

REVIEW

Current concepts in the treatment of hereditary ataxias

Conceitos atuais no tratamento das ataxias hereditárias

Pedro Braga-Neto^{1,2}, José Luiz Pedroso², Sheng-Han Kuo³, Marcondes C. França Junior⁴, Hélio Afonso Ghizoni Teive⁵, Orlando Graziani Povoas Barsottini²

ABSTRACT

Hereditary ataxias (HA) represents an extensive group of clinically and genetically heterogeneous neurodegenerative diseases, characterized by progressive ataxia combined with extra-cerebellar and multi-systemic involvements, including peripheral neuropathy, pyramidal signs, movement disorders, seizures, and cognitive dysfunction. There is no effective treatment for HA, and management remains supportive and symptomatic. In this review, we will focus on the symptomatic treatment of the main autosomal recessive ataxias, autosomal dominant ataxias, X-linked cerebellar ataxias and mitochondrial ataxias. We describe management for different clinical symptoms, mechanism-based approaches, rehabilitation therapy, disease modifying therapy, future clinical trials and perspectives, genetic counseling and preimplantation genetic diagnosis.

Keywords: hereditary ataxias, treatment, rehabilitation therapy, disease modifying therapy.

RESUMO

As ataxias hereditárias representam um grupo complexo de doenças neurodegenerativas, e se caracterizam por ataxia cerebelar progressiva, associada a sinais e sintomas extra-cerebelares e sistêmicos, os quais incluem: neuropatia periférica, sinais piramidais, distúrbios do movimento, convulsões e disfunção cognitiva. Não existe um tratamento efetivo para a cura das ataxias hereditárias. Até o momento os tratamentos disponíveis são apenas sintomáticos. Nesta revisão vamos abordar tratamento sintomático das principais ataxias autossômicas recessivas, ataxias autossômicas dominantes, ataxias ligadas ao X e ataxias mitocondriais. Descrevemos os diferentes sintomas, abordagens terapêuticas baseadas no mecanismo fisiopatológico, terapia de reabilitação, terapia modificadora da doença, futuros ensaios clínicos, perspectivas, níveis de evidência, aconselhamento genético e diagnóstico genético pré-implantacional.

Palavras-chave: ataxias hereditárias, tratamento, terapia de reabilitação, terapia modificadora da doença.

Ataxia is a disorder of balance and coordination and may be classified in different forms¹. Hereditary ataxias (HA) represents an extensive group of clinically and genetically heterogeneous neurodegenerative diseases, characterized by progressive ataxia combined with extra-cerebellar and multi-systemic involvements, including peripheral neuropathy, pyramidal signs, movement disorders, seizures, and cognitive dysfunction¹. HA are divided by different inheritance patterns, such as, autosomal recessive, autosomal dominant, X-linked, and mitochondrial ataxias¹. In this group of HA we can add two other forms of ataxia: hereditary episodic ataxias (EA) and congenital ataxias (CA)¹. There is no effective treatment for HA, and management remains supportive and symptomatic.

SYMPTOMATIC TREATMENT

Autosomal recessive ataxias

Autosomal recessive cerebellar ataxias are a group of heterogeneous disorders, usually caused by the loss function of key enzymes and/or functional proteins in the metabolic pathways of lysosomes and/or mitochondria^{2,3}. Therefore, several mechanism-based therapies are available to correct the underlying defective metabolic pathways. Friedreich's ataxia (FRDA) is the most common autosomal recessive cerebellar ataxia and therapy this condition has been extensively reviewed⁴.

Therefore, we will focus on the treatment for the following autosomal recessive ataxias that have known

¹Universidade Estadual do Ceará, Center of Health Sciences, Fortaleza CE, Brazil;

²Universidade Federal de São Paulo Departamento de Neurologia e Neurocirurgia, São Paulo SP, Brazil;

³Columbia University, Department of Neurology, New York NY, United States;

⁴Universidade Estadual de Campinas, Departamento de Neurologia, Campinas SP, Brazil;

⁵Universidade Federal do Paraná, Hospital de Clínicas, Serviço de Neurologia, Curitiba PR, Brazil.

Correspondence: José Luiz Pedroso; Universidade Federal de São Paulo – Neurologia; Rua Pedro de Toledo, 650; 04041-002; São Paulo SP, Brasil; E-mail: jlpedroso.neuro@gmail.com

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Table 1. Summary of main symptomatic treatment for patients with autosomal recessive hereditary ataxias.

Autosomal recessive ataxia	Symptomatic treatment	Level of evidence/ Grade of recommendation
Friedreich ataxia	ldebenone 5-20 mg/kg day or CoQ10 30 mg/kg day	Class I / A
Ataxia with vitamin E deficiency	Vitamin E supplementation	Class III / B
Abetalipoproteinemia	Vitamin E supplementation 150 mg/kg; Vitamin A; Medium-chain triglyceride supplement and/or low fat diet	Class IV / Good practice point
Refsum's disease	Diet modification to decrease intake of phytanic acid; Plasmapheresis	Class IV / Good practice point
Niemann-Pick type C	Miglustat	Class III / B
Cerebrotendinous xanthomatosis	Chenodeoxycholic acid 750 mg/day, HMG-CoaA reductors	Class III / C
Ataxia associated with CoQ10 deficiency	CoQ10 supplementation 30 mg/kg/day	Class IV / Good practice point
Glut1 deficiency syndrome	Ketogenic diet	Class III / C

mechanism-based treatment for different clinical symptoms: ataxia with vitamin E deficiency (AVED), abetalipoproteinemia, Refsum's disease, Niemann-Pick type C (NPC), cerebrotendinous xanthomatosis (CTX), ataxia associated with coenzyme Q10 (CoQ10) deficiency, and glucose transporter type 1 (Glut1) deficiency syndrome^{5,6,7,8,9,10}. Table 1 describes the main current symptomatic treatment proposed for autosomal recessive cerebellar ataxia. In addition to cerebellar ataxia, patients with these autosomal recessive ataxias usually have peripheral neuropathy (AVED, abetalipoproteinemia, Refsum's disease, and CTX), retinitis pigmentosa (AVED, abetalipoproteinemia and Refsum's disease), movement disorders (dystonia in AVED, NPC and Glut1 deficiency syndrome, and head tremor in AVED), other neurological impairment (swallowing problem in NPC, cataplexy and epilepsy in Glut1 deficiency syndrome, impaired cognition in NPC and CTX), and other systematic symptoms (steatorrhea in abetalipoproteinemia, ichthyosis and cardiac arrhythmia in Refsum's disease, and tendon xanthoma in CTX)^{3,5,6,8,10,11-14}. These disorders are relatively rare and large-scaled randomized, controlled clinical trials are usually not available. Nonetheless, successful treated cases can provide guidelines to manage these rare disorders.

Ataxia

Treatment of the underlying metabolic abnormality in autosomal recessive ataxias could usually lead to stabilization or improvement of ataxic symptoms. Twenty-four patients with AVED treated with oral vitamin E (800-1200 mg/day) for 12 months had normalization of vitamin E levels and significant improvement in cerebellar ataxia¹¹. Vitamin E was also employed to treat abetalipoproteinemia⁵. Patients were treated with large doses of oral 30-88mg/kg/day vitamin E, 10,500- 29,000 IU/day vitamin A, and 1.5-45 IU/day vitamin K for 9-15 years and had a normalized blood vitamin E level and the stabilization of ataxic symptoms⁵.

Refsum's disease is associated with excessive phytanic acid. Therefore, diet modification to decrease the intake of phytanic acid or plasma exchange has been recommended. Low phytanic acid diet (<10mg/day, no green fruits and vegetables that contain phytol) in combination with plasma exchange lead to improvement of ataxic symptoms¹². Plasma phytanic acid levels and clinical symptoms might improve only after several month of diet modification¹².

Miglustat is a glucosylceramide synthase inhibitor that reduces the accumulating glycolipids⁸. NPC patients treated with miglustat 200mg three times a day had slower deterioration of ambulatory function and disease stabilization¹⁵. Therefore, early diagnosis is crucial for NPC patients¹².

CTX is a cholesterol metabolism disorder and the treatment involves the intervention on the cholesterol biosynthetic pathway. Chenodeoxycholic acid (CDCA) 750mg/day has been used to treat CTX. A combination of CDCA and statins have been proposed, which effectively normalized the blood bile acid biochemistry but did not improve cerebellar ataxia¹⁶. LDL apheresis was also effective in reducing the cholestanol levels without dramatic effects in ataxic symptoms¹⁶.

Ataxia associated with CoQ10 deficiency can be divided into primary and secondary CoQ10 deficiency. Primary CoQ10 deficiency is caused by mutations of genes directly involving in CoQ10 synthetic pathways, such as *COQ2*, *COQ9*, *PDSS1/2*, and *ADCK3*. Secondary CoQ10 deficiency is associated with other genetic mutations such as *aprataxin* and mitochondrial genes¹⁷. High dose CoQ10 supplementation (30 mg/kg/day) has been shown to be effective to treat ataxia associated with CoQ10 deficiency¹⁸.

Finally, cerebellar ataxia associated with Glut1 deficiency syndrome can be treated with ketogenic diet¹⁰. Alternatively, modified Atkins diet with low carbohydrate and high protein and fat content has been shown to improve ataxia symptoms in patients with Glut1 deficiency.

Table 2. Main symptomatic treatment proposed for patients with autosomal dominant hereditary ataxias.

Symptomatic treatment	Hereditary ataxia type	Level of evidence / Grade of recommendation
Riluzole 100 mg/ day	SCAs and other etiologies (recessive and sporadic)	Class II / B
Varenicline 1 mg twice day	SCA3	Class II / B
Buspirone 30 mg twice daily	SCAs	Class III / C
Oral zinc 50 mg/ day	SCA3	Class I / B
Insulin-like growth factor-1	SCA3	Class III / C
Acetazolamide 250 mg – 1000 mg	EA2	Class III / C
4-aminopyridine 5 mg 3 times a day	EA2	Class II / A
Mexiletine and Carbamazepine	SCA3 (pain and cramps)	Class III / C
Botulinum toxin type A	SCA3 (dystonia and spasticity)	Class III / C

Alpha lipoic acid can facilitate glucose transport and has been proposed to treat Glut1 deficiency¹⁹.

Peripheral neuropathy

Peripheral neuropathy is frequent in autosomal recessive cerebellar ataxic disorders. Physiological studies showed improvement of motor and sensory conduction velocity in 1 AVED patient treated with vitamin E. A high dose of vitamin A and vitamin E supplementation could lead to improvement of sensory examination in abetalipoproteinemia patients. In Refsum's disease, low phytanic acid diet and plasma exchange could consistently lead to either stabilization or improvement of peripheral neuropathy and distal muscle strength in several reports⁶. Despite the inconsistency of CDCA to treat ataxia in CTX, peripheral neuropathy seems to be more responsive to CDCA treatment in both clinical and physiological assessment, at least in a subset of the patients.

Movement disorders

Dystonia and head tremor are the common clinical features for AVED⁵. Vitamin E supplementation was reported to be helpful in AVED patients with dystonia. Head tremor in AVED did not improve after vitamin E therapy¹¹. Miglustat was recommended to treat dystonic symptoms in CTX¹⁴. Ketogenic diet and modified Atkins diet were effective to treat dystonia in Glut1 deficiency¹⁰.

Generalized dystonia can be treated with trihexypenidyl and benzodiazepine whereas cervical dystonia can be treated with botulinum toxin injections in AVED and NPC¹⁴. Parkinsonism suggesting nigrostriatal dysfunction should be treated with levodopa. Propranolol and primidone should be tried in patients with postural and action tremor.

Other neurological symptoms

Visual symptoms are common in autosomal recessive cerebellar ataxias but the responses to therapy are generally

poor. Retinitis pigmentosa is common in AVED and abetalipoproteinemia¹⁵. However, retinitis pigmentosa seemed not to improve on vitamin E replacement in these disorders, and patients could develop retinitis pigmentosa while on therapy. Cataract in NPC did not improve with low phytanic acid diet and plasma exchange. Miglustat consistently improved swallowing functions in NPC patients in multiple studies²⁰. Epilepsy is very common in Glut1 deficiency syndrome and diet modifications are highly effective in either reducing or even eliminating the seizures in these patients¹⁰. Cataplexy could be seen in NPC patients also but the responses to miglustat were not impressive; instead, the conventional therapy such as tricyclic antidepressants or central stimulants should be used¹⁴. Finally, CDCA and miglustat have been reported to be beneficial to cognitive function in NPC and CTX patients, respectively.

Non-neurological symptoms

Non-neurological symptoms could also impact the quality of life in patients with autosomal recessive cerebellar ataxias and proper treatment is also important. Vitamin supplementation can improve the growth rate in the pediatric patients with abetalipoproteinemia. Medium-chain triglyceride supplement and/or low fat diet can help with steatorrhea⁵. Ichthyosis and cardiac arrhythmia are common in Refsum's disease and can be effectively treated with low phytanic acid diet and plasmapheresis⁶. Finally, the size of tendon xanthoma did not seem to regress with CDCA therapy in CTX patients.

Autosomal dominant cerebellar ataxias

There are a few randomized trials for symptoms treatment in autosomal dominant ataxias. Autosomal dominant cerebellar ataxias are divided in two main groups: spinocerebellar ataxias (SCAs) and episodic ataxias (EAs). The role for symptomatic treatment on autosomal dominant ataxias is divided into the following symptoms: ataxia, other

movement disorders, spasticity, pain and cramps. Table 2 describes the main symptomatic treatment proposed for autosomal dominant cerebellar ataxia. A specific topic on motor rehabilitation will also be discussed²¹.

Ataxia

One of the first proposed treatments for cerebellar symptoms is riluzole. This drug acts opening small-conductance potassium-channels, exerting an important regulatory effect on the firing rate of neurons on deep cerebellar nuclei. As a result, riluzole may reduce neuronal hyperexcitability. A study evaluated 40 patients with different cerebellar ataxias and the number of patients with a 5-point ICARS decrease was significantly higher in the riluzole group (100 mg/day) comparing to placebo. Although these findings may indicate potential effectiveness, experience of many ataxic clinics is less promising²². Recently, Romano et al. observed a decrease in SARA scale in patients with different cerebellar ataxias using riluzole, but longer studies and disease-specific trials are needed to confirm whether these findings can be applied in clinical practice²³.

Recently, a phase 2 study assessed the safety and efficacy of lithium carbonate (0.5-0.8 milliequivalents per liter) in patients with SCA3. Mean Neurological Examination Score for the Assessment of Spinocerebellar Ataxia (NESSCA) after 48 months did not differ between groups as well as the SARA scores²⁴.

A randomized double-blind study evaluated the effect and safety of oral zinc (50mg) supplementation for 36 patients with SCA2. A mild decrease in SARA scores for gait, posture, stance and alternating hand movements and a reduced of saccadic latency were observed. The treatment was also safe and well tolerated²⁵.

Varenicline was also studied. This drug is a partial $\alpha 4\beta 2$ agonist neuronal nicotinic acetylcholine receptor used for smoking cessation. A trend toward improvement in SARA total score in the varenicline group of SCA3 patients was observed. Considerable side effects were detected with nausea the most common one²⁶.

The prominent serotonergic innervation of the cerebellum could be a promising therapeutic for the symptomatic of ataxia. It is well known that a deficit of serotonin has been proposed as the neurochemical basis of several ataxias. The use of buspirone for the treatment of ataxia has been evaluated in several studies. Buspirone was not shown to be superior to placebo in the treatment²⁷. Moreover, a recent experimental mouse model study of SCA3 described that citalopram, another a selective serotonin reuptake inhibitor, significantly reduced ataxin 3 neuronal inclusions and astrogliosis, rescued diminished body weight and strikingly ameliorated motor symptoms, becoming a promising therapeutic target for SCA3 patients.

The insulin-like growth factor-1 (IGF-1) performs important neuromodulatory functions in the central nervous system.

Taking this theory in mind, a 2-year prospective clinical trial was conducted in patients with SCA3 and SCA7 with subcutaneous IGF-1 treatment. The treatment with 50 $\mu\text{g}/\text{kg}/\text{twice}$ a day sc of IGF-1 resulted in improved SARA of SCA3 patients after 8 months of treatment. Unfortunately, as this study was uncontrolled, it could not exclude a placebo effect²⁸.

Besides SCAs, episodic ataxias (EA) are a diverse group of autosomal dominant cerebellar ataxias characterized by attacks of imbalance and incoordination. Several different drugs have been reported to improve symptoms of EA1 and EA2. Carbamazepine, acetazolamide, valproic acid and lamotrigine have been reported to be effective for EA1. Acetazolamide and the potassium channel blocker 4-aminopyridine seems to be effective in EA2^{29,30}.

Other movement disorders

Movement disorders are quite common in SCAs and may be a prominent symptom. Some patients with SCA3 may have a levodopa-responsive-Parkinsonism^{31,32}. Other drugs should be tried: anticholinergics, benzodiazepines, baclofen and carbamazepine. Botulinum toxin injection may be used in focal or segmental cases of dystonia³¹.

Sleep disorders

Sleep disorders have already been recognized as one of the most important non-motor manifestations in SCAs. The main described sleep disorders includes: restless leg syndrome (RLS), REM sleep behavior disorder (RBD), excessive daytime sleep (EDS), insomnia and sleep apnea³³. The general recommendation of pharmacological and non-pharmacological treatment should be addressed as in other diseases.

Pain, cramps and spasticity

Symptomatic treatment for pain, cramps and spasticity are not well studied in patients with SCA. Pain is more frequent musculoskeletal, but in a smaller subset may be related to dystonia or neuropathy. These patients may have chronic daily pain, specially evolving back and legs³⁴. Improvement of pain may be obtained with usual doses of baclofen, cyclobenzaprine and amitriptyline. Carbamazepine and mexiletine lead to improvements in intensity and frequency of cramps. Sulfamethoxazole-trimethoprim and baclofen were also described to ameliorate spasticity and rigidity in patients with SCA3³⁵. Botulinum toxin injection may improve spasticity in patients with SCAs³¹.

Psychiatric symptoms

Psychiatric symptoms are very common in SCA. A recent systematic review described a great number of depressive and anxiety symptoms with important difference of the profile according to the subtype of SCA. A previous cohort study with 526 patients described worse quality of life in patients with depressive symptoms. As a result, specific approaches with psychotherapy and antidepressants should be performed in patients with SCA.

X-linked cerebellar ataxias (XLCA)

X-Linked Cerebellar Ataxias (XLCA) are a heterogeneous group of genetic disorders with onset in early childhood or adulthood. The “hallmarks” are cerebellar dysgenesis associated with imbalances on the X chromosome or gene mutations. The neurological features of XLCA include hypotonia, developmental delay, intellectual impairment and ataxia³⁶.

The best characterized phenotypical forms are X-linked syndromes with associated cerebellar hypoplasia due to *OPHN* (X-linked mental retardation with cerebellar hypoplasia and distinctive facial appearance), *CASK* (cognitive deficiency, microcephaly, hypotonia and optic nerve hypoplasia), *SLC9A6* (Syndromic X-linked mental retardation, Christianson type gene mutations) and *ABCB7* (X-linked sideroblastic anemia and ataxia)³⁷.

There are no specific or curative treatments for XLCA and the optimal management is directed to provide better quality of life with comprehensive rehabilitation program, including interdisciplinary care such as occupational and physical therapy, for behavioral and cognitive impairment and motor incoordination. Speech therapy may benefit patients with dysarthria and dysphagia³⁷.

Fragile X-associated Tremor/Ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder characterized by adult-onset progressive intention tremor and gait ataxia. It affects more than 33% of male and 10% of female carriers of expanded CGG triplets alleles in the premutation range (50-200 repeats) of the *FMRI* gene³⁸.

There are no effective therapies for the treatment of FXTAS. There is one reported clinical trial for FXTAS treatment utilized memantine and the results suggested that this drug may have beneficial effects on verbal memory³⁹. Primidone and propranolol may improve the intention tremor and selective serotonin and selective norepinephrine reuptake inhibitors are effective for anxiety and depression. Recently, deep brain stimulation (DBS) has shown favorable outcome for tremor and in few cases for ataxia, especially bilateral DBS in VoP/zona incerta^{40,41}.

Mitochondrial ataxias

Mitochondrial diseases are clinically heterogeneous disorders resulted from dysfunction of the mitochondrial respiratory chain, which is the final common pathway for aerobic metabolism. As a result, tissues that are highly dependent on aerobic metabolism are preferentially involved in mitochondrial disorder. Regarding nervous system, the most common manifestations are encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, spasticity, chorea and myopathy⁴². One of the most common manifestations of mitochondrial diseases is ataxia.

The management of mitochondrial diseases is usually supportive which includes: medications for diabetes mellitus, cardiac pacing, ptosis correction, intraocular lens replacement for cataracts, cochlear implantation for sensorineural

hearing loss and symptomatic treatment for spasticity, chorea and epilepsy⁴³. A great number of vitamins and co-factors have been used in individuals with mitochondrial disorders, although a recent Cochrane systematic review did not identify clear evidence supporting the use of any intervention in mitochondrial disorders⁴³. Some patients may have subjective benefit on treatment with CoQ10. As previously mentioned, CoQ10 and idebenone is specifically indicated in persons with defects of CoQ10 biosynthesis and FRDA.

REHABILITATION THERAPY

Rehabilitation therapy is not well studied in hereditary ataxias. Table 3 describes the main rehabilitation strategies in hereditary ataxias. Physical therapy, speech therapy and occupational therapy are often recommended in patients with SCA in order to minimize dependency and decrease secondary motor complications. SCA patients have significant static and dynamic balance impairment, high risk of fall with a great impact in the ability to function⁴³. A recent systematic review evaluated this approach in patients with hereditary ataxias. Physical therapy may lead to improvement in ataxia symptoms and daily life functions; occupational therapy may improve global function status and diminish symptoms of depression. Conventional physical therapy exercises, treadmill training, relaxation and biofeedback therapy, computer-assisted training and supervised sports are one of the intervention approaches. Intensive rehabilitation therapy combining physical therapy and occupational may provide the best results⁴⁴. An intensive coordinative therapy with 3 sessions of 1 hour per week has been described as effective plan⁴⁵. Another recent review considered different training strategies for spinocerebellar ataxia patients and individually tailored according to each individual's ataxia type, disease stage, and personal training preferences. For very early stages of ataxia, sportive exercises might be selected which place high challenges to the coordination system, for example, table tennis, squash, or badminton. Virtual reality rehabilitation systems like XBOX Kinect games or Wii games could be used as complementary strategies. In mild-to-moderate ataxia stages, a coordinative physiotherapy program may include the training of secure fall strategies in addition of training to avoid falls. Virtual reality systems should also used. In advanced ataxia stages, there is no clear benefit of physiotherapy approaches. However, treadmill training with potential weight support may be helpful to increase walking capabilities. Virtual reality systems is of less clear benefit⁴⁶. More recently, another approach for SCA patients have been studied using leg cycling therapy. A 4-week cycling regimen could normalize the modulation of reciprocal inhibition and functional performance in individuals with SCA⁴⁷.

Another study evaluated the effect of inpatient rehabilitation of patient with FRDA. A period of inpatient rehabilitation

Table 3. Rehabilitation strategies for hereditary ataxias.

Rehabilitation therapy	Level of evidence / Grade of recommendation
Conventional physical therapy	Class II / B
Treadmill training	Class III / C
Relaxation and biofeedback training	Class III / C
Videogames/computer assisted training	Class III / C
Supervised sports / endurance training	Class III / C
Occupational therapy	Class III / C
Speech and language therapy	No evidence

appears to reverse or halt the downward decline in function for people with FRDA identified as requiring rehabilitation. Intervention comprised strength and stretching exercises, education, functional and balance retraining, aquatic physiotherapy, and development of a home or community program⁴⁸. Another potential strategy recently reported for FRDA is a medically supervised endurance training program to increase aerobic work capacity and promote weight loss.

On the other hand, there is insufficient information for speech therapy. A recent Cochrane Review concluded that there is insufficient evidence from either randomized control trials or observational studies to determine the effectiveness of any treatment for speech disorder in any of the hereditary ataxia syndromes. Nevertheless, speech therapy should go beyond assessment. Clinical guidelines for management of speech, communication and swallowing should be performed⁴⁹.

DISEASE MODIFYING THERAPIES

The past few years witnessed remarkable advances in the identification of genes and mechanisms underlying inherited forms of ataxia. In addition, techniques capable of interfering with gene expression are now available, such as RNA interference, oligo antisense nucleotides, gene therapy and epigenetic-based therapy. Regarding ataxias, no curative treatment has emerged, but there are clinical studies currently underway using this kind of approaches.

FRDA is probably the single disease within this group with the larger number of clinical trials. Most of these studies investigated drugs with symptomatic effects, but there are a few using disease-modifying agents. Experimental data indicates that inhibition of histone deacetylase corrects this pathological heterochromatinisation and leads to increased expression of frataxin (*FXN*)⁵⁰. In this scenario, two agents with such epigenetic effects were recently tested in

patients with FRDA^{51,52}. Libri et al. performed an exploratory study with 10 patients with FRDA followed over 8 weeks to investigate the effects of high dose nicotinamide (2-8g/day). They showed an increase in *FXN* expression, but no significant clinical change⁵¹. Soragni et al. assessed the safety and efficacy of RG2833 (drug in development) in a neuronal cell culture model and in a clinical cohort of 20 patients (Phase I study). Authors found dose-dependent increased expression of *FXN* and no significant safety issues after single doses of the drug. This was a proof-concept study and no clinical parameter was reported. These results suggest that epigenetic approaches might prove useful for FRDA, but further studies are necessary.

Most autosomal dominant ataxias are related to ‘toxic gain of function’ of related proteins. Therefore, therapeutic strategies capable of down regulating the expression of the mutant genes look promising⁵³. This is particularly evident for the polyglutamine diseases (SCA1, 2, 3, 6 and 7). Preclinical studies have shown that gene silencing using RNA interference delivered directly to the cerebellum of SCA3 transgenic mice resulted in improvement of motor behavior and neuropathological abnormalities⁵⁴. Scoles et al. showed that intracerebroventricular injections of antisense oligonucleotides against *ATXN2* improved motor function and preserved the firing pattern of Purkinje cells in a transgenic mouse model of SCA2⁵⁵. These reports indicate that it is possible to selectively “turn off” mutant alleles (with no modification in the expression of the normal allele) and this can attenuate neurodegeneration. In the near future, we shall see clinical studies using these gene silencing techniques, but some important aspects, such as the best strategy to deliver the agents to the CNS and the adequate dosing scheme, still need to be addressed.

Recently, trehalose (Cabaletta®) drug has been tested in SCA3. This is a chemical chaperone that protects against pathological processes in cells. It has been shown to prevent pathological aggregation of proteins within cells in several diseases associated with abnormal cellular-protein aggregation. A current trial has started in 2014 (ClinicalTrials.gov Identifier: NCT02147886).

FUTURE CLINICAL TRIALS AND PERSPECTIVES

The remarkable advances in the understanding of inherited ataxias and the appearance of molecular tools capable of interfering with gene expression (RNAi, antisense oligonucleotides, HDAC inhibitors) turn the scenario more optimistic for the next years. Some phase I clinical trials using these targeted therapies have been already completed (mostly for FRDA) and others are about to begin. We shall see an increase in the number of clinical trials for ataxias in the near future. This is certainly positive, but it also demands clinical researchers to identify the best outcome measures and the more appropriate experimental designs

in order to make the studies faster, cheaper and more sensitive⁵⁶. Most ataxias are very slowly progressive disorders, so that clinical scales appear not to be sensitive enough to detect longitudinal changes in the short term. Other putative biomarkers must be identified and validated to speed up the therapeutic trials for ataxias.

These therapies will hopefully slow down disease progression, but those subjects in the late stages of the disease might notice no clinical improvement because neurodegeneration had already taken place. Therefore, research efforts should also focus on regenerative therapies, such as the use of stem cells. Early reports raised concerns about the safety of stem cells in ataxic subjects because of a patient with ataxia-telangiectasia who developed a multifocal glioneural tumor after intracerebellar injections of human fetal neural stem cells⁵⁷. Several studies are now looking at the effects of umbilical mesenchymal stem cells as neuroprotective agents, rather than neural stem cells.

GENETIC COUNSELING AND PREIMPLANTATION GENETIC DIAGNOSIS

Genetic counseling is necessary if parents or close relatives have an inherited disease. Considering the SCAs, the risk for a genetic transmission from affected parents is 50%. Therefore, many couples with an affected parent decide not having children. The last two decades were marked for the developmental of the preimplantation genetic diagnosis

(PGD) which consist in testing the fertilized ova (*in vitro* fertilization) for the affected gene mutation, and implanting of selected healthy embryos ensuring that the pathogenic mutation from parents will be not transmitted to children⁵⁸.

PDG has been used for neurological conditions with several forms of inheritance, including Huntington's disease, spinal-muscular atrophy, myotonic dystrophy, X-linked disorders, and mitochondrial or chromosomal disorders^{58,59}. Clinical applications of PDG for SCA have already been performed with successful results⁶⁰.

Several societies for reproductive health have proposed that counseling of family members must include PGD in order to prevent transmission of a genetic mutation to future generations as part of the standard care^{58,59}.

FINAL REMARKS

The hereditary ataxias are a group of neurodegenerative diseases for which no curative treatment is available. On the other hand, several symptomatic options used to extra-cerebellar signs and rehabilitation therapy may promote some benefit. Furthermore, neurologists must bear in mind that some types of hereditary ataxias such as vitamin E and CoQ10 deficiency are treatable. Finally, PGD may work as a promising preventive option for hereditary ataxias, particularly in autosomal dominant forms. Future trials with disease modifying drugs and cell therapies are expected in the following years.

REFERENCES

1. Teive HA, Ashizawa T. Primary and secondary ataxias. *Curr Opin Neurol*. 2015;28:413-22. doi:10.1097/WCO.0000000000000227
2. Anheim M, Tranchant C, Koenig M. The autosomal recessive cerebellar ataxias. *N Engl J Med*. 2012;366(7):636-46. doi:10.1056/NEJMra1006610
3. Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. *Lancet Neurol*. 2007;6(3):245-57. doi:10.1016/S1474-4422(07)70054-6
4. Abrahão A, Pedroso JL, Braga-Neto P, Bor-Seng-Shu E, Carvalho Aguiar P, Barsottini OG. Milestones in Friedreich ataxia: more than a century and still learning. *Neurogenetics*. 2015;16(3):151-60. doi: 10.1007/s10048-015-0439-z
5. Hentati F, El-Euch G, Bouhail Y, Amouri R. Ataxia with vitamin E deficiency and abetalipoproteinemia. *Handb Clin Neurol*. 2012;103:295-305. doi:10.1016/B978-0-444-51892-7.00018-8
6. Weinstein R. Phytanic acid storage disease (Refsum's disease): clinical characteristics, pathophysiology and the role of therapeutic apheresis in its management. *J Clin Apher*. 1999;14(4):181-4. doi:10.1002/(SICI)1098-1101(1999)14:4<181::AID-JCA5>3.0.CO;2-Z
7. Mengel E, Klünemann HH, Lourenço CM, Hendriksz CJ, Sedel F, Walterfang M, et al. Niemann-Pick disease type C symptomatology: an expert-based clinical description. *Orphanet J Rare Dis*. 2013;8(1):166. doi:10.1186/1750-1172-8-166
8. Björkhem I. Cerebrotendinous xanthomatosis. *Curr Opin Lipidol*. 2013;24(4):283-7. doi:10.1097/MOL.0b013e328362df13
9. Emmanuele V, López LC, Berardo A, Naini A, Tadesse S, Wen B et al. Heterogeneity of coenzyme Q10 deficiency: patient study and literature review. *Arch Neurol*. 2012;69(8):978-83. doi:10.1001/archneurol.2012.206
10. Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T, Engelen BG et al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. *Brain*. 2010;133(3):655-70. doi:10.1093/brain/awp336
11. Gabsi S, Gouider-Khouja N, Belal S, Fki M, Kefi M, Turki I et al. Effect of vitamin E supplementation in patients with ataxia with vitamin E deficiency. *Eur J Neurol*. 2001;8(5):477-81. doi:10.1046/j.1468-1331.2001.00273.x
12. Jansen GA, Waterham HR, Wanders RJA. Molecular basis of Refsum disease: sequence variations in phytanoyl-CoA hydroxylase (PHYH) and the PTS2 receptor (PEX7). *Hum Mutat*. 2004;23(3):209-18. doi:10.1002/humu.10315
13. Verrips A, Hoefsloot LH, Steenbergen GC, Theelen JP, Wevers RA, Gabreëls FJ et al. Clinical and molecular genetic characteristics of patients with cerebrotendinous xanthomatosis. *Brain*. 2000;123(5):908-19. doi:10.1093/brain/123.5.908
14. Patterson MC, Hendriksz CJ, Walterfang M, Sedel F, Vanier MT, Wijburg F et al. Recommendations for the diagnosis and management of Niemann-Pick disease type C: an update. *Mol Genet Metab*. 2012;106(3):330-44. doi:10.1016/j.ymgme.2012.03.012
15. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE, Miglustat for treatment of Niemann-Pick C disease: a randomised

- controlled study. *Lancet Neurol.* 2007;6(9):765-72. doi:10.1016/S1474-4422(07)70194-1
16. Verriss A, Wevers RA, Van Engelen BG, Keyser A, Wolthers BG, Barkhof F et al. Effect of simvastatin in addition to chenodeoxycholic acid in patients with cerebrotendinous xanthomatosis. *Metabolism Clin Exp.* 1999;48(2):233-8. doi:10.1016/S0026-0495(99)90040-9
 17. Quinzii CM, Hirano M. Primary and secondary CoQ(10) deficiencies in humans. *Biofactors.* 2011;37(5):361-5. doi:10.1002/biof.155
 18. Pineda M, Montero R, Aracil A, O'Callaghan MM, Mas A, Espinos C et al. Coenzyme Q(10)-responsive ataxia: 2-year-treatment follow-up. *Mov Disord.* 2010;25(9):1262-8. doi:10.1002/mds.23129
 19. Pascual JM, Wang D, Lecumberri B, Yang H, Mao X, Yang R et al. GLUT1 deficiency and other glucose transporter diseases. *Eur J Endocrinol.* 2004;150(5):627-33. doi:10.1530/eje.0.1500627
 20. Fecarotta S, Amitrano M, Romano A, Della Casa R, Bruschini D, Astarita L et al. The videofluoroscopic swallowing study shows a sustained improvement of dysphagia in children with Niemann-Pick disease type C after therapy with miglustat. *Am J Med Genet A.* 2011;155A(3):540-7. doi:10.1002/ajmg.a.33847
 21. Ilg W, Bastian AJ, Boesch S, Burciu RG, Celnik P, Claaßen J et al. Consensus paper: management of degenerative cerebellar disorders. *Cerebellum.* 2014;13(2):248-68. doi:10.1007/s12311-013-0531-6
 22. Ristori G, Romano S, Visconti A, Cannoni S, Spadaro M, Frontali M et al. Riluzole in cerebellar ataxia: a randomized, double-blind, placebo-controlled pilot trial. *Neurology.* 2010;74(10):839-45. doi:10.1212/WNL.0b013e3181d31e23
 23. Romano S, Coarelli G, Marcotulli C, Leonardi L, Piccolo F, Spadaro M et al. Riluzole in patients with hereditary cerebellar ataxia: a randomized, double-blind, placebo-controlled trial. *Lancet Neurol.* 2015;14(10):985-91. doi:10.1016/S1474-4422(15)00201-X
 24. Saute JA, Castilhos RM, Monte TL, Schumacher-Schuh AF, Donis KC, D'Ávila R et al. A randomized, phase 2 clinical trial of lithium carbonate in Machado-Joseph disease. *Mov Disord.* 2014;29(4):568-73. doi:10.1002/mds.25803
 25. Velázquez-Pérez L, Rodríguez-Chanfrou J, García-Rodríguez JC, Sánchez-Cruz G, Aguilera-Rodríguez R, Rodríguez-Labrada R et al. Oral zinc sulphate supplementation for six months in SCA2 patients: a randomized, double-blind, placebo-controlled trial. *Neurochem Res.* 2011;36(10):1793-800. doi:10.1007/s11064-011-0496-0
 26. Zesiewicz TA, Greenstein PE, Sullivan KL, Wecker L, Miller A, Jahan I et al. A randomized trial of varenicline (Chantix) for the treatment of spinocerebellar ataxia type 3. *Neurology.* 2012;78(8):545-50. doi:10.1212/WNL.0b013e318247cc7a
 27. Assadi M, Campellone JV, Janson CG, Veloski JJ, Schwartzman RJ, Leone P. Treatment of spinocerebellar ataxia with buspirone. *J Neurol Sci.* 2007;260(1-2):143-6. doi:10.1016/j.jns.2007.04.019
 28. Arpa J, Sanz-Gallego I, Medina-Báez J, Portela LV, Jardim LB, Torres-Aleman I et al. Subcutaneous insulin-like growth factor-1 treatment in spinocerebellar ataxias: an open label clinical trial. *Mov Disord.* 2011;26(2):358-9. doi:10.1002/mds.23423
 29. Ramirez-Zamora A, Zeigler W, Desai N, Biller J. Treatable causes of cerebellar ataxia. *Mov Disord.* 2015;30(5):614-23. doi:10.1002/mds.26158
 30. Strupp M, Kalla R, Claassen J, Adrion C, Mansmann U, Klopstock T et al. A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. *Neurology.* 2011;77(3):269-75. doi:10.1212/WNL.0b013e318225ab07
 31. D'Abreu A, França Junior MC, Paulson HL, Lopes-Cendes I. Caring for Machado-Joseph disease: current understanding and how to help patients. *Parkinsonism Relat Disord.* 2010;16(1):2-7. doi:10.1016/j.parkreldis.2009.08.012
 32. Shan DE, Soong BW, Sun CM, Lee SJ, Liao KK, Liu RS. Spinocerebellar ataxia type 2 presenting as familial levodopa-responsive parkinsonism. *Ann Neurol.* 2001;50(6):812-5. doi:10.1002/ana.10055
 33. Pedroso JL, Braga-Neto P, Felício AC, Aquino CC, Prado LB, Prado GF et al. Sleep disorders in cerebellar ataxias. *Arq Neuropsiquiatr.* 2011;69(2A):253-7. doi:10.1590/S0004-282X2011000200021
 34. Kanai K, Kuwabara S, Arai K, Sung JY, Ogawara K, Hattori T. Muscle cramp in Machado-Joseph disease: altered motor axonal excitability properties and mexiletine treatment. *Brain.* 2003;126(4):965-73. doi:10.1093/brain/awg073
 35. Schulte T, Mattern R, Berger K, Szymanski S, Klotz P, Kraus PH et al. Double-blind crossover trial of trimethoprim-sulfamethoxazole in spinocerebellar ataxia type 3/Machado-Joseph disease. *Arch Neurol.* 2001;58(9):1451-7. doi:10.1001/archneur.58.9.1451
 36. Zanni G, Bertini ES. X-linked disorders with cerebellar dysgenesis. *Orphanet J Rare Dis.* 2011;6(1):24. doi:10.1186/1750-1172-6-24
 37. Muzar Z, Lozano R. Current research, diagnosis, and treatment of fragile X-associated tremor/ataxia syndrome. *Intractable Rare Dis Res.* 2014;3(4):101-9. doi:10.5582/irdr.2014.01029
 38. Yang JC, Niu YQ, Simon C, Seritan AL, Chen L, Schneider A et al. Memantine effects on verbal memory in fragile X-associated tremor/ataxia syndrome (FXTAS): a double-blind brain potential study. *Neuropsychopharmacology.* 2014;39(12):2760-8. doi:10.1038/npp.2014.12
 39. Hagerman J, Jamie SP, Ortigas M, Olichney J, Frysinger R, Harrison M et al. Case Series: Deep brain stimulation in patients with FXTAS. *Brain Disord Ther.* 2012;1:2. doi:10.4172/2168-975X.1000104
 40. Santos Ghilardi MG, Cury RG, Ângelos JS, Barbosa DC, Barbosa ER, Teixeira MJ, et al. Long-term improvement of tremor and ataxia after bilateral DBS of VoP/zona incerta in FXTAS. *Neurology.* 2015;84(18):1904-6. doi:10.1212/WNL.0000000000001553
 41. Chinnery PF. Mitochondrial disorders overview. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amernia A, Bean LJH et al., editors. *GeneReviews®*. Seattle: University of Washington, Seattle; 1993-2015 [cited 2015 Nov 17]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1224/>
 42. Pfeffer G, Majamaa K, Turnbull DM, Thorburn D, Chinnery PF. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev.* 2012;4:CD004426. doi:10.1002/14651858.CD004426.pub3
 43. Aizawa CY, Pedroso JL, Braga-Neto P, Callegari MR, Barsottini OG. Patients with autosomal dominant spinocerebellar ataxia have more risk of falls, important balance impairment, and decreased ability to function. *Arq Neuropsiquiatr.* 2013;71(8):508-11. doi:10.1590/0004-282X20130094
 44. Fonteyn EM, Keus SH, Verstappen CC, Schöls L, Groot LJ, Warrenburg BP. The effectiveness of allied health care in patients with ataxia: a systematic review. *J Neurol.* 2014;261:251-8. doi:10.1007/s00415-013-6910-6
 45. Ilg W, Synofzik M, Brötz D, Burkard S, Giese MA, Schöls L. Intensive coordinative training improves motor performance in degenerative cerebellar disease. *Neurology.* 2009;73(22):1823-30. doi:10.1212/WNL.0b013e3181c33adf
 46. Synofzik M, Ilg W. Motor training in degenerative spinocerebellar disease: ataxia-specific improvements by intensive physiotherapy and exergames. *Biomed Res Int.* 2014;2014:ID583507. doi:10.1155/2014/583507
 47. Chang YJ, Chou CC, Huang WT, Lu CS, Wong AM, Hsu MJ. Cycling regimen induces spinal circuitry plasticity and improves leg muscle coordination in individuals with spinocerebellar ataxia. *Arch Phys Med Rehabil.* 2015;96(6):1006-13. doi:10.1016/j.apmr.2015.01.021
 48. Milne SC, Campagna EJ, Corben LA, Delatycki MB, Teo K, Churchyard AJ et al. Retrospective study of the effects of inpatient rehabilitation on improving and maintaining functional independence in people with Friedreich ataxia. *Arch Phys Med Rehabil.* 2012;93(10):1860-3. doi:10.1016/j.apmr.2012.03.026
 49. Schalling E, Hartelius L. Speech in spinocerebellar ataxia. *Brain Lang.* 2013;127(3):317-22. doi:10.1016/j.bandl.2013.10.002

50. Chan PK, Torres R, Yandim C, Law PP, Khadayate S, Mauri M et al. Heterochromatinization induced by GAA-repeat hyperexpansion in Friedreich's ataxia can be reduced upon HDAC inhibition by vitamin B3. *Hum Mol Genet.* 2013;22(13):2662-75. doi:10.1093/hmg/ddt115
51. Libri V, Yandim C, Athanasopoulos S, Loyse N, Natisvili T, Law PP et al. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study. *Lancet.* 2014;384(9942):504-13. doi:10.1016/S0140-6736(14)60382-2
52. Soragni E, Miao W, Iudicello M, Jacoby D, De Mercanti S, Clerico M et al. Epigenetic therapy for Friedreich ataxia. *Ann Neurol.* 2014;76(4):489-508. doi:10.1002/ana.24260
53. Underwood BR, Rubinsztein DC. Spinocerebellar ataxias caused by polyglutamine expansions: a review of therapeutic strategies. *Cerebellum.* 2008;7(2):215-21. doi:10.1007/s12311-008-0026-z
54. Nóbrega C, Nascimento-Ferreira I, Onofre I, Albuquerque D, Hirai H, Déglon N et al. Silencing mutant ataxin-3 rescues motor deficits and neuropathology in Machado-Joseph disease transgenic mice. *PLoS One.* 2013;8(1):e52396. doi:10.1371/journal.pone.0052396
55. Scoles D, Hung G, Pflieger L, Thai K, Bennett F, Pulst S. Treatment Of Spinocerebellar Ataxia Type 2 (SCA2) with MOE Antisense Oligonucleotides. *Neurology.* 2015;82(10 Suppl):S47.006.
56. Saute JA, Rieder CR, Castilhos RM, Monte TL, Schumacher-Schuh AF, Donis KC et al. Planning future clinical trials in Machado Joseph disease: lessons from a phase 2 trial. *J Neurol Sci.* 2015;358(1-2):72-6. doi:10.1016/j.jns.2015.08.019
57. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L et al. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Med.* 2009;6(2):e1000029. doi:10.1371/journal.pmed.1000029
58. Tur-Kaspa I, Jeelani R, Doraiswamy PM. Preimplantation genetic diagnosis for inherited neurological disorders. *Nat Rev Neurol.* 2014;10(7):417-24. doi:10.1038/nrneurol.2014.84
59. Bushara K. We cannot cure ataxia, we can only eradicate it. *JAMA Neurol.* 2013;70(9):1099. doi:10.1001/jamaneurol.2013.3026
60. Drüsedau M, Dreesen JC, De Die-Smulders C, Hardy K, Bras M, Dumoulin JC et al. Preimplantation genetic diagnosis of spinocerebellar ataxia 3 by (CAG)(n) repeat detection. *Mol Hum Reprod.* 2004;10(1):71-5. doi:10.1093/molehr/gah008