Treating Hereditary Ataxias—Where Can We Help?

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Abstract

Hereditary ataxias comprise a group of neurological disorders which affect different levels of the neurological axis including the cerebellum, peripheral nerves, cognition, and the extrapyramidal system. These are categorized by the mode of inheritance as autosomal recessive, autosomal dominant, X-linked, and mitochondrial cerebellar ataxia. Definitive curative therapy is not available for these disorders. However, a wide array of emerging treatment options, especially in terms of symptomatic therapy, rescues this group from therapeutic nihilism. Several drugs have been assessed including riluzole, valproate, lithium, etc., as well as rehabilitative, and neuromodulatory strategies. In addition, symptomatic therapies for ancillary symptoms, such as seizures, movement disorders, spasticity, dystonia, etc., should also be targeted. Lastly, molecular therapeutic possibilities are also being explored in animal studies. In this review, we elucidate on the current treatment options available for hereditary ataxias.

Keywords
- ataxia
- treatable
- cerebellar
- hereditary ataxia

Introduction

Hereditary ataxias (HAs) are a group of neurodegenerative disorders with variable and multiple neuraxial involvement, including cognition, seizures, movement disorders, extrapyramidal systems, and peripheral neuropathy.[1] The implications of a diagnosis of HAs include not only an inexorably progressive course but also a lack of curative therapies. In the absence of the same, management remains essentially supportive and symptomatic. We review the current therapeutic options available in this group of disorders.

Approach to Treating Hereditary Ataxias

HAs are categorized based on the pattern of inheritance into autosomal recessive and dominant ataxia, mitochondrial ataxia syndromes, X-linked HAs, as well as episodic, and congenital ataxias. There are no U.S. Food and Drug Administration–approved medications till date for the treatment of HAs. Most of the drug usage is based on case series and small trials. Such studies often have limited clinical translation. Also, the treatment duration is usually brief, and therefore long-term treatment effect is uncertain.[2]

A presumptive diagnosis about the cause is imperative, since the treatment depends upon it. However, this is challenging because of the myriad of etiologies that can present similarly.[3]

Autosomal Recessive Cerebellar Ataxias

Autosomal recessive cerebellar ataxias (ARCA) occur due to functional impairment of proteins involved in the lysosomal or mitochondrial pathways.[4] This opens up potential therapeutic avenues that target the pathogenic pathway in autosomal recessive ataxias. ARCAs are not just ataxia syndrome but involve a huge range of symptomatology including peripheral neuropathy, intellectual disability, dementia, extrapyramidal syndrome, oculomotor apraxia, etc.[5] ►**Table 1** summarizes treatment options of autosomal recessive ataxias. We also discuss below the management of neurological and nonneurological features in this group.

Treatment of Ataxia

Ataxia, secondary to a metabolic mechanism, responds to and slows down in response to appropriate supplementation. The disorders amenable to this form of therapy include

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Table 1 Treatment options in autosomal recessive cerebellar ataxias

Disorder	Drug	Dose
Friedreich ataxia	Idebenone Coenzyme Q10	5–20 mg/kg/day 30 mg/kg/day
Ataxia with vitamin-E deficiency	Vitamin E	800–1,200 mg per day
Abetalipoproteinemia	Vitamin E Vitamin A low-fat diet Medium-chain triglyceride	150 mg/kg
Refsum's disease	Low phytanic acid diet Plasma exchange	Below 10 mg per day
Niemann–Pick type C	Miglustat	200 mg thrice daily
Cerebrotendinousxanthomatosis	Chenodeoxycholic acid	750 mg/day
Ataxia with CoQ10 deficiency	CoQ10 supplementation	30 mg/kg/day
Ataxia with glut-1 deficiency	Ketogenic diet, modified Atkin's diet	

Abbreviation: Co, coenzyme.

ataxia with vitamin-E deficiency (AVED), Refsum's disease, Niemann–Pick disease type C (NPC), cerebrotendinous xanthomatosis (CTX), ataxia with Coenzyme Q10 deficiency, and ataxia with glut-1 deficiency.

Friedreich's ataxia (FRDA) is an autosomal recessive guanine, adenine, adenine (GAA) triplet repeat expansion disorder on the frataxin gene on chromosome 9q13.[6] It is the most frequent form of inherited ataxia. Frataxin, a mitochondrial protein, is involved in iron–sulfur cluster biosynthesis. Multiple therapeutic strategies have been used to address the primary mechanism of injury that includes increasing frataxin levels by histone deacetylase (HDAC) inhibitors or by recombinant human erythropoietin; use antioxidants, such as coenzyme Q10 and vitamin E; lowering mitochondrial iron stores with deferiprone; and improving energy metabolism by supplementation of L-carnitine.[7] However, despite promising results in some earlier studies, controlled studies have failed to demonstrate halting of disease progression with these approaches. Several open-label studies have demonstrated beneficial effects of idebenone on cardiac hypertrophy in FRDA.[7] Treatment with it should therefore be individualized to a subgroup of patients with severe hypertrophic cardiomyopathy and those with early disease.

AVED is an autosomal recessive disease caused by mutations on chromosome 8q13 in the α-tocopherol transfer protein (*TTPA* gene). It presents as a slowly progressive spinocerebellar ataxia (SCA) syndrome, closely resembling Friedreich's (FRDA) ataxia. Cardiomyopathy is less common in AVED, whereas titubation and dystonia are more specific for it.[8] They also have a slower course, with milder neuropathy compared with patients with FRDA. Daily, divided, high doses of vitamin E (800 mg/day) usually lead to cessation of disease progression and neurological improvement, although recovery may be slow and often incomplete. The results of vitamin-E supplementation are more beneficial if started before 15 years of disease duration; the earlier, the better. In a group of 24 patients with AVED, oral vitamin-E supplementation (doses of 800–1,200 mg/day) for 1 year led to symptomatic improvement.[9]

Abetalipoproteinemia is a rare metabolic disease caused by mutations in the gene encoding for the large subunit of microsomal triglyceride transfer protein (*MTTP* gene), on chromosome 4q22–24. This mutation leads to absence of plasma apolipoprotein B containing lipoproteins, which in turn leads to the impaired utilization of fat and fat-soluble vitamins leading to deficiency states. Symptoms usually begin before the age of 20 years.[10] Retinitis pigmentosa also may be seen. The "gold standard" diagnostic test is by sequencing the *MTTP*. Dietary modification consists of a low-fat diet and vitamin replacement of fat-soluble vitamins, such as vitamins E and A. Ataxia in abetalipoproteinemia may also respond to vitamin-E supplementation in large doses (30–88 mg/kg/day), along with vitamins A and D.[8] However, this may require prolonged supplementation (up to 15 years) to bring about stabilization of the ataxic syndrome.

Refsum's disease is a rare autosomal recessive disorder of fatty acid metabolism, caused by mutations of the gene encoding for the peroxisomal enzyme phytanoyl-CoA hydroxylase, on chromosome 10. This enzyme catalyzes the first step in the α oxidation of phytanic acid.[11] Impaired fatty acid oxidation of phytanic acid (found predominantly in dairy products, meat, and fish) leads to accumulation in the body. Analysis of serum phytanic acid levels is done to confirm the diagnosis. Dietary restriction halts disease progression and the goal of therapy is reduction of normal daily intake of phytanic acid to a maximum of 10 mg/day.[12] This is sometimes not sufficient to prevent acute attacks and stabilize the progressive course. Plasma exchange or chronic lipid apheresis can be done in such cases.[12]

Niemann–Pick type-C disease (NPC) is a rare autosomal-recessive lipid storage disorder, characterized by unique abnormalities of intracellular transport of endocytosed cholesterol along with sequestration of unesterified cholesterol in lysosomes. *NPC1* gene (chromosome 18q11) mutations occur in 95% and *NPC2* gene on chromosome 14q24.3 occur in the remaining. These result in accumulation of glucosylceramide, lactosylceramide, and GM2 and GM3 gangliosides in the brain. This may be a factor contributing to its neurological manifestations. Neurological manifestation predominates in the adult and juvenile forms of the disease, the most common features ones being cerebellar ataxia, vertical supranuclear ophthalmoplegia, dysarthria, dysphagia, intellectual impairment, and movement disorders. Splenomegaly and psychiatric disorders are common accompaniments. Vertical supranuclear palsy is usually present early in the disease but also occasionally develops later in the disease. Miglustat, a glucosylceramide synthase inhibitor which prevents glycolipid accumulation, dosed at 200 mg thrice daily, stabilizes disease progression in most patients treated for

1 year or more, based on a composite assessment of parameters: horizontal saccadic eye movement velocity, ambulation, swallowing, and cognition. The overall benefits are generally modest, suggesting that miglustat may slow, but not halt, the progression of neurological abnormalities.[13,14] Cyclodextrin, a cholesterol-sequestering agent, has also shown some possible therapeutic value in preliminary studies in NPC, and clinical trials are underway for the same.[13]

CTX is a rare, autosomal recessive disorder of lipid storage caused by a mutation of the enzyme 27-sterol hydroxylase (*CYP27* gene) on chromosome 2, which forms a part of the hepatic pathway for bile-acid synthesis. Reduction in their synthesis leads to an increase in levels of serum cholestanol and urinary bile alcohols. They get deposited as xanthomatous lesions in various tissues, particularly the brain, ocular lenses, and tendons, resulting in a variable clinical phenotype, which consists of both neurological and systemic manifestations. Neurological symptoms usually start around 20 years of age and predominantly include cerebellar ataxia, spastic paraparesis, sensorimotor peripheral neuropathy, extrapyramidal signs, seizures, psychiatric problems, and cognitive impairment. Juvenile cataracts, progressive neurological dysfunction, along with mild pulmonary insufficiency, are unique symptoms distinguishing CTX from ataxic disorders. CTX can be diagnosed by testing serum cholestanol and urinary bile alcohol levels. MRI brain reveals global atrophy and parenchymal lesions, nerve conduction studies show an axonal neuropathy, delayed central conduction times are seen on evoked potentials(visual, brainstem auditory, and somatosensory), and electroencephalography typically shows diffuse slowing with paroxysmal discharges. It is treatable by supplementation with oral chenodeoxycholic acid (CDCA), the recommended dose being 250 mg thrice a day. Side-effects include diarrhea, restlessness, and irritability, although infrequent. A combination of CDCA and statins has also been studied but this did not improve ataxia. LDL apharesis has also been used to reduce the cholestanol levels but this did not lead to an improvement in ataxia.[15]

Ataxia with coenzyme Q 10 (CoQ10) deficiency may be due to primary or secondary CoQ10 deficiency. Primary CoQ deficiency occurs due to mutations of genes involved in the coenzyme Q pathway (CoQ2, CoQ9, etc.).[16] Secondary deficiency is due to other genetic mutations (e.g., aprataxin). High doses of CoQ10 (30 mg/kg/day) are shown to be effective in the treatment.[17]

Ataxia with glut-1 deficiency is treated with ketogenic diet and modified Atkin's diet. Alphalipoic acid facilitated glucose transport and may also be of benefit in this condition.[18]

Treatment of Peripheral Neuropathy

Autosomal recessive ataxias are often associated with peripheral neuropathy. Neuropathy in AVED patients responds to vitamin E supplementation. In patients with abetalipoproteinemia, vitamins A and E supplementation improve sensory examination. In Refsum's disease, several reports describe stabilization of peripheral neuropathy with low phytanic acid and plasma exchange.[19] Although patients with CTX may not exhibit much improvement in ataxia, CDCA supplementation may lead to improvement in peripheral neuropathy in a subset of patients.

Treatment of Epilepsy

Glut-1 deficiency is strongly associated with seizures which are highly responsive to diet modifications described above.[20] Cataplexy in NPC patients may respond to antidepressant and central stimulants instead of miglustat.[14]

Treatment of Cognitive Impairment

Miglustat in NPC and CDCA in CTX patients have been shown to improve cognition.[13,15]

Treatment of Movement Disorders

AVED patients often have head tremor and dystonia, the latter being responsive to vitamin-E therapy but not the former. Dystonia in CTX may be treated with miglustat. Dystonia in glut-1 deficiency responds to ketogenic and modified Atkin's diet. Other symptomatic measures including anticholinergics for dystonia, β-blockers/primidone for postural tremor, botulinum toxin therapy for focal dystonia, and levodopa therapy for parkinsonism should also be added.

Treatment of Visual Abnormalities

Although autosomal recessive ataxias exhibit characteristic visual involvement, the response to therapy is poor. AVED and abetalipoproteinemia have retinitis pigmentosa which does not respond to vitamin E. NPC patients develop cataracts unresponsive to dietary therapy and plasma exchange.[21]

Autosomal Dominant Ataxias

Autosomal dominant cerebellar ataxias are classified into SCAs and episodic ataxias (►**Table 2**). These disorders are managed as follows.

Treatment of Ataxia

Riluzole is a potassium channel opener and regulates the activity of deep cerebellar nuclei leading to reduction in neuronal hyperexcitability. In a study of 40 patients with various cerebellar ataxia, 100 mg per day of riluzole led to a reduction in the scale for the assessment and rating of ataxia (SARA) compared with placebo.[22] These findings were also replicated in another study on different forms of cerebellar ataxia in which 50% of patients in the riluzole arm showed improvement compared with placebo arm (11%) in the SARA scale.[23] Although a promising drug, further studies are essential to evaluate its efficacy in HAs.

Lithium carbonate has also been studied in patients with SCA type 3 (SCA3) by a phase-II clinical trial. The outcome scales used were the mean neurological examination score

Table 2 Treatment options in autosomal dominant cerebellar ataxias

Therapy	Disorder	Dose
Riluzole	SCAs and other HAs	100 mg/day
Varenicline	SCA3	1 mg twice daily
Buspirone	SCAs	30 mg twice daily
Zinc	SCA3	50 mg twice daily
Insulin-like growth factor 1	SCA3	50 mcg subcutaneously twice daily
Acetazolamide	EA2	250–1,000 mg per day
4-amino pyridine	EA2	5 mg thrice daily
Mexiletine and carbamazepine	SCA3	For cramps
Botulinum toxin type A	SCA3	For dystonia and spasticity

Abbreviations: EA, episodic ataxias; HA, hereditary ataxia; SCA, spinocerebellar ataxia.

for the assessment of spinocerebellar ataxia (NESSCA) which did not show a difference between groups.[24]

Zinc therapy (50 mg per day) was also evaluated in 36 Cuban patients with SCA type 2 (SCA2) in a randomized double-blind trial.[25] A small benefit in terms of decrease in ataxia scores and saccadic latency on the SARA scale was reported. Zinc therapy was also tolerated well by study participants.

Varenicline, a partial α4β2 agonist at the neuronal nicotinic acetylcholine receptor used for smoking cessation, has also been studied in SCA3 in 20 patients.[26] There was a trend toward improvement of SARA scores in axial and rapid alternating movements in patients with SCA3 at the end of 8 weeks.

Serotonin deficiency has been hypothesized to play a basis in the development of ataxia. Buspirone was shown to be not superior to placebo when administered over 3 months.[27] However, citalopram, a selective serotonin reuptake inhibitor, was shown in a SCA3 mouse model to reduce ataxin deposits, as well as improve motor symptoms.[28] This could be a promising therapy.

The insulin-like growth factor-1 (IGF-1) is a central nervous system (CNS) neuromodulator. It has been studied in patients with SCA3 and SCA type 7 (SCA7) in a 2-year prospective uncontrolled clinical trial. Administration of IGF-1 in the doses of 50 µg/kg/twice a day subcutaneously have been found to improve ataxia in SCA3 patients over 8 months.[29]

The second group of autosomal dominant cerebellar ataxias includes episodic ataxias (EA). EA1 may respond to various drugs, such as acetazolamide, valproate, and carbamazepine- and lamotrigine in EA1. EA2 is managed with acetazolamide and 4-aminopyridine, a potassium channel blocker.[30]

As per the American Academy of Neurology (AAN) comprehensive systematic review summary published in 2018,[31] in episodic ataxia type 2, 4-aminopyridine at 15 mg/day probably reduces ataxia over 3 months. In ataxia of mixed etiology, riluzole probably improves ataxia over 8 weeks. For FRDA and SCA, riluzole probably improves ataxia at 1 year. For SCA3, valproic acid at 1,200 mg/day, possibly improves ataxia at 12 weeks. Thyrotropin-releasing hormone possibly improves some ataxia signs over 10 to 14 days. For ambulatory, SCA3 patients, lithium probably is not effective over 48 weeks.

Treatment of Movement Disorders

Patients with SCA often have movement disorders. SCA3 patients may exhibit Parkinsonism that responds to levodopa therapy to some extent.[32] Other medications for symptomatic benefit include anticholinergics, benzodiazepines, baclofen, and carbamazepine, as well as botulinum toxin therapy.

Treatment of Sleep Abnormalities

Sleep disorders including restless leg syndrome, rapid eye movement sleep behavior disorder, excessive daytime sleep (EDS) predominate among the nonmotor manifestations in patients with SCA.[33] These are managed with appropriate therapy as in any other condition.

Treatment of Other Motor Symptoms

Pain in SCA patients may be musculoskeletal, or secondary to dystonia and spasticity. Pain may respond to baclofen and amitriptyline. Cramps may be treated with carbamazepine and mexiletine.[34] Sulfamethoxazole-trimethoprim and baclofen have been reported to benefit spasticity and rigidity in patients with SCA3.[35] Botulinum toxin injection may also be used for the treatment of dystonia.

Treatment of Psychiatric Issues

Patients with SCA may have associated anxiety and depression. These issues should be screened for and treated appropriately in all patients with SCA.

X-Linked Cerebellar Ataxias

These disorders have an onset during childhood to early adulthood and are associated with cerebellar dysgenesis.[36] Clinically, these disorders present with ataxia, hypotonia, and cognitive dysfunction. These chiefly include oligophrenin, calcium/calmodulin-dependent serine protein kinase, Solute Carrier Family 9 Member A6, and ABC-binding cassette transporter B7. Management of these disorders is supportive and symptomatic in the absence of any specific curative therapy.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a form of late-onset cerebellar ataxia associated with intention tremors. It is a neurodegenerative disorder that occurs due to expanded cytosine guanine guanine triplet repeats in the *FMRI* gene.[37] There is no specific therapy for FXTAS. Propranolol and primidone are used for intention tremor. Memantine in one trial was shown to impart some benefit in verbal memory.[38] Bilateral deep brain stimulation in the zona incerta/VoP has recently shown to be of benefit in tremor, as well as ataxia, to some extent in recent reports.[39]

Mitochondrial Ataxias

Mitochondrial disorders affect the respiratory chain, leading to impairment of tissues highly dependent on aerobic metabolism. Neurological mitochondrial disorders include ataxia,

dementia, epilepsy, stroke-like episodes, encephalopathy, and movement disorders. Although a Cochrane review did not identify any specific therapeutic benefit, several vitamins, and other cofactors have been used in management of mitochondrial disorders.[40] As such, the treatment is largely supportive, including cataract surgery, pacing for cardiac arrythmias, and medical management of endocrinopathies, such as diabetes mellitus.

Disease Modifying Therapies

These therapies target the genetic abnormality in HA to circumvent the syndrome. FRDA has been evaluated extensively in this regard. One approach has been to increase frataxin expression by histone deacetylase inhibition. High-dose nicotinamide (2–8 g/day) has been studies in ten patients for 2 weeks. Patients in this study had increased frataxin expression. However, these were not associated with clinical improvement.[41] RG2833 is a drug in phase-I trial that leads to increased frataxin expression.[42] These limited studies support the potential role of epigenetic interventions in FRDA.

Diseases with polyglutamine repeat, such as SCA have "toxic gain of function" in the related protein expression. Hence, therapies for downregulation of pathogenic gene expression are potentially beneficial.

Gene silencing strategies administered to SCA3 transgenic mice led to motor and pathological improvement. Intracerebral injection in SCA2 transgenic mice of antisense oligonucleotides against *ATXN2* also led to improved motor function.

Recently, trehalose, a chemical chaperone protective against cell toxicity has been tested in SCA3.[43] It prevents pathological protein aggregation within cells. A trial is currently underway (ClinicalTrials.gov Identifier: NCT02147886).

Neurorehabilitation in Hereditary Ataxias

Strategies for rehabilitation in patients with HA include physical therapy, speech therapy, and occupational therapy. Physical therapy incorporates conventional physical therapy, treadmill exercises, biofeedback therapy, as well as computer-assisted training. A combination of intensive physical therapy with occupational therapy may be of most benefit.[44] In a systematic review of rehabilitation in degenerative ataxias, 17 studies met the inclusion criteria. Fifteen of these 17 studies showed an improvement in at least one outcome of gait, ataxia, balance, and function.[45] The other conclusions of this review were that greater intensity (60 minutes or more at least thrice weekly) had improved effectiveness and 4 weeks of rehabilitation was needed to see benefit on ataxia, and three for benefit on balance. Also, multifaceted programs may have greater effect. Various rehabilitation strategies may be employed, personalized to the patient. For initial ataxia stages, sport-based exercises, such as tennis and badminton, may be preferred as they challenge the coordination system. Virtual reality systems, such as XBOX games could also be used in addition.[46] In patients with moderate ataxia, physiotherapy, in addition to falls, training should be employed. In advanced ataxia, physiotherapy may not be of great benefit, but treadmill training may be of benefit. The role of speech therapy is less certain. A Cochrane review concluded that evidence so far is insufficient to support a role of speech therapy in HA.[47]

As per the AAN systematic review,[31] among nonpharmacologic options for degenerative ataxias, a 4-week inpatient rehabilitation probably improves ataxia and function. Transcranial magnetic stimulation possibly improves cerebellar motor signs at 21 days.

Genetic Counseling

Genetic counseling is the process of education of patients and family members about a genetic disorder to assist them in making medical and personal decisions. If a proband is afflicted with a specific ataxia syndrome, he or she should be provided appropriate counseling about it. For autosomal dominant cerebellar ataxias, most probands have an affected family member. Family history may be negative in the event of early parental death, late onset of the disease in the parent, incomplete penetrance of the disease, or de novo mutations. The risk to the proband's siblings is 50% if one parent is afflicted. The offspring of the proband also has a 50% risk of inheriting the pathogenic mutation. For proband with autosomal recessive cerebellar ataxia, the parents are obligate heterozygotes and are asymptomatic. The sibling has a 25% chance of being affected, 25% chance of being unaffected and 50% chance of being a carrier. The offspring of these probands are obligate heterozygotes. In X-linked ataxias, the father of a male proband is neither affected nor a carrier. The mother with an affected male relative is an obligate heterozygote. Male siblings will be affected; female siblings will be carriers.

For at-risk adult asymptomatic individuals, genetic testing should be offered in the context of genetic counseling and only after the genetic diagnosis is confirmed in the proband.[48] For at-risk asymptomatic individuals below the age of 18 years, genetic testing for a disorder that does not have treatment is not considered to be appropriate and may have debilitating personal and social implications.[48] Recent advances have made possible preimplantation genetic diagnosis (PGD).[49] Once the pathogenic mutation has been identified in an affected individual, prenatal testing, as well as PGD, is possible. In this procedure, genetic testing of ova during in vitro fertilization is conducted, and embryos free from the pathogenic mutation undergo implantation to ensure disease-free progeny.

Neuromodulation

Noninvasive cerebellar stimulation using anodal transcranial direct current stimulation (tDCS) have shown some benefit in ataxia in terms of posture and gait.[50,51] In one randomized trial, a combination of cerebellar anodal tDCS in combination with spinal cathodal tDCS has been studied in 21 patients with neurodegenerative ataxia. In this study, 2 weeks of cerebellospinal tDCS showed a significant

improvement in SARA, International Cooperative Ataxia Rating Scale, 9-Hole Peg Test, and 8-m walking time compared with sham stimulation.[52] Transcranial magnetic stimulation (TMS) has also been assessed in one randomized double-blind sham controlled trial with 74 patients with mixed ataxias. Patients undergoing TMS showed some improvement in 10-minute walk time, number of steps in 10 m walk, and standing capacities.[53]

Molecular Therapeutics

With advances in genetics, antisense oligonucleotides (ASO) have already become available as molecular therapies in a range of neurodegenerative disorders, such as nusinersen for spinal muscle atrophy, eteplirsen for Duchenne's Muscle Dystrophy and Inotersen for familial amyloid polyneuropathy. In two complimentary mouse models of SCA3, ASOs that targeted human ATXN3 were targeted. ASOs were shown to suppress ATXN3 in the Q84 model but not in the second model (Q135 cDNA).[54] Such studies are paving the way forward in the development of genetic therapies.

Conclusion

HAs are a group of neurodegenerative syndromes without any curative therapy. However, a wide range of supportive and symptomatic therapies are available which should form the backbone of management in these patients. Riluzole has the best evidence for ataxia treatment so far. However, studies that have assessed riluzole have been small and clinical benefits modest. Rehabilitation also has a role with some evidence for multiple modality rehabilitation strategies and increased intensity, neuromodulation through transcranial magnetic simulation, and transcranial direct current stimulation have a possible role and demand more exploration. Several trials are ongoing targeting treatment of HA which may yield fruitful results in the future. As in several neurological disorders, perhaps molecular therapeutics, hold the key to the treatment of hereditary ataxias in coming times.

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None declared.

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