HHS Public Access

Author manuscript

Neurol Clin. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

Neurol Clin. 2020 May ; 38(2): 449–467. doi:10.1016/j.ncl.2020.01.008.

AN OVERVIEW OF THE CURRENT STATE AND THE FUTURE OF ATAXIA TREATMENTS

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Abstract

Cerebellar ataxia can be caused by a variety of disorders, including degenerative processes, auto-immune and paraneoplastic illness as well as by gene mutations inherited in autosomal dominant, autosomal recessive or X-linked fashions. As we broaden our knowledge of the causes of cerebellar ataxia, we have also vastly increased our ability to treat cerebellar diseases, both symptomatically and targeting specific disease types. In this review, we highlight the treatments for cerebellar ataxia in a systematic way, to provide guidance for clinicians to treat patients with cerebellar ataxia. In addition, we review therapies currently under development for ataxia, which is one of the most exciting fields in neurology. Because strong genetic components underlie many types of ataxia, identifying the causes and developing individualized treatment for each ataxia patient is the key for patient care and research. Therefore, ataxia can also be considered a prototypical model for personalized medicine development. The advancement of neuroscience and our ever-increasing understanding of the cerebellum has led to many emerging therapies for ataxia, bringing with it the hope that soon we will have even more ways to improve the quality of life and possibly modify the disease trajectory of patients living with cerebellar ataxia.

Keywords

Cerebellum; Ataxia; Multiple system atrophy; Spinocerebellar ataxia; Friedreich Ataxia; Ataxia Treatment

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Disclosure Statement:

The authors have no relationship with a commercial company that has a direct financial interest in the subject matter or materials discussed in this article or with a company making a competing product.

1. Introduction

The cerebellum is responsible for a multitude of motor functions through the coordination of movements by prediction and is modulated by sensory feedback. Cerebellar ataxia refers to the dysfunction of the cerebellum that leads to problems with gait and balance, eye movements, speech, and hand dexterity[1]. The cerebellum is comprised of two hemispheres separated by the vermis. The 10 lobules of the cerebellum are grouped in three lobes; lobules I to V make up the anterior lobe of the cerebellum, lobules VI-IX make up the posterior lobe and lobule X is the flocculonodular lobe. From functional imaging studies of the cerebellum, the anterior lobe is thought to be important for motor control while the posterior lobe is more involved in cognitive processing[2]. Thus, patients with cerebellar ataxia may have a variety of motor and non-motor symptoms impacting their daily activities.

The prevalence of ataxia varies depending on ethnic background and geographic region, as different populations have founder effects for certain types of hereditary ataxias. Most studies have focused on the prevalence of hereditary ataxias. However, some estimates suggest that the prevalence of ataxia ranges from 2.7 to 38.35 per 100,000[3] A study looking at the global distribution of hereditary ataxias found that the most common autosomal dominant (AD) cerebellar ataxia is spinocerebellar ataxia typa 3 (SCA3), and the most common autosomal recessive (AR) ataxia is Friedreich ataxia[4].

Cerebellar dysfunction can be caused by nutritional deficiencies, immune-mediated cerebellar degeneration, gene defects inherited in AD, AR or X-linked fashion, as well as neurodegenerative conditions. In the work-up of ataxia, it is important to understand the age of onset and time course of ataxia, family history, and associated medical conditions and signs and symptoms. There are several excellent papers describing the work-up of ataxia[5–7], and the focus of this paper is not to re-summarize an ataxia work-up but instead to highlight current treatments for ataxia as well as those looming on the horizon. Figure 1 summarizes current and potential treatments for ataxia.

In order to understand the development of therapy for ataxia, it is important to know how the severity of ataxia is measured. There are two rating scales commonly used to measure ataxia severity. The Scale for the Assessment and Rating of Ataxia (SARA) score is a 40-point scale taking into account gait, stance, and upper and lower extremity motor deficits[8]. It is relatively easy to use in a clinical setting as it is not particularly time consuming. The annual rate of SARA score increase has been found to be 2.11 in SCA1, 1.49 in patients with SCA2, 1.56 in SCA3 patients and 0.80 in SCA6 patients in a natural history study in Europe[9]. A US natural history study of SCA also showed comparable disease progression using SARA[10]. Another commonly used scale is the International Cooperative Ataxia Rating Scale (ICARS), which is a 100-point measure of cerebellar dysfunction taking into account eye movement abnormalities, upper and lower extremity coordination deficits, speech, stance and gait[11]. A study of 18 patients with static and progressive cerebellar lesions found that the ICARS score can differentiate between the two on certain measures and can detect yearly changes in ataxia in the patients with degenerative cerebellar diseases[12]. Although ICARS was developed earlier than the SARA score, the latter is now the more commonly used clinical measure for ataxia.

2a. Symptomatic Treatment of Ataxia

Many medications have been examined in an effort to find symptomatic treatment for ataxia, by modulating cerebellar function through changes in ion channel function and/or cerebellar physiology. However, most symptomatic treatments have not been tested for an extended period of time, and there is a lack of replicate studies. It is also unknown whether these medications can have additional disease-modifying effects. Nonetheless, the effects of these treatments may provide some symptomatic relief and improve quality of life. Table 1 summarizes the symptomatic treatments for cerebellar ataxias[13–19], a few of which we will highlight below. Supplementary table 1 lists medications that have been tested and were proven non-effective.

Riluzole has been shown to improve function in patients with ataxia as measured by SARA and ICARS scores. It mostly affects axial domains by improving speech and gait. Side effects of riluzole include mild liver enzyme increases and transient vertigo but it is generally well-tolerated. Although the initial study only observed the effects of riluzole over 8 weeks, a longer study over 12 months demonstrated continued benefits[20,21]. Riluzole is thought to modulate SK channels, which are enriched in Purkinje cells, thereby partially normalizing neuronal firing patterns.

Varenicline is a partial agonist of the alpha-4 beta-2 nicotinic acetylcholine receptor, and was studied in 20 SCA3 patients. A randomized, double-blind, placebo-controlled trial of varenicline demonstrated improved axial symptoms and rapid alternating movements measured by SARA scores. Although relatively well tolerated, varenicline was associated with depression and irritability[22].

Acetazolamide has been shown to reduce the severity of ataxia in SCA6 patients, who have repeat expansions in the *CACNA1A* gene[23]. The *CACNA1A* gene encodes a voltage-dependent calcium channel, and acetazolamide is thought to be helpful in channelopathies because it lowers the pH and may thus change channel properties. An open label trial of 6 SCA6 patients treated with acetazolamide had improvement in ataxia rating scale scores and decreased body sway but the effects were somewhat lessened after 1 year. Similarly, patients with episodic ataxia 2, which is also caused by *CACNA1A* gene mutations, had improvement in cerebellar symptoms with acetazolamide[24–26]. Acetazolamide has also been shown to be effective in treating patients with PMM2 congenital disorder of glycosylation (PMM2-CDG), which causes a cerebellar syndrome that may be mediated by abnormal glycosylation of calcium channels[27]. PMM2-CDG is inherited in an AR manner. Side effects of acetazolamide include low bicarbonate levels and paresthesia.

2b. Neuromodulation of Ataxia

Neuromodulation of the cerebellum has shown promising results for treating cerebellar ataxia[28]. Various studies have used transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), as well as deep brain stimulation (DBS) to test the effects on cerebellar ataxia. While DBS involves surgical implantation of electrodes, both TMS and tDCS are noninvasive and all have relatively few side effects. TMS can directly induce action potentials whereas tDCS can modulate local membrane potentials and neuronal

plasticity[29]. Studies of cerebellar neuromodulation are highlighted in Table 2[30–40], but we will focus on a few tDCS studies in more depth here because tDCS is most studied in cerebellar ataxia with a potential for larger-scaled studies in the future.

A case report of two patients with SCA2 showed improvement in SARA score, tremor and upper limb dysmetria immediately after cerebellar tDCS[41]. Nineteen patients with various forms of neurodegenerative ataxias received anodal cerebellar tDCS in a double blind, sham-controlled crossover study[35]. There was a statistically significant improvement in 1.40 points of SARA score and 4.37 points in ICARS score between the sham and stimulation trials. A drawback of these studies was that the effect was only tested immediately after stimulation, making it unclear the duration of symptomatic improvement in these patients after cessation of tDCS.

A follow-up double blind, randomized, sham-controlled crossover study looked at cerebellar anodal and spinal cord cathodal tDCS stimulation in 21 patients with degenerative ataxias[42]. This study had a longer stimulation period (2 weeks of stimulation) and had SARA and ICARS performed before the stimulation or sham stimulation, immediately after the 2-week stimulation, and then 1 and 3 months after the stimulation. There was an improvement in SARA and ICARS scores in the stimulation group at all time points post-stimulation when compared to pre-stimulation and also when compared to sham. This study provides evidence of long-duration responses of ataxia with tDCS to the cerebellar region. The ease of use of tDCS and its relatively longer-lasting effects may be a useful adjunct to symptomatic medical therapy, especially in those patients who do not experience improvement in ataxia from medical therapy.

2c. Exercise as treatment for ataxia

Exercise or physical therapy has been a cornerstone in helping patients with cerebellar ataxia. Studies of intensive rehabilitation have shown long-lasting effects physical therapy. A study of 42 patients with degenerative ataxia were separated into two groups to receive either 4 weeks of intensive rehabilitation or a delayed start of the same rehabilitation schedule[43]. The immediate rehabilitation group had a greater improvement in SARA scores compared to the delayed start group at 4 weeks post-rehabilitation. Although the improvement was attenuated at 12 and 24 weeks post-rehabilitation, a significant number of patients still had improvement compared to baseline, which is notable given the progressive worsening of symptoms in degenerative ataxia.

A study of 38 SCA2 patients, randomized into a 24-week neurorehabilitation therapy program or no therapy, showed that there was a significant improvement in SARA scores in those receiving rehabilitation[44]. Notably the improvement in SARA scores between the therapy and no-therapy groups were in the sub-scores of gait, stance and sitting, and this improvement occurred in patients across different disease duration. Another study randomized 30 preclinical SCA2 patients into either a neurorehabilitation or control group[45]. While the study did not find differences in SARA scores between the two groups after the intervention, there was an improvement in tandem gait, finger-to-nose and heel-shin tasks in the rehabilitation group only.

Of note, a diverse range of physical activity has been shown to be helpful in improving cerebellar dysfunction. A study showed that intensive cycling in 20 patients with various SCAs led to an improvement in ICARS scores after 4 weeks of cycling[46]. Patients with cerebellar ataxia might be able to engage in diverse exercise and physical therapy, such as rock climbing[47]. Working through rehabilitation on physical functions as basic as swallowing may even be helpful in patients with cerebellar ataxia[48]. These studies highlight the long-lasting effects of exercise and physical therapy in improving ataxia, and may point to a neuromodulatory effect of exercise or to enhance other brain regions.

3. Disease modifying treatments for ataxia

The cerebellum is thought to be somewhat flexible in its ability to recover from injury and some investigators have even coined the phrase “time is cerebellum” to describe the abundance of cellular and synaptic plasticity within the cerebellum in ataxia patients, which can be enhanced by treatment[49], when administered in the early stage of the diseases. We will highlight some current treatments that may be disease modifying as well as hopeful looming prospects in the next few sections. Perhaps the most important message is that identifying the cause of a patient’s cerebellar ataxia can be incredibly important as there are a multitude of treatments that can slow down and even halt the progression of ataxia.

3a. Treatment for nutritional and immune-mediated ataxias

Table 3 lists common causes of nutritional and immune-mediated ataxias, which occur on a time course of weeks to months[50–52]. It is critically important to examine serum B12 and B1 levels and potential auto-immune antibodies in a patient with cerebellar ataxia as these causes could potentially be reversed with the appropriate treatment especially early on in the disease course. The classic triad of Wernicke encephalopathy is altered mental status, ophthalmoplegia and cerebellar ataxia[53], and often occurs in the setting of chronic alcoholism. Cancer and gastric bypass surgeries can be causes for Wernicke encephalopathy[54]. Prompt thiamine administration is the treatment for Wernicke encephalopathy.

The most common cause of vitamin B12 deficiency is pernicious anemia, which is an autoimmune atrophic gastritis[55]. Although the gait dysfunction in vitamin B12 deficiency is due to both demyelination of the dorsal columns and central nervous system involvement, there have been cases of vitamin B12 deficiency that cause cerebellar degeneration only[56]. Prompt detection of vitamin B12 deficiency in a patient with cerebellar ataxia is critical to prevent clinical worsening and may even reverse the symptoms.

Finally, there are several auto-antibodies and paraneoplastic syndromes associated with cerebellar ataxia, and the identification of these causes are important in order to administer treatment promptly. The most common paraneoplastic autoantibodies are the anti-Yo (associated with breast, uterine and ovarian cancers), anti-Hu (associated with small cell lung cancer), anti-Tr (associated with Hodgkin’s lymphoma), and anti-CV2 (associated with SCLC and thymoma) antibodies. Guidelines on the treatment for paraneoplastic ataxias suggest that if treating the underlying cancer does not help, a round of immunotherapy may be helpful. Patients who have autoantibodies detected in the serum may receive a spinal tap

to further investigate whether these antibodies are present in the cerebrospinal fluid. These patients with autoantibodies can be treated with either immunoglobulin therapy (IVIG), steroids or other immuno-modulatory agents. More randomized controlled trials need to be conducted to examine autoantibody-mediated cerebellar ataxia to determine the optimal immunotherapy tailored to ataxia associated with each individual autoantibody.

3b. Treatment for AR ataxias

AR ataxias are comprised of a diverse group of progressive gataxias often resulting from dysfunctional metabolic pathways. Most AR ataxias can be categorized in one of three subgroups: defective mitochondrial metabolism, dysfunctional lipid metabolism and impaired DNA repair[58]. Some of these AR mutations lead to accumulation of toxic downstream metabolites and reduction of these metabolites can ameliorate the symptoms of the illness and/or modify the disease course.

Wilson disease, which causes a multitude of neurologic, psychiatric and ophthalmologic symptoms including ataxia due to copper accumulation in the brain and liver resulting from a mutation in the *ATP7B* gene that encodes a protein for copper transport. Lifelong treatment with oral copper chelators such as penicillamine and trientene may reverse symptoms[59].

The clinical hallmarks of cerebrotendinous xanthomatosis (CTX) include tendon xanthomas, cerebellar ataxia, dementia, cataracts, premature atherosclerosis, and pulmonary dysfunction, with elevated cholestenol and bile alcohols found in serum and urine[60]. Supplementation with chenodeoxycholic acid (CDCA) inhibits abnormal bile acid synthesis by providing feedback inhibition which is deficient in these patients. A hallmark 1984 study showed that in 17 CTX patients given CDCA, several patients had improvement of dementia and cerebellar ataxia[61]. A more recent study in two patients with CTX started on CDCA at 3 and 5 months showed that the neurologic deficits could be improved but not completely reversed, suggesting that there even earlier detection and treatment of CTX may lead to normal development[62].

Niemann Pick type C (NPC) is caused by a mutation in the *NPC1* or *NPC2* gene, and the adolescent onset forms of NPC usually result in cerebellar dysfunction including ataxia, dysarthria, dysmetria and dysphagia, as well as gelastic cataplexy[63]. On exam, NPC patients have characteristic impaired vertical saccades[64]. Miglustat inhibits the synthesis of glycosphingolipids and has been approved for the treatment of NPC. Miglustat improves swallowing function and stabilizes other neurologic manifestations in the years following its administration in NPC patients[65]. Other potential treatments for NPC include 2-hydroxypropyl-beta-cyclodextrins which may delay Purkinje cell loss and slows disease progression in patients with NPC[66].

Other AR ataxias that are due to nutritional deficiencies may be stabilized or improved with correct nutritional supplementation. In a patient with ataxia, dysarthria, vision loss due to retinitis pigmentosa, head tremor and areflexia, ataxia with vitamin E deficiency (AVED) must be considered. AVED patients have mutations in the alpha tocopherol transfer protein (alpha-TTP) lead to reduced intrahepatocyte vitamin E incorporation into very low density

lipoproteins. Serum vitamin E levels are very low in AVED patients, and early supplementation of vitamin E in these patients can improve cerebellar ataxia[67]. AR cerebellar ataxia type 2 (ARCA2) is caused by a mutation in the *ADCK3* gene which results in coenzyme Q10 deficiency. Studies show that patients seem to respond to idebenone supplementation[68].

A success in AR cerebellar ataxia treatment is seen in patients with biotinidase deficiency identified on newborn screen, who subsequently received biotin supplementation[69]. A study following 44 patients started on biotin supplementation as infants lived normal adult lives, significantly different from the natural history of biotinidase deficiency. Interestingly, biotin supplementation seems only to slow or stop disease progression but cannot reverse symptoms. A case report described patients with novel mutations in the *SLC19A3* gene that have recurrent episodes of encephalopathy and at baseline have generalized dystonia, epilepsy and bilateral caudate and putaminal hyperintensities had clinical improvement during encephalopathic episodes with administration of high doses of biotin and thiamine[70].

The most common AR cerebellar ataxia is Friedreich ataxia, accounting for ~25% of all AR cerebellar ataxias. Friedreich ataxia is caused by a homozygous GAA trinucleotide repeat in intron 1 of the *FXN* gene on chromosome 9q13[71], which reduces expression of the protein products, frataxin. Several pre-clinical studies in rodents and cell lines have shown that administration of wild-type frataxin either through bone-marrow transplants[72], administration of antisense oligonucleotides (ASOs)[73], or injecting *FXN* expressing adeno-associated virus[74] can improve some of the symptoms of Friedreich ataxia in preclinical models.

Table 4 provides a more comprehensive summary of the different AR cerebellar ataxias and their treatments[75–84]. The majority of the evidence for the treatments of AR cerebellar ataxias rely on case reports and open label studies, likely because of the rarity of the illnesses. However, it is still important to consider the possibility of AR cerebellar ataxias in patients with early onset ataxia with or without sensory neuropathy, since many AR ataxias can stabilize or improve if treatments are started early. The potential for gene therapy or strategies to enhance *FXN* expression in the treatment of Friedreich ataxia portends great hope for the treatment of AR cerebellar ataxias.

3c. Treatment for AD cerebellar ataxias

In patients presenting with a slowly progressive cerebellar ataxia in middle-age who may have a family history of ataxia, the diagnosis of AD ataxias should be aggressively pursued. The majority of AD cerebellar ataxias are categorized as SCAs with exceptions such as dentatorubro-pallidoluysian atrophy (DRPLA) and episodic ataxias. The most common SCAs involve poly-glutamine expansion repeats, which lead to protein misfolding and aggregation[85], and SCA1, 2, 3, 6, 7, and 17 belong to this group. There are no definitive disease-modifying therapies for AD cerebellar ataxias. Nonetheless, we list several relevant clinical and preclinical studies as potential therapies for AD cerebellar ataxias.

A randomized, open-label study of valproic acid in 12 SCA3 patients showed improvement in SARA scores, with dizziness and loss of appetite as side effects[86], with two patients

dropping out as a result of these side effects. The possible mechanism of action is thought to be inhibition of histone deacetylases to regulate the expression of pathological proteins. Proteins carrying poly-glutamine repeats are known to activate the mitochondrial apoptotic pathway leading to neuronal death; therefore, mitochondrial dysfunction might be one of the shared pathways for SCAs. A retrospective study demonstrated that SCA patients who took coenzyme Q10, a co-factor in the mitochondrial respiratory chain, had better SARA scores than those who did not. In addition, a dose-dependent effect was found in SCA3 patients[87]. This study suggests coenzyme Q10 may have disease-modifying effects for SCAs, and warrants further randomized, placebo-controlled trials.

Citalopram was initially identified in a screen of Food and Drug Administration-approved drugs to rescue neuronal dysfunction in an SCA3 *C.elegans* model. Citalopram, a serotonin reuptake inhibitor, was further demonstrated to reduce ataxin-3 neuronal inclusions, astrogliosis, as well as improving motor symptoms in SCA3 mouse models[88]. These preclinical animal studies provide strong rationale for future randomized placebo-controlled trials for citalopram in SCA3. Excessive glutamate-mediated neuronal transmission leading to neuronal toxicity is a major mechanism for neurodegenerative disorders; therefore, modulating glutamatergic neuronal transmission could be disease modifying in SCAs. Towards this goal, there is an ongoing clinical trial treating SCA patients with a glutamate modulator, troriluzole, to examine its effects on slowing disease progression.

As SCAs are monogenetic disorders, therapies specifically through ASO targeting mutated genes hold promise as disease modifying therapy. There are several preclinical studies showing that knocking down of mutated protein expression by gene therapy can be disease modifying therapy in animal models of SCAs. ASOs targeting *ATXN2* in a SCA2 mouse model improved motor function and Purkinje cell firing[89]. A similar study in showed efficacy of ASOs in reducing ATXN1 protein in a SCA1 mouse model with improvement in motor coordination[90]. ASOs targeting ATXN3 also showed promising results in SCA3 mouse models[91], while knockout of the entire *ATXN3* gene is well-tolerated in a SCA3 mouse model[92], which provide some preclinical safety evidence. Other than ASOs, intraventricular injections of shRNA silencing mutant *ATXN3* have also been shown to improve motor symptoms in SCA3 mouse models[93]. In a SCA6 mouse model, delivery of microRNA against the toxic gene product can also improve the motor performance and halt Purkinje cell degeneration[94].

Table 5 summarizes the potential disease modifying treatments highlighted above, as well as other promising preclinical studies not mentioned in the text[95–99].

3d. Treatments for idiopathic neurodegenerative ataxias

Multiple system atrophy (MSA) is a common diagnosis in patients with late onset, progressive cerebellar ataxia, and is often accompanied by parkinsonism and autonomic dysfunction. A recent genetic study found an association between a rare variant of *COQ2* and MSA in East Asian populations[100,101]. *COQ2* encodes for a protein that is essential in the synthesis of coenzyme Q10. Interestingly, reduction of coenzyme Q10 levels is observed both in the serum[93], and in the postmortem cerebellum of MSA patients[102]. A clinical trial of ubiquinol, a form of coenzyme Q10, in the treatment of MSA is currently underway.

Other potential treatments for MSA include modulation of the serotonergic system with the selective serotonergic reuptake inhibitors, which have been shown to reduce alpha-synuclein uptake in neuronal and oligodendroglial cells and thus could be disease-modifying[103]. A small double-blind, placebo controlled study of 19 MSA patients showed that paroxetine, a serotonin reuptake inhibitor, treated patients showed better limb agility compared to placebo-treated patients[104]. Another promising potential treatment for MSA are myeloperoxidase inhibitors, which have been shown to improve motor function in an MSA mouse model and to reduce alpha-synuclein aggregates[105]. A phase III trial of an irreversible myeloperoxidase inhibitor, BHV-3241, is currently underway.

4. Conclusions

The purpose of this paper is to describe the wide range of treatments available for cerebellar ataxia and to highlight promising therapies on the horizon. With the recent advances in gene therapy and ASO approaches, targeted therapies for ataxia hold the promise of improving quality of life for patients with ataxia and possibly even slow or reverse the disease course. Moreover, continued improvement of clinical trial design for ataxia will also advance our ability to demonstrate therapeutic efficacy.

Several challenges remain to be addressed in the currently burgeoning field of ataxia research. First, while most studies rely on SARA or ICARS scores, additional patient-oriented outcome measures need to be developed to demonstrate improvement in quality of life for ataxia patients. Second, as we begin to understand the role of the cerebellum in cognitive and emotional processing, non-motor rating scales, such as the cerebellar cognitive affective scale[106], will need to be implemented to comprehensively assess the aspects of patients' lives affected by cerebellar dysfunction. Third, all clinical rating scales are limited by their ability to capture only a moment in time in the clinic and as such the development of wearable instruments are needed to more fully describe "real life" motor performance at home. Fourth, imaging and fluid biomarkers should be used as part of clinical trials for ataxia to test for target engagement and as additional evidence for disease modifying effects.

There are currently a multitude of treatments for ataxia that can be offered, both symptomatic therapies that may help regardless of the cause of ataxia as well as potential disease-modifying therapies targeting specific types of ataxia. It is not only the time to dispel the myth that there is no treatment for ataxia, but in fact there is a reason to be hopeful about the current state and future of ataxia treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Kuo is supported by the NINDS K08 NS083738 (Kuo), R01 NS104423 (Kuo), National Ataxia Foundation, Louis V. Gerstner Jr. Scholarship, Parkinson Foundation, Brain Research Foundation, and International Essential Tremor Foundation.

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Key Points

- A review paper summarizing current treatments for cerebellar ataxia.
- Review categorizing treatments for cerebellar ataxia by symptomatic treatment and disease modifying treatments.
- We further separate disease modifying treatments into those for autosomal dominant, autosomal recessive and immune-mediated cerebellar ataxias.
- We discuss preclinical and clinical trials currently underway for the treatment of cerebellar ataxia.

Synopsis

Cerebellar ataxia can be caused by a variety of disorders, including degenerative processes, auto-immune and paraneoplastic illness as well as by gene mutations inherited in autosomal dominant, autosomal recessive or X-linked fashions. In this review, we highlight the treatments for cerebellar ataxia in a systematic way, to provide guidance for clinicians to treat patients with cerebellar ataxia. In addition, we review therapies currently under development for ataxia, which is one of the most exciting fields in neurology.

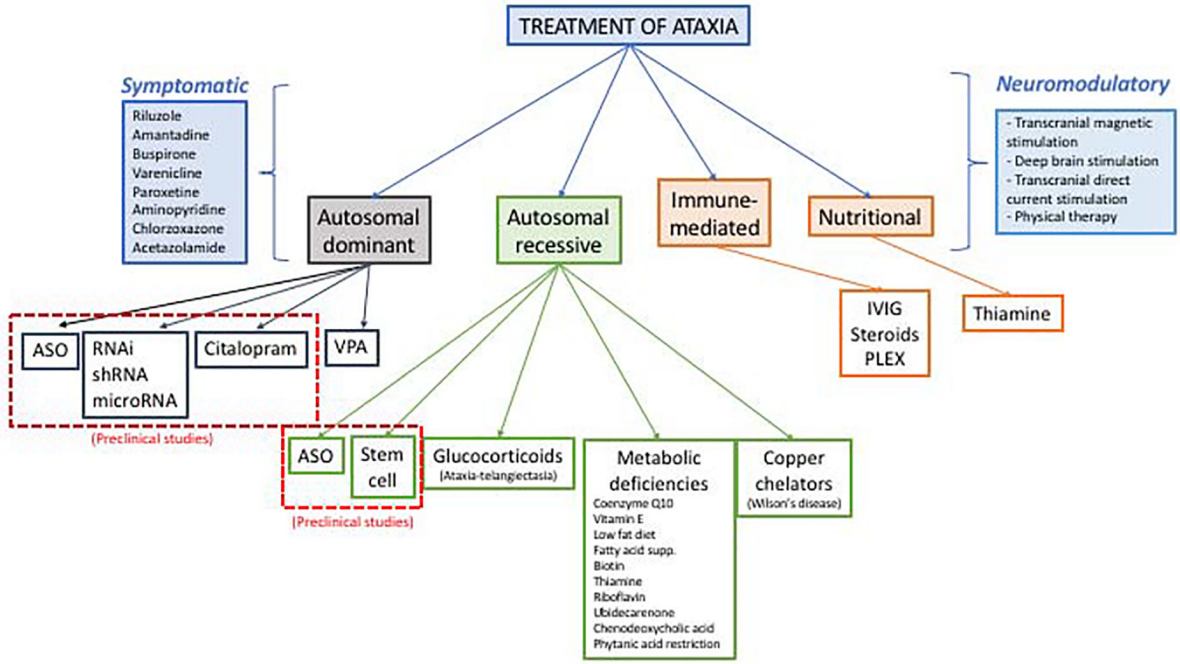

Figure 1.
Summary of current and potential treatments for ataxia.

Table 1:

Symptomatic treatment for ataxia

Treatment	Ataxia type	Evidence	References
Riluzole	SCA, FA	Randomized, double-blind, placebo-controlled trial	(Ristori et al., 2010; Romano et al., 2015)
Varenicline	SCA3	A randomized, double-blind, placebo-controlled trail	(Zesiewicz et al., 2012)
Paroxetine	MSA	A randomized, double-blind, placebo-controlled study	(Friess et al., 2006)
Aminopyridine	EA2	A randomized, double-blind, placebo-controlled, crossover study	(Strupp et al., 2011)
	SCA6, ADCA	Observational studies	(Tsunemi et al., 2010)
Amantadine (IV)	MSA	A short-term, open label study	(Youn et al., 2012)
Buspirone	MSA-C	Open label studies	(Heo et al., 2008)
Acetazolamide	SCA6, EA	Open label studies and case reports	(Baloh and Winder, 1991; Griggs et al., 1978; Harno et al., 2004) (Yabeet al., 2001)
	PMM2-CDG	A single-blind, randomized withdrawal trial	(Martinez-Monseny etal.,2019)
Citalopram	FA	Case series (2 patients)	(Rohretal., 1999)
Chlorzoxazone	SCA1, SCA2	Rodent studies	(Egorova et al., 2016) (Bushart et al., 2018)

EA2: episodic ataxia type 2, FA: Friedreich ataxia, MSA: multiple system atrophy, SCA: spinocerebellar ataxia, PMM2-CDG: phosphomannomutase congenital disorder of glycosylation

Table 2:

Neuromodulation and physical exercise for ataxia

Treatment	Ataxia type	Evidence	References
Physical merapy	SCA7, SCA2, FA	A randomized, open label study	(llg et al., 2009; Tercero-Pérez et al., 2019; Velázquez-Pérez et al., 2019)
Transcranial magnetic stimulation	SCA1, SCA6, SCA7	A randomized, sham-controlled study and case reports	(Kawamura et al., 2018; Shiga et al., 2002; Shimizu et al., 1999)
	Posterior circulation stroke	A randomized, double-blind trial	(Kim et al., 2014)
Transcranial direct current stimulation	SCA, MSA, FA	A randomized, double-blind, sham-controlled study and case report	(Benussi et al., 2015, 2018; Grimaldi and Manto, 2013)
Deep brain stimulation	SCA	Case report	(Hashimoto et al., 2018)
	FXTAS	Case report	(dos Santos Ghilardi et al., 2015)
	Cerebellar stroke	Case report	(Teixeira et al., 2015; Weiss et al., 2015)

FA: Friedreich ataxia, FXTAS: Fragile X-associated tremor/ataxia syndrome, MSA: multiple system atrophy, SCA: spinocerebellar ataxia

Table 3:

Treatment for immune-mediated and nutritional ataxias.

Treatment	Ataxia type	Evidence	References
IVIG	Opsoclonus myoclonus ataxia syndrome	A randomized, open label study	(de Alarcon et al., 2018)
Gluten-free diet, IVIG, steroids	Anti-DGP, anti-gliadin cerebellar ataxias	Open label	(Nanri et al., 2016)
IVIG, steroids	Anti-GAD, anti-TPO	Open label	(Nanri et al., 2016)
Thiamine	Wernicke's encephalopathy	Case reports	(Chataway and Hardman, 1995; Sinha et al., 2019)
Vitamin B12	Pernicious anemia, dietary deficiency	Case reports	(Chakrabarty et al., 2014; Stabler, 2013)

Anti-DGP: anti-deamidated gliadin peptide, anti-GAD: anti-glutamic acid decarboxylase antibody, anti-TPO: anti-thyroperoxidase antibody, IVIG: intravenous immunoglobulin

Table 4:

Disease modifying therapies for autosomal recessive ataxias

Ataxia type	Treatment	Evidence	Mechanism of action	References
Wilson disease	Copper chelators	Observational studies	Blockade of intestinal copper absorption	(Aggarwal and Bhatt, 2018)
Niemann-Pick Disease	Miglustat	A prospective randomized control studies	Inhibition of glycosphingolipid synthesis	(Pineda et al., 2018)
Niemann-Pick Disease	Intrathecal 2-hydroxypropyl-β-cyclodextrins	An open label, observational study	Unclear	(Ory et al., 2017)
Ataxia Telangiectasia	Glucocorticoids	An prospective, cohort study	Unclear, possible restoration of ATM gene expression	(Menotta et al., 2017; Zannolli et al., 2012)
Cerebrotendinous xanthomatosis	Chenodeoxycholic acid supplementation	An open label, observational study	Replace missing bile acids; lipid metabolism deficit	(Berginer et al., 1984; Nie et al., 2014; Pierre et al., 2008)
Ataxia with vitamin E deficiency	Vitamin E	An open label, observational study	Replacement therapy	(Gabsi et al., 2001)
Riboflavin transporter deficiency neuronopathy (*SLC52A2* gene mutation)	Riboflavin	An open label, observational study	Supplementation to boost absorption	(Foley et al., 2014; Guissart et al., 2016)
Autosomal recessive cerebellar ataxia 2	Ubidecarenone	An open label, observational study	Replacement therapy	(Mignot et al., 2013)
Abetalipoproteinemia	Low-fat diet, essential fatty acid supplementation	A case series	Replacement therapy	(Chardon et al., 2009; Lee and Hegele, 2014)
Biotinidase deficiency	Biotin	A case series	Replacement therapy	(Wolf, 2017)
SLC19A3 gene mutation	Biotin, thiamine	A case series	Replacement therapy	(Debs et al., 2010)
CoQ10, CoQ4 deficiency	Coenzyme Q10	A case series	Replacement therapy	(Caglayan et al., 2019)
Refsum disease	Phytanic acid restriction, lipid apheresis	A case report and 2 case series	Toxic substrate reduction	(Baldwin et al., 2010; Gibberd et al., 1979; Zolotov et al., 2012)
Friedreich ataxia	Frataxin-expressing adeno-associated virus	A preclinical, rodent study	Frataxin replacement	(Piguet et al., 2018)
Friedreich ataxia	Allogenic stem cell transplantation	A preclinical, rodent study	Increasing frataxin levels	(Kemp et al., 2018)
Friedreich ataxia	ASO targeting triplet expansion in frataxin	A preclinical, rodent study	Increasing frataxin expression	(Li et al., 2018)

CoQ4: Coenzyme Q4, CoQ10: Coenzyme Q10

Table 5:

Disease modifying therapy in autosomal dominant ataxias

Treatment	Ataxia type	Evidence	Mechanism of action	References
Valproic acid	SCA3	A randomized, open-label, doseescalation	Histone deacetylase inhibition	(Lei et al., 2016)
Coenzyme Q10	SCA 1, SCA3	An observational study	Enhancing mitochondrial respiratory chain	(Lo et al., 2015)
Troriluzole (BHV4157)	SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10	An ongoing phase III, randomized, double-blind, placebo-controlled study	Modulation of glutamate neurotransmission	ClinicalTrials.gov Identifier: NCT03701399
Citalopram	SCA3	A preclinical, rodent study	Reduction of ATXN3 neuronal inclusions and astrogliosis	(Teixeira-Castro et al., 2015)
ASO targeting ATXN1	SCA1	A preclinical, rodent study	Downregulation of ATXN1	(Friedrich et al., 2018)
ASO targeting ATXN2	SCA2	A preclinical, rodent study	Downregulation of ATXN2	(Scoles et al., 2017)
ASO vitreal injections	SCA7	A preclinical, rodent study	Downregulation of ATXN7	(Niu et al., 2018)
ASO targeting ATXN3	SCA3	A preclinical, rodent study	Downregulation of ATXN3	(Toonen et al., 2017) (Moore et al., 2017)
shRNA silencing ATXN3	SCA3	A preclinical, rodent study	Downregulation of ATXN3	(Nóbrega et al., 2013, 2019)
RNAi targeting ATXN7	SCA7	A preclinical, rodent study	Reduction of WT and mutant ATXN7	(Ramachandran et al., 2014)
MicroRNA blocking IRES driven translation *CACNA1A* second cistern	SCA6	A preclinical, rodent study	Selective downregulation of toxic gene product	(Miyazaki et al., 2016)
Gluten-free diet	SCA35	A case report	Toxic substrate reduction	(Lin et al., 2019)

ASO: antisense oligonucleotide, SCA: spinocerebellar ataxia