross-over design was therefore not performed. There is unanimous assent that 4-aminopyridine is effective in episodic ataxia type 2 and in downbeat nystagmus syndrome [9-12] Therefore, so far, the only treatment recommendation has been physiotherapy [8].

This overview gives an update on the actual treatment options for cerebellar diseases and the most widely recognized types of central nystagmus, which are often associated with cerebellar degeneration. The ongoing trials are also described and perspectives for future pharmacological interventions are discussed.

2. AMINOPYRIDINES (APs) AND THEIR MODE OF ACTION IN CEREBELLAR DISORDERS

In recent years, advance has been made in the pharmacological treatment of cerebellar disorders, for example episodic ataxia type 2 (EA2) and in adition downbeat nystagmus (DBN), specifically because of the utilization of aminopyridines (AP) [10-13]. This agent is a nonselective blockers of the Kv family, mainly the Kv1.5 voltage-activated potassium channels, thereby prolonging the duration of action potentials in axons because of delayed repolarization [14]. *In vitro* studies showed that 4-aminopyridine (4-AP) increases the resting discharge rate and excitability of cerebellar Purkinje cells (PCs) of the guinea pig cerebellum [15], and regulates the PC firing in brain slices of the rat [16, 17], Due to an increased activity of PC [13] the GABAergic inhibitory influence on the deep cerebellar nuclei mediated by the vestibulo-cerebellum is restored. This is assumed to be the mechanism behind the therapeutic influence of AP in cerebellar disorders. This increased inhibitory influence has been confirmed by findings in patients with ataxia telangiectasia, where the ingestion of 10 mg 4-AP resulted in a shortened time constant of the angular vestibulo-ocular reflex (VOR) [18]. Clinically, both 4-AP and 3,4-diaminopyridine (3,4-DiAP) are currently used but for different indications: 4-AP in central nervous disorders because it better penetrates the blood-brain barrier [19] and 3,4-DAP in Lambert-Eaton myasthenic syndrome (LEMS). In an animal model of EA2 (tottering mouse), 4-AP restored the decreased accuracy of pacemaking in PCs by prolonging the action potential and expanding the action potential after hyperpolarization [20]. Furthermore, 4-AP and 3,4-DiAP, reduced the frequency of restraint- and caffeine-induced attacks in the tottering mouse, by increasing the threshold for the attacks [21].

3. TREATMENT OF DIFFERENT CEREBELLAR DISORDERS WITH APs

3.1. Downbeat Nystagmus

Cerebellar degeneration, when affecting the vestibulocerebellum, leads to DBN, which is the most frequent form of acquired fixation nystagmus [22], mostly due to an impaired function of the cerebellar floccular lobe due to neurodegeneration [22, 23]. Patients with DBN suffer from postural instability, cerebellar gait disorder, and blurred vision due to oscillopsia [24, 25]. Additional ocular motor signs, for example, insufficient smooth pursuit eye movements and gaze-evoked nystagmus are frequently connected with DBN and demonstrate a cerebellar dysfunction [24, 26]. In the past, diverse GABAergic substances have been used to treat downbeat nystagmus, however with just moderate improvement (18). In 2003, the first randomized controlled trial (RCT) showed a significant effect of a single dosage of 20 mg 3,4-DiAP on effectively suppressing DBN most likely by means of potassium channels of Purkinje cells [27]. 4-aminopyridine (4-AP) additionally alleviates the symptoms of DBN, especially in patients with cerebellar atrophy [28]. It even restored neural integrator function, explaining its effects on gaze-evoked nystagmus [28]. In a double-blind prospective crossover study, equivalent doses of 4-AP were better than 3,4-DAP decreasing the slow-phase velocity (SPV) of DBN [29], since 4-AP is more lipid-soluble and crosses the blood-brain-barrier more easily. Both aminopyridines were well tolerated and showed, aside from transient paraesthesia, nausea, or headache, no major side effects. A recent randomized double-blind crossover trial proved the effect of 4-AP in DBN (5 mg QID) in reducing not only the mean SPV of DBN by about 50%, but also improving the postural sway particularly in older patients [9]. However, there were no differences between 4-AP and placebo with respect to patient satisfaction and side effects; this was discussed as probably being caused by the short half-life of 4-AP [9]. This absence of improvement may be overcome by the sustained-release form of 4-AP (4-AP-SR; Fampyra, Biogen Idec, Mississauga, Canada), which has shown its efficacy in observational case series in a dosage of 10-20 mg/d [30]. Therefore, the use of 4-AP (5 mg 2-4 times daily) or 4-AP-SR (10-20 mg/d) is generally recommended for the treatment of DBN [8, 31]. Patients should have an electrocardiogram both at baseline and around 45 min subsequent to taking 4-AP to exclude QT interval prolongation.

4. EPISODIC ATAXIA TYPE 2

EA2 is the most frequent form of episodic ataxia with recurrent attacks of vertigo and ataxia, which belongs to the growing number of ion channel disorders. It is caused by mutations of the CACNA1A gene encoding the α-subunit of

a P/Q-type calcium channel in about 60% of patients [32, 33]. Symptoms are recurrent vertigo and ataxic manifestations enduring up to a few hours, which are frequently elicited by alcohol, physical activity, or stress [33]. More than 90% of patients present with oculomotor disturbances for example gaze-holding deficits, smooth pursuit, or DBN even outside of attacks [34], which may permit the clinican to separate EA2 from vestibular migraine with minor ocular motor deficits [35, 36]. About two thirds of EA2 patients respond to the carboanhydrate inhibitor acetazolamide (250–1000 mg/d) [37], which has been the treatment of choice in the past. However, there are so far no randomized, placebo-controlled trials on the efficacy of acetazolamide. Furthermore, its adverse effects (*e.g*., kidney stones, nephrocalcinosis, paresthesia, muscle stiffening with easy fatigability, hyperhydrosis) often limit its therapeutic use in clinical practice.

In 2004, a case series on three patients with EA2 showed a reduction of the number of attacks [38]. These findings were confirmed in an RCT in 10 subjects with EA2 in 2011. During the study, the median monthly attack frequency under placebo was 6.5 and decreased to 1.65 under medication with 4-AP [39]. Furthermore, the median monthly attack duration was reduced and the quality of life as measured by the Vestibular Disorders Activities of Daily Living Scale improved. These results are in line with animal studies in EA2 mutant mice, which showed that 4-AP raised the threshold for the triggering of the episodic attacks [20]. Moreover, the precision of pacemaking in PCs was restored by prolonging and increasing the action potential after hyperpolarization by targeting the K(v)1 family of K(+) channels [20]. Recently, a case series showed the efficacy of the sustained-release form of 4-AP in EA2 [40]. Nowadays the recommended dosage of 4-AP is 5 to 10 mg TID. There are currently two ongoing RCT on 4-AP in EA2, a European study examining 4-APS-SR vs acetazolamide *vs* placebo (University of Munich, EAT2TREAT) and another in the US comparing 4-APS-SR vs placebo (University of California, NCT01543750).

5. CEREBELLAR DISORDERS

Cerebellar syndromes due to hereditary or neurodegenerative diseases frequently lead to postural instability associated with cerebellar oculomotor deficits such as impaired smooth pursuit, DBN and gaze-evoked nystagmus [24]. These oculomotor deficits are leading symptoms that might help to reveal mild forms of cerebellar ataxia in the absence of further deficits such as speech disturbances or ataxia of the limbs. However, the treatment of cerebellar motor deficits remains difficult in cerebellar disorders. Large RCTs on cerebellar symptoms are lacking and clinical studies are often performed in genetically heterogeneous or genetically non-defined degenerative cerebellar syndromes. So far no pharmacological intervention has been proven effective [8].

Aminopyridines also improved the motor behavior in a mouse model of spinocerebellar ataxia type 1 [41]. In SCA1 a reduced firing rate of PCs is associated with a reduction in the efficiency of the main glutamatergic synapse onto Purkinje cells and with increased A-type potassium current. In young SCA1 mice, APs normalized the firing rate of PCs and the motor behavior of the animals, while in chronically treated old SCA1 mice, 3,4-DiAP improved the firing rate of PCs, the motor behavior of the animals, and partially protected against cell atrophy [42]. Remarkably, animals treated early demonstrated better motor function in the longer term, which may be mediated by neuroprotective beneficial effects due to increased production of growth factors such as BDNF secondary to the enhanced electrical activity of PCs [42].

Based on the effects of aminopyridines in cerebellar oculomotor dysfunction, it was hypothesized that they might have an effect on cerebellar locomotion. In a case description of 2 patients, 4-AP improved gait variability (the coefficient of variation of stride time) in cerebellar ataxia due to CACNA 1A mutation [43]. In a retrospective case series with 31 patients with cerebellar gait disorders due to various etiologies (cerebellar stroke, DBN, multisystem degeneration with cerebellar ataxia, sporadic adult-onset ataxia, CACNA1A mutations), 25 patients showed an improvement of gait performance from 4-AP [44]. The treatment with 5 mg 4-AP decreased the coefficient of variation of stride time and enhanced the preferred walking speed, independent of the severity of ataxia. In a recent case study, the SR-form of 4-AP showed modest short-term improvements in a short-term trial with 16 patients with cerebellar ataxia (SAOA, SCA1/3/6, POLG mutation) [45]. These findings are further evaluated in an ongoing randomized, placebo-controlled monocentric study with Fampyra (FACEG) to further evaluate the effect of 4-AP-SR on walking performance and gait stability in patients with different forms of ataxia as well in a placebo-controlled trial at the University of Florida (NCT01811706).

6. NEW THERAPIES IN CEREBELLAR DISORDERS

6.1. Effects of Acetyl-DL-leucine

In a case series on 13 patients with different types of cerebellar ataxia it was shown that the modified amino-acid acetyl-DL-leucine (AL) (5 g per day for one week) significantly improved the symptoms, measured by the Scale for the Assessment and Rating of Ataxia (SARA), the Spinocerebellar Ataxia Functional Index (SCAFI) and EuroQol-5D-5L; the agent was very well tolerated [46]. Mean total SARA diminished ($p = 0.002$) from a baseline of 16.1 ± 7.1 to 12.8 ± 6.8 (mean ± SD) on medication. There were likewise significant improvements in sub-scores for speech, nose-finger-test, finger-chase, rapid-alternating-movements, heel-to-shin and gait. Moreover, patients demonstrated improved performance in the SCAFI consisting of the 8m- walking-time, 9-Hole-Peg-Test of the dominant hand and the PATA rate. Quality of life increased during treatment ($p = 0.003$). No side effects were reported. Taking everything into account, acetyl-DL-leucine significantly improved ataxic symptoms without side effects and along these lines demonstrated a good risk-benefit profile. Videos documenting the effects can be found on the webpage of the German Neurological Society (www.dgn.org). The daily dosage of 5 g per day used in this study was in the upper range of the recommended dosages and, as expected from the safety-profile of acetyl-DL-leucine, well tolerated.

In another case series on twelve patients with Niemann-Pick type C, AL (3 g/d for 1 week and afterward with 5 g/d for 3 weeks) significantly improved ataxic symptoms without relevant side effects [47]. The SARA score changed from the baseline (median [±SD, interquartile range]) of 10.8 (11.2, 8-24.6) to 7.0 (10.7, 5.6-19.6) on medication (difference: 3.8 points). The SCAFI subscore 9-Hole Peg Test, VAS score, and mDRS score also improved on medication. No side effects with the exception of transient dizziness in one patient were reported, thus demonstrating a reasonable risk-benefit profile.

In the third case series the effect of a treatment with acetyl-DL-leucine on the walking stability of patients with cerebellar ataxia (SAOA/n=10, MSA-C/n=2, ADA/n=2, CACNA-1A mutation/n=1, SCA 2/n=2, SCA 1/n=1) was investigated [48]. Acetyl-DL-leucine (500 mg; 4-3-3) significantly improved the coefficient of variation of stride time in 14 out of 18 patients. In addition, subjective ambulatory scores (FES-I and ABC) and the SARA scores also improved under treatment.

With everything taken into account these observational examinations showed some evidence for a potential efficacy of acetyl-LD-leucine in ataxia. One must, however, carefully interpret these studies since they are not controlled and a placebo-effect has to be taken into account. What really counts in the end are randomized placebo-controlled trials.

Although it has been used for more than 50 years, the therapeutic mode of action of acetyl-DL-leucine has so far not been very well examined. It might act because of its immediate impact on neurons as was shown in the vestibular nuclei. Due to the phylogenetical and electrophysiological similarities and close interactions amongst vestibular and deep cerebellar neurons [49], it has been hypothesized that there may likewise be a positive effect on ataxic symptoms in cerebellar disorders.

In one-sided labyrinthectomy (UL) of guinea pigs, acetyl-DL-leucine restores the membrane potential of hyperpolarized/depolarized vestibular neurons [50]. This mechanism is most likely mediated by its immediate interactions with membrane phospholipids such as phosphatidylinositol 4,5-bisphosphate, which influences ion channel activity [51]. In this way, acetyl-DL-leucine can stabilize the membrane potential. The contribution from cerebellar Purkinje cells and mossy/climbing fiber collaterals controls the action potential of the vestibular and the cerebellar nuclei [52], which thus project to the brainstem, thalamus and spinal cord [49]. In this manner, acetyl-DL-leucine may act through afferent and efferent projections on upstream and downstream structures, subsequently influencing movement control.

In another animal study, the effect of N-acetyl-DL-leucine (Tanganil®), N-acetyl-D-leucine as well as N-acetyl-L-leucine on central vestibular compensation following one-sided UL was explored utilizing behavioral testing and serial [^{18}F]-Fluoro-desoxyglucose ([^{18}F]-FDG)-μPET [53]. A significant reduction of postural imbalance scores was identified on day 7 post UL in the N-acetyl-L-leucine ($p < 0.01$) and N-acetyl-DL-leucine ($p < 0.03$) groups compared to the control group, but not in the N-acetyl-D-leucine group. Measurements of the regional cerebral metabolic rate for glucose (rCGMglc) by means of μPET revealed that N-acetyl-L-leucine but not N-acetyl-D-leucine caused a significant increase of rCGMglc in the vestibulocerebellum and a decrease in the posterolateral thalamus and subthalamic region on days 3 and 7. As major findings of this study N-acetyl-DL-leucine accelerated the postural compensation after unilateral vestibular damage, while N-acetyl-L-leucine is the pharmacologically active enantiomer that induces this effect. The potential mechanism of N-acetyl-L-leucine action for enhancing vestibular compensation consists of an activation of the vestibulocerebellum and a deactivation of the posterolateral thalamus. Based on these results, further studies are currently being performed to reveal the putative mechanisms of N-acetyl-DL-leucine modulating the glutamate neurotransmission in the cerebellum *via* the branched-chain amino acid transferases [51, 54, 55], as the activation of metabotropic glutamate receptors (mGluR) is required for cerebellar plasticity [56, 57].

Based on these observational studies, an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled, crossover phase III trial (ALCAT) will be carried out [58]. The primary objective is to examine the efficacy and tolerability of a symptomatic therapy with AL (up to 5 g per day) compared to placebo on motor function measured by absolute change in the SARA total score in patients with CA. The results will indicate whether symptomatic treatment with the modified amino-acid acetyl-DL-leucine is a worthy candidate for a new drug therapy to relieve ataxia symptoms.

CONCLUSION

There are new treatment options for cerebellar disease available. Aminopyridines have been demonstrated to be effective for the symptomatic treatment of certain forms of cerebellar disorders. As a current key-therapy for downbeat nystagmus 4-AP is suggested. In episodic ataxia type 2 the efficacy of 4-AP has been shown in a RCT. Further trials in patients with cerebellar gait disorder and EA2 with the sustained-release form of 4-AP have been completed and the results are awaited soon. A new treatment option for cerebellar disorders is the amino-acid acetyl-DL-leucine, which has significantly improved cerebellar symptoms in three case series. A multinational RCT is currently investigating the effect of the amino-acid acetyl-DL-leucine on cerebellar symptoms (ALCAT,). New therapeutic strategies are needed, which enhance symptom control in cerebellar ataxia and should decrease the burden of disease for patients and caregivers. An improvement in symptoms will also result in less impaired patients who can better participate in social and working environments for a longer period of time.

DISCLOSURES

M. Strupp serves on scientific advisory boards for Abbott, Actelion, Sensorion, Heel, IntraBio, and Pierre-Fabre; has received speaker honoraria from Abbott, GlaxoSmith-Kline, Merck Serono, HENNIG ARZNEIMITTEL GmbH & Co. KG, Pierre Fabre Laboratories, UCB, TEVA, Heel, Biogen Idec, MSD, and Eisai Inc.; serves as Joint-Chief Editor of the Journal of Neurology, Editor-in-Chief of Frontiers in

Neuro-otology, and Section Editor of F1000; and receives publishing royalties for Leitsymptom Schwindel (Springer, 2012) and Vertigo and Dizziness: Common Complaints (Springer, 2013). R. Kalla has received speaker honoraria from Actelion Pharmaceuticals GmbH.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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