Article published online: 2023-09-06

DOI: 10.1590/0004-282X20160038

REVIEW

Current concepts in the treatment of hereditary ataxias

Conceitos atuais no tratamento das ataxias hereditárias

Pedro Braga-Neto[1,2], José Luiz Pedroso[2], Sheng-Han Kuo[3], Marcondes C. França Junior[4], Hélio Afonso Ghizoni Teive[5], Orlando Graziani Povoas Barsottini[2]

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 forms[1]. 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[1]. HA are divided by different inheritance patterns, such as, autosomal recessive, autosomal dominant, X-linked, and mitochondrial ataxias[1]. 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 reviewed[4].

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

[1]Universidade Estadual do Ceará, Center of Health Sciences, Fortaleza CE, Brazil;
[2]Universidade Federal de São Paulo Departmento de Neurologia e Neurocirurgia, São Paulo SP, Brazil;
[3]Columbia University, Department of Neurology, New York NY, United States;
[4]Universidade Estadual de Campinas, Departmento de Neurologia, Campinas SP, Brazil;
[5]Universidade Federal do Paraná, Hospital de Clinicas, 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

Conflict of interest: There is no conflict of interest to declare.

Received 15 December 2015; Accepted 04 January 2016.

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	Idebenone 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
Abetalipropoteinemia	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 ataxia[11]. Vitamin E was also employed to treat abetalipoproteinemia[5]. 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 symptoms[5].

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 symptoms[12]. Plasma phytanic acid levels and clinical symptoms might improve only after several month of diet modification[12].

Miglustat is a glucosylceramide synthase inhibitor that reduces the accumulating glycolipids[8]. NPC patients treated with miglustat 200mg three times a day had slower deterioration of ambulatory function and disease stabilization[15]. Therefore, early diagnosis is crucial for NPC patients[12].

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 ataxia[16]. LDL apheresis was also effective in reducing the cholestanol levels without dramatic effects in ataxic symptoms[16].

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 *apratаxin* and mitochondrial genes[17]. High dose CoQ10 supplementation (30 mg/kg/day) has been shown to be effective to treat ataxia associated with CoQ10 deficiency[18].

Finally, cerebellar ataxia associated with Glut1 deficiency syndrome can be treated with ketogenic diet[10]. 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 zync 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 deficiency[19].

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 reports[6]. 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 AVED[5]. Vitamin E supplementation was reported to be helpful in AVED patients with dystonia. Head tremor in AVED did not improve after vitamin E therapy[11]. Miglustat was recommended to treat dystonic symptoms in CTX[14]. Ketogenic diet and modified Atkins diet were effective to treat dystonia in Glut1 deficiency[10].

Generalized dystonia can be treated with trihexyphenidyl and benzodiazepine whereas cervical dystonia can be treated with botulinum toxin injections in AVED and NPC[14]. 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 abetalipoproteinemia[15]. 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 studies[20]. Epilepsy is very common in Glut1 deficiency syndrome and diet modifications are highly effective in either reducing or even eliminating the seizures in these patients[10]. 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 used[14]. 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 abetaliproproteinemia. Medium-chain triglyceride supplement and/or low fat diet can help with steatorrhea[5]. Ichthyosis and cardiac arrhythmia are common in Refsum's disease and can be effectively treated with low phytanic acid diet and plasmapheresis[6]. 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 discussed[21].

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 promising[22]. 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 practice[23].

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 scores[24].

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 tolerated[25].

Varenicline was also studied. This drug is a partial $\alpha4\beta2$ 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 one[26].

The prominent serotoninergic 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 treatment[27]. 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 μg/kg/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 no exclude a placebo effect[28].

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 dystonia[31].

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 apnea[33]. 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 legs[34]. 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 SCA3[35]. Botulinum toxin injection may improve spasticity in patients with SCAs[31].

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 ataxia[36].

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 dysphagia[37].

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 *FMR1* gene[38].

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 memory[39]. 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].

Mithocondrial 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 myopathy[42]. 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 epilepsy[43]. 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 disorders[43]. 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 function[43]. 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 results[44]. An intensive coordinative therapy with 3 sessions of 1hour per week has been described as effective plan[45]. 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 use 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 benefit[46]. 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 SCA[47].

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 program[48]. 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 performed[49].

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 change[51]. 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 promising[53]. 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 abnormalities[54]. 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 SCA2[55]. 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 sensitive[56]. 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 cells[57]. 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 children[58].

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 results[60].

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.

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