Current concepts in the treatment of hereditary ataxias
Conceitos atuais no tratamento das ataxias hereditárias

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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 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.

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 mitochondria23. 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 mechanisms: Friedreich’s ataxia (FRDA), Ataxia Telangiectasia (AT), Ataxia with Ocular Peculiarities (AOP), Ataxia with Vestibular Ocular Reflexes (AVOR), Ataxia with Mental Retardation (AMR), and Ataxia with Retinitis Pigmentosa (ARP).
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. 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, and head tremor in AVED), other neurological impairment (swallowing problem in NPC, cataplexy and epilepsy in Glut1 deficiency syndrome, and head tremor in AVED), and other systematic symptoms (steatorrhea in abetalipoproteinemia, ichthyosis and cardiac arrhythmia in Refsum’s disease, and tendon xanthoma in CTX). 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 abetalipoproteinemia2. 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 genes7. 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 diet8. 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.
Alpha lipoic acid can facilitate glucose transport and has been proposed to treat Glut1 deficiency.

**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. 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. Vitamin E supplementation was reported to be helpful in AVED patients with dystonia. Head tremor in AVED did not improve after 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. 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.

**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. 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. 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. 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. 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 steatorrhea. Ichthyosis and cardiac arrhythmia are common in Refsum’s disease and can be effectively treated with low phytanic acid diet and plasmapheresis. 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.

**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. 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.

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.

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.

Varenicline was also studied. This drug is a partial α4β2 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.

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. 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 astrogliosia, 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.

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.

**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. Other drugs should be tried: anticholinergics, benzodiazepines, baclofen and carbamazepine. Botulin toxin injection may be used in focal or segmental cases of dystonia.

**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. 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. 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 SCA. Botulin toxin injection may improve spasticity in patients with SCAs.

**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.

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).

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.

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.

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. 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.

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 myopathy. 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. 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. 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. 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. An intensive coordinative therapy with 3 sessions of 1 hour per week has been described as effective plan. 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 benefit. 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.

Another study evaluated the effect of inpatient rehabilitation of patient with FRDA. A period of inpatient rehabilitation
Table 3. Rehabilitation strategies for hereditary ataxias.

<table>
<thead>
<tr>
<th>Rehabilitation therapy</th>
<th>Level of evidence / Grade of recommendation</th>
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<tbody>
<tr>
<td>Conventional physical therapy</td>
<td>Class II / B</td>
</tr>
<tr>
<td>Treadmill training</td>
<td>Class III / C</td>
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<tr>
<td>Relaxation and biofeedback training</td>
<td>Class III / C</td>
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<tr>
<td>Videogames/computer assisted training</td>
<td>Class III / C</td>
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<tr>
<td>Supervised sports / endurance training</td>
<td>Class III / C</td>
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<tr>
<td>Occupational therapy</td>
<td>Class III / C</td>
</tr>
<tr>
<td>Speech and language therapy</td>
<td>No evidence</td>
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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 FRDA51,52. 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 change53. 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 sensitive\(^6\). 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 development 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\(^58\).

PGD 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\(^56,59\). 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\(^56,59\).

**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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