Chapter from the book *Spinocerebellar Ataxia*

Downloaded from: [http://www.intechopen.com/books/spinocerebellar-ataxia](http://www.intechopen.com/books/spinocerebellar-ataxia)
Neurochemistry and Neuropharmacology of the Cerebellar Ataxias

José Gazulla\textsuperscript{1}, Cristina Andrea Hermoso-Contreras\textsuperscript{2} and María Tintoré\textsuperscript{3}

\textsuperscript{1}Department of Neurology, Hospital Universitario Miguel Servet, Zaragoza, 
\textsuperscript{2}School of Medicine, University of Zaragoza, Zaragoza, 
\textsuperscript{3}Nucleic Acid Chemistry Group, Chemistry and Molecular Pharmacology Programme, 
Institute for Research in Biomedicine of Barcelona, Barcelona, Spain

1. Introduction

The aim of this work has been to review the neurochemical alterations described in the cerebellar ataxias, and to enumerate the attempts made at their pharmacological treatment. As will be shown, little use has been made of the neurochemical information available, and the therapeutic trials have been far from successful.

The predominant (though not exclusive) reference to degenerative ataxias is due to the fact that the specificity of the affected cell populations should allow anticipation of more or less specific neurochemical alterations. This information could be used to look for therapeutic strategies, given the absence of curative treatments for the majority of ataxic disorders. This review covers only the pharmacologic attempts performed to treat ataxic symptoms, and is not exhaustive in terms of nosology, genetics or congenital errors of metabolism. The neurochemical basis of some non-degenerative ataxias that demonstrate favourable responses to pharmacological treatment are also reviewed. An outline of the physiological neurotransmission in the cerebellum opens this chapter (Table 1).

2. Neurotransmission in the cerebellum

The cerebellum is made up of four pairs of nuclei located in the deep white matter that covers the fourth ventricle, and is surrounded by a superficial layer of grey matter. The cerebellar cortex has a very uniform cellular structure and great cell density.

In the cortex of the cerebellum, there are several types of inhibitory interneurons that utilize \(\gamma\)-aminobutyric acid (GABA) as neurotransmitter. These are Golgi cells (that coexpress GABA with glycine), stellate cells, basket cells and Lugaro cells.

Purkinje cells are also GABAergic; they are the only ones whose axons exit the cortex of the cerebellum, projecting towards the cerebellar and vestibular nuclei. They use taurine as an osmotic regulator.
The excitatory amino acid glutamate is used in the cerebellar cortex by granule cells and unipolar brush cells. The axons of the granule cells constitute the parallel fibres of the molecular layer.

Most of the afferent fibres of the cerebellum are excitatory and use glutamate as main neurotransmitter. The climbing fibres that leave the contralateral inferior olive and synapse with the Purkinje cell dendrites are mostly glutamatergic, in addition to using aspartate and homocysteic acid. The mossy fibres are more numerous and originate in a number of areas, such as the pontine nuclei, reticular formation, spinal cord, deep cerebellar nuclei (as collaterals to the nuclear axons) and unipolar brush cells. They reach the dendrites of the granule cells in the so called glomerular structures. The great majority of mossy fibres use glutamate; a small proportion, acetylcholine (afferents from the vestibular nuclei and others from the cerebellar nuclei) and peptides such as enkephalins, cholecystokinin, corticotrophin, or calcitonin gene related peptide (CGRP). Part of the climbing and mossy fibres which originate in precerebellar structures, emit a collateral ramification that reaches the deep cerebellar nuclei on their trajectory toward the cortex. The efferent nuclear fibres are excitatory, with the exception of those destined for the inferior olives, which have an inhibitory function.

In addition to the mossy and climbing fibres, there is a group of beaded fibres that use monoamines as neurotransmitters, and reach the three layers of the cerebellar cortex.

| Neurotransmitter | Layer/Cell Type |
|------------------|-----------------|
| Glutamate        | Mossy fibers    |
|                  | Climbing fibers |
|                  | Granule cells   |
|                  | Parallel fibers |
|                  | Unipolar brush cells |
| GABA             | Golgi cells     |
|                  | Stellate cells  |
|                  | Basket cells    |
|                  | Lugaro cells    |
|                  | Purkinje cells  |
| Glycine          | Golgi cells (coexpressed with GABA) |
| Noradrenaline    | Origin in locus ceruleus |
| Serotonin        | Origin in reticular formation |
| Acetylcholine    | Origin in vestibular nuclei |
| Histamine        | Origin in hypothalamus |

Table 1. Neurotransmitters in the cerebellum (references 1-7).
A contingent of noradrenergic fibres stems from the locus ceruleus, and there seems to be a group of dopaminergic afferents of indeterminate origin. Serotonergic fibres originate at the paramedian and lateral reticular nuclei, the periolivary reticular formation and the lateral tegmental region; it has not been possible to demonstrate connections between the raphe nuclei and the cerebellar cortex. Some histaminergic fibres reach the cerebellar cortex from the hypothalamus.

Nitric oxide (NO) is a non-synaptic neurotransmitter present in the cerebellar cortex, mostly generated in the soma and parallel fibres of the granule cells. This substance spreads through the cell membranes and acts on glial cells and some neurons, stimulating the synthesis of cyclic guanosine-monophosphate. Basket and unipolar brush cells also synthesise NO, although not so Purkinje cells (1-7).

In conclusion, neurotransmission in the cerebellum implicates the amino acids glutamate and GABA, which establish an equilibrium between excitatory and inhibitory phenomena (Table 1).

Figures of the anatomy of the cerebellum and its connections, and of the neurochemical organization of the cerebellar cortex may be found the works of Colin et al (5), and Ottersen et al (1).

3. Neurochemistry and pharmacological therapy of the cerebellar ataxias

The abundance of neurotransmitters in the cerebellum complicates the task of determining which among them are implicated in disease pathogenesis. In addition, neurochemical data about many diseases is fragmentary. This section reviews the available neurochemical information (Table 2) and attempts at pharmacological treatment (Table 3) of the following conditions:

1. Cortical cerebellar atrophies
2. Atrophies of the cerebellar cortex and afferent fibres from the brainstem (olivopontocerebellar atrophies, OPCA).
3. Spinocerebellar atrophies.
4. Degenerations of the dentate nucleus and efferent tracts of the cerebellum.
5. Episodic ataxias.

4. Cortical cerebellar atrophies

The cortical cerebellar atrophy (CCA) of idiopathic etiology constitutes a relatively straightforward neurochemical model: the loss of Purkinje cells in the cerebellar vermis (8) causes a selective decrease of the concentration of GABA in the dentate nuclei (9) and cerebrospinal fluid (CSF) (10-13), with no reduction in that of glutamate (9), homovanillic acid (HVA), 5-hydroxindolacetic acid (5-HIAA), or the noradrenergic metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) (14). Reduced consumption of glucose in the cerebellum has been determined by positron emission tomography (PET) (15). This condition presents as a late-onset, pure cerebellar syndrome (8). Autosomal dominant spinocerebellar ataxias (SCA) that exhibit a progressive and isolated cerebellar syndrome include SCA 5, 6, 11, 15, 22, 26 and 30.
Spinocerebellar Ataxia

Cortical cerebellar atrophy
Decreased content of GABA in the dentate nuclei and CSF.

Oivopontocerebellar atrophy
Decreased levels of GABA and glutamate in the cerebellar cortex, and of GABA in the dentate nuclei. Decreased concentration of dopamine and HVA in putamen, caudate and nucleus accumbens. CSF: decreased levels of GABA and glutamate

Friedreich's ataxia
Decreased glutamate concentration in the grey substance and dorsal columns in the lumbar spinal cord. Low glutamate and GABA concentrations in the cerebellar cortex.

Machado-Joseph disease
Decreased HVA in CSF.

Dentatorubral-pallidoluysian atrophy
Decreased GABA and substance P in globus pallidus and substantia nigra, and of choline-acetyltransferase in putamen and caudate nucleus. Reduced GABA in CSF.

Episodic ataxia type 6
Defective glutamate uptake

Table 2. Neurochemistry of the cerebellar ataxias.

| Ataxia Type                  | Treatment                                                                 |
|------------------------------|---------------------------------------------------------------------------|
| Cortical cerebellar atrophy  | Anticholinesterase drugs: physostigmine (13,53)                          |
|                              | Serotonergic drugs: L-5-hydroxytryptophan (38-41), buspirone (43-47), tandospirone (48) |
|                              | Serotonergic antagonists: ondansetron (49)                                |
|                              | Peptides: TRH (51,52)                                                     |
|                              | GABAergic drugs: gabapentin (25), pregabalin (31)                         |
|                              | NMDA agonists: D-cicloserine (54)                                         |
|                              | Carbonic anhydrase inhibitors: acetazolamide (55,56), Piracetam (32,33) |
| Oivopontocerebellar atrophy  | Anticholinesterase drugs: physostigmine (53,94)                          |
|                              | Serotonergic drugs: L-5-hydroxytryptophan (40,91), buspirone (46)        |
|                              | Dopaminergic drugs: amantadine (89)                                       |
|                              | Peptides: TRH (52)                                                        |
|                              | Cholinergic drugs: lecithin (95), L-acetylcarnitine (99)                  |
|                              | GABAergic drugs: vigabatrin (90), gabapentin (103), zolpidem (101)        |
|                              | Glucocorticoid drugs: betamethasone (105)                                |
|                              | Glutamatergic drugs: ramified amino acids (100)                          |
|                              | Riluzole (102)                                                           |
| Friedreich's ataxia          | Cholinergic drugs: L-acetylcarnitine (99)                                 |
|                              | Serotonergic drugs: L-5-hydroxytryptophan (40,91)                        |
|                              | Tandospirone (48)                                                         |
|                              | Dopaminergic drugs: amantadine (89,115)                                   |
|                              | GABAergic drugs: vigabatrin (116)                                         |
|                              | Peptides: TRH (52)                                                        |
|                              | Iron chelators: deferiprone (133)                                         |
|                              | Antioxidant agents: idebenone (118-121,123, 126,127)                     |
|                              | Erythropoietin (131, 132)                                                |
| Machado-Joseph disease       | Tetrahydrobiopterin (140)                                                |
|                              | Trimethoprim-sulfamethoxazole (141,145)                                   |
|                              | Serotonergic drugs: buspirone (92), fluoxetine (120), tandospirone (147,48) |
|                              | Antiepileptic drugs: lamotrigine (146)                                    |
|                              | Antiarrhythmic drugs: mexiletine (148) Riluzole (102)                     |
| Episodic ataxia type 1       | Acetazolamide, phenytoin (156)                                           |
| Episodic ataxia type 2       | Acetazolamide (161)                                                      |
| Episodic ataxia type 3       | Acetazolamide (164)                                                      |
| Episodic ataxia type 4       | Dimehydrinate (166)                                                      |
| Episodic ataxia type 5       | Acetazolamide (169)                                                      |

Table 3. Pharmacological therapy of the cerebellar ataxias. Boliographic references are in brackets.
A deficiency of GABA in the cerebellum may lead to cerebellar ataxia, as suggested by abnormal GABAergic neurotransmission in the presence of antibodies directed against the enzyme glutamic decarboxylase (GAD) (16), and the coexistence of ataxia with the aforementioned antibodies (17-19). Anti-GAD antibodies are present in juvenile neuronal ceroid-lipofuscinosis, a disorder that may associate ataxia (20), and a selective vulnerability of GABAergic neurons has been found in other lysosomal disorders (21). Besides, an amelioration of ataxia was achieved with the use of GABAergic drugs in a case of adult GM2 gangliosidosis (22), and administration of gabapentin improved motor coordination in potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1) knockout mice, which exhibit a decreased content of GABA in the cerebellum (23).

The pharmacological trials in CCA are reviewed in the following section.

An open-label trial of gabapentin reported a substantial clinical improvement, and statistically significant differences in the scores of some items selected from the International Cerebellar Ataxia Rating Scale (ICARS) (24). Ten patients were initially given a single dose of 400 mg of gabapentin, followed by doses between 900 and 1600 mg per day during four weeks. Every patient experienced an improvement in ataxia, and in three, gait became normal (25). Gabapentin interacts with the α2-δ subunit of the P/Q type voltage-dependent calcium channels (VDCC) (26), stimulates GABAergic neurotransmission by presynaptic mechanisms (27) and increases the concentration of GABA in the brain of healthy adults (28). More recently, gabapentin treatment decreased ICARS scores by more than 10% in 11 patients with SCA 6 (caused by an abnormal expansion in \textit{CACNA1A}, 19p13, that encodes the α1A subunit of the P/Q-type VDCC), indicating that the drug could be beneficial in this disease (29).

Pregabalin, a molecule closely related to gabapentin, improved the scores in the Scale for the Assessment and Rating of Ataxia (SARA) (30) in a single blind, placebo controlled trial that included two patients with CCA (31).

A patient with cortical cerebellar ataxia was administered piracetam in a single-blind trial. Piracetam (a derivative of GABA that binds to H3-glutamate sites) improved tandem gait and gait ataxia in a dose of 60 g per day, and the authors concluded that this drug might have an anti-ataxic effect when used in high doses (32). Subsequently, 60 g per day of piracetam was given to a group of two patients with hereditary CCA, and six with other hereditary ataxias (excluding Friedreich ataxia, FRDA), in an open-label trial. The reduction obtained in the mean total score of ICARS (from 39.4±17, to 30.9±14.9), and in that of the posture and gait item, reached statistical significance (33).

Chan-Palay et al induced ataxia in animals through thiamine deprivation, and found a loss of serotonergic fibres in the nervous system (34). As a consequence, the authors suggested that a deficiency of serotonin might constitute the neurochemical basis for ataxia in humans (35). Anyway, neither a deficiency of serotonin nor atrophy of structures that could cause serotonergic denervation have been demonstrated in humans with CCA. The modulating effect of serotonin on GABAergic neurotransmission could explain some of the results reported below (36,37).

In two studies on the serotonergic precursor L-5-hydroxytryptophan, improved stance and speech were obtained in patients with degenerative and secondary ataxias, CCA among
them (38,39). However, in a double-blind placebo crossover study of 13 patients with CCA, seven with OPCA, and 19 with FRDA, no improvement in ataxia was observed (40), although the inclusion of different diseases in the mentioned trials prevented a clear assessment of the effect of L-5-hydroxytryptophan on CCA. In addition, this drug was administered to six patients with CCA in an open-label study, without finding changes in the amplitude of voluntary movement or in the latency of electromyographic activity in antagonist muscles, showing that L-5-hydroxytryptophan was not an effective therapeutic agent for CCA (41).

The drug buspirone stimulates the serotonergic 5-HT1A receptor. It is currently used as an anxiolytic (42), so this effect must be ruled out in its assessment as a treatment for CCA (43-47). Trouillas et al. studied the effect of buspirone on CCA in an open-label (42) and in two placebo-controlled studies (44,45). They defined their results as “a progressive modulation, rather than a radical transformation of ataxic symptoms” (43,45), referring to the limited and delayed improvement achieved. Lou et al (46) used buspirone in an open-label study in 14 patients with CCA and six with OPCA; the drug was administered in accordance with the severity of the ataxia. The authors found that buspirone was effective in cases of mild or moderate ataxia, though they did not individualize its effect on any of the two disorders. Andrade-Filho et al (47) noted improvement in 11 patients with CCA, with the addition of buspirone to other anti-ataxic and antiepileptic drugs. However, the methodology employed in this work did not make clear the aetiology of the ataxias, nor did it measure accurately the effectiveness of the drug.

The serotonergic agonist tandospirone was given during four weeks to 5 patients with SCA 6, 5 with SCA 1, 6 with SCA 2, 14 with Machado Joseph disease (MJD), and 9 with multisystem atrophy. This was an open-label, non blinded trial, and obtained reductions in the ICARS scores of the SCA 6 (p 0.043) and MJD (p 0.005) subgroups that reached statistical significance. It must be remarked, however, that the two tables in this article mentioned different values for the pre-treatment mean ICARS score of the cerebellar-multisystem atrophy subgroup, that the discussion incorporated results not specified in the corresponding section, and that the value of probability (p<0.0001) for the reduction of ICARS scores after treatment with tandospirone for the entire group, was out of proportion with the results of p for every subgroup of patients (48).

A double-blind, placebo controlled study of the serotonergic antagonist ondansetron showed worsening of the knee-heel manoeuvre in 15 patients with CCA (49).

Thyrotropin-releasing hormone (TRH) increases noradrenaline turnover, facilitates cholinergic transmission, and adjusts GABAergic neurotransmission (50). Although its intravenous administration had no effect on one patient with familial CCA (51), a study of patients with CCA, OPCA and FRDA showed an amelioration of postural instability (52). Obviously, the risk of hyperthyroidism prevents the prolonged use of this potentially beneficial agent.

The use of the anti-cholinesterase drug physostigmine in two double-blind, placebo controlled studies in patients with CCA, obtained no improvement in ataxia. The authors of both articles concluded that physostigmine was not effective in the treatment of this disease (13,53).
The amino-acid D-cycloserine, a partial agonist of the N-metil-D-aspartate (NMDA) glutamate receptor, was used in a placebo controlled trial in two patients with CCA, two with SCA 6 (53), 10 patients with multisystem atrophy and one with degenerative spinocerebellar ataxia. Mild improvements were found in some items of ICARS, and it was suggested that activation of NMDA receptors could lead to symptomatic improvement in spinocerebellar ataxia (54).

Finally, the use of acetazolamide in three patients with SCA 6 was found to have no effect on ataxia (55). Nevertheless, an open-label study of 9 patients with SCA 6 treated with 500 mg per day of acetazolamide, achieved a statistically significant improvement in ICARS scores and in the results of posturographic analysis (56).

Some forms of CCA have a non-degenerative etiology. Chronic abuse of ethanol may cause loss of neurons with GABA-A receptors, especially in the Purkinje cell layer, and vermian atrophy. Abstention from alcohol has been proposed to halt progression of ataxia (57).

Cerebellar paraneoplastic degeneration is a remote consequence of cancer. It is characterised histologically by loss of Purkinje cells and the presence of perivascular and leptomeningeal inflammatory infiltrates (58). An autoimmune cause is invoked by the presence of antibodies directed against epitopes common to the tumour and: 1) Purkinje cells (Yo, Tr) (59,60), 2) Hu and Ri nuclear proteins (60), 3) Tr dendritic protein (61), 4) P/Q-type VDCC (62,63), and 5) mGluR1 type glutamate metabotropic receptors (64). The latter are capable of altering both the acute and plastic response of Purkinje cells, causing cerebellar dysfunction (64). Antineoplastic treatment is recommended, or immunotherapy in its defect (60).

5. Olivopontocerebellar atrophies

The olivopontocerebellar atrophies comprise a heterogeneous group of disorders (degenerative diseases, prionopathies, hereditary errors of metabolism and mitochondrial encephalopathies) whose histological substrate is: 1) loss of neurons in the inferior olive and ventral portion of the pons; 2) loss of mossy and climbing fibres, and 3) atrophy of the cerebellar cortex (65). There is depletion of Purkinje and granule cells in the cerebellar cortex, especially in the hemispheres (8). This expresses clinically a global cerebellar syndrome, accompanied by additional neurological signs. It may be sporadic or familial; familial cases are associated with a greater frequency of medullar signs (with the exception of spasticity), dystonia and oculomotor abnormalities (65). Autosomal dominant spinocerebellar ataxias in which OPCA constitutes the pathological or radiological substrate are SCA 1, 2, 7, 12 and 13 (66).

A fourth part of sporadic OPCA cases develop multisystem atrophy (which associates parkinsonism and autonomic failure) (66,67). Analysis of pathological material has shown immunoreactive inclusions to alpha-synuclein in oligodendrocytes (68) and neurons (69) in this disease. However, this is not the case with SCA1 or SCA2 (disorders caused by expansion of CAG triplets in 6p22.3 and 12q24.13), in which olivopontocerebellar atrophy constitutes the pathological basis (66). The frequency of associated lesions (locus coeruleus, red nucleus, substantia nigra, dentate, hypoglossal and dorsal motor nuclei, nucleus ambiguus, etc) with those described, blurs the nosological limits of OPCA (70).

Neurochemical studies in OPCA have demonstrated an important decrease of GABA content in the dentate nuclei (9,71,72) and cerebellar cortex (71).
The content of glutamate in the cerebellum varied between an important reduction and normality, in different sources (9,71,72). Kanazawa et al. established correlation in brains with OPCA, between: 1) the content of glutamate in the anterior vermis, and the density of granule cells; 2) the concentration of glutamate in the posterior vermis and the cerebellar hemispheres, and the cellular density of the inferior olive; 3) the content of GABA in the dentate nuclei, and the density of Purkinje cells (9).

In an autoradiographic receptor study, Albin and Gilman found a statistically significant reduction in the density of GABA, benzodiazepine (BZD) and glutamate receptors in the cerebellar cortex of OPCA brains, compatible with loss of granule and Purkinje cells (73). A PET study found diminished flumazenil binding in the brainstem and cerebellum, confirming the deficiency of GABA observed in OPCA (74).

A study of a patient with sporadic OPCA found IgM antibodies directed against the glutamate receptor subunit GluR2. Antibodies were demonstrated on Purkinje cells, basal portion of the pons and inferior olive, by immunohistochemical methods. The antibodies were shown to be able to depolarise neurons *in vitro*, a fact that pointed to excitotoxicity of autoimmune origin in the genesis of the disease (75).

A low activity of the enzyme glutamate dehydrogenase was previously considered a biochemical hallmark of OPCA (76), although later studies demonstrated a lack of specificity of this metabolic alteration (77,78).

PET studies have shown decreases in dopamine and HVA levels in the striatum in familial (79) and sporadic (80) OPCA. The density of dopamine D2 receptors was normal in the putamen and caudate nuclei in one parkinsonian patient who exhibited OPCA at autopsy, demonstrating the possibility of presynaptic parkinsonism in this disease (81).

A reduced acetylcholinesterase activity and a low density of muscarinic receptors in the cerebellar cortex were found in familial OPCA, suggesting that cholinergic denervation was a major neurochemical anomaly in this variant (82,83). Nevertheless, choline-acetyltransferase activity in mossy fibres (1,3) was greater in familial OPCA than in control cases (82), disproving the previously mentioned proposal.

In CSF, in addition to a low content of GABA (9-11), a low glutamate level was found in sporadic OPCA (11), as well as low levels of HVA, thiamine and MHPG in hereditary OPCA (84-86), with those of tryptophan and 5-HIAA in normal ranges (85).

In addition, a decrease in the levels of pontine and cerebellar N-acetylaspartate (reflecting neuronal loss), was found by high field proton magnetic resonance spectroscopy (1H MRS) in patients with SCA 2 and cerebellar multisystem atrophy. An increase in myoinositol, that points to involvement of glial cells, was also found in multisystem atrophy (87).

To summarise, deficiencies of GABA, glutamate, dopamine and possibly noradrenaline, are present in the nervous system of OPCA patients, although no deficiencies of serotonin or acetylcholine have been documented (79,85).

In an ataxia-telangiectasia (AT) brain with cerebellar, inferior olive and dentate nuclei atrophy, the contents of GABA and glutamate in the cerebellar cortex, and of GABA in the dentate nuclei, were lower than those in controls (88). These neurochemical findings were similar to those in hereditary OPCA (71), and demonstrate that the neurochemical abnormalities of the ataxias are independent of the underlying condition.
The neurochemical complexity of OPCA makes successful pharmacological therapy difficult. As outlined below, a large number of clinical trials have been done, in an attempt to find a remedy.

A double-blind placebo controlled study using amantadine hydrochloride in 30 patients with OPCA without akinesia, obtained improvements in simple and movement reaction times in response to visual and auditory stimuli, that reached statistical significance. The beneficial results were attributed, either to a dopaminergic effect of the drug, or to blockade of NMDA receptors, an effect similar to that exercised by memantine (89).

In a group of 14 patients (one with sporadic OPCA, four with familial OPCA and nine with FRDA), a double-blind comparative trial of vigabatrin (an irreversible inhibitor of GABA-transaminase) with placebo, yielded no apparent benefit (90).

A previously mentioned trial (40) did not find improvement in ataxia with L5-hydroxytryptophan in a group that included seven patients with OPCA. This conclusion was shared by Currier et al, using the same drug in a group that included three patients with OPCA (91).

A group of 20 patients (5 with SCA 2, 2 with SCA 3, 4 with FRDA, and the remaining with other degenerative ataxias) was given buspirone at doses of 60 mg per day, in a double-blind, placebo-controlled, cross-over trial; buspirone was not superior to placebo in the amelioration of ataxia (92). The potential effects of oestrogen on neuroprotection, and of buspirone on ataxia, were combined in an open-label study with 18 OPCA patients. The participants were allocated either to buspirone, 15 mg/day, or to buspirone and oestrogen, 0.625 mg/day. No statistically significant differences were found in ICARS scores, compared with baseline, in any group, although a trend of improvement in gait speed and knee-tibia test was observed in the first one, suggesting that oestrogen was not beneficial in cerebellar dysfunction (93). The work of Lou et al, using buspirone in seven patients with OPCA and 14 with CCA, has been detailed earlier (46).

In another previously mentioned study, the administration of physostigmine to 10 patients with OPCA and nine with CCA gave no apparent benefit (53), although this drug was found to have a favourable effect when used in a heterogeneous group that included three cases of OPCA (94).

The administration of the cholinergic precursor lecithin to 11 patients with OPCA induced a clinical worsening coincident with elevated plasma choline levels (95). Results obtained with choline chloride (96) and physostigmine, led Harding (97) and Manyam (13) to conclude that cholinergic drugs were not effective to treat cerebellar ataxias, probably because no deficit in cholinergic neurotransmission has been confirmed in these diseases (50). In spite of this, a double-blind, placebo controlled analysis of the cholinomimetic agent L-acetylcarnitine obtained a mild improvement in the coordination items of ICARS, in a group of 14 patients with sporadic and hereditary OPCA (98), and in another group of 11 patients with FRDA (99).

Based on the hypothesis that stimulation of glutamate metabolism could favour its neurotransmission in the cerebellum, and so prevent excitotoxic damage, Mori et al gave branched amino-acids to a group of 16 patients (five with sporadic OPCA, and 11 with SCA6 and SCA7) in a double-blind crossover study. They used doses of 1.5g, 3g, 6g and
placebo (100). Starting with an ICARS score average of 42.44 ± 16.60, reductions of 2.92 ± 3.35 were obtained with a 1.5g dose, and of 4.31 ± 4.57 with a 3g dose. These modest results were nevertheless statistically significant, though the effect on patients with OPCA could not be individualized.

The favourable effect of TRH in a group of patients with several types of ataxia (including 12 with OPCA) has been referred to already (52).

In four out of five patients with SCA 2, an improvement of ataxia and intention tremor was observed after administration of zolpidem in single doses of 10 mg. In one patient, a SPECT scan verified normalization of a previously diminished Tc\textsuperscript{99}exametazime binding. The drug’s beneficial effect was attributed to reversion of a phenomenon of diaschisis (101).

In a randomized, double-blind, placebo-controlled trial, 40 patients (4 with SCA 2, 6 with multisystem atrophy, 8 with FRDA, and others with degenerative and acquired ataxias) were assigned to riluzole (100 mg/day) or placebo, during 8 weeks. The number of patients with a 5-point drop in ICARS compared to baseline (primary endpoint of the study) was significantly higher in the riluzole group after 4 and 8 weeks of treatment, with a mean change of −7.05 [± 4.96] points in the total score, versus 0.16 [± 2.65] with placebo (102).

Gabapentin was found to improve gait in a patient with sporadic OPCA, and dysarthria and oscillopsia in another (103). Duhigg described an unexpected regression of ataxia in a patient with OPCA that received 30 mg/day of propranolol (104).

Finally, inhaled betamethasone led to improvement in the ataxia of a patient with infantile AT (105), whilst pregabalin in combination with tiagabine ameliorated ataxia in a patient with adult-onset AT (106).

6. Spinocerebellar atrophies

The most frequent and severe spinocerebellar atrophy is Friedreich’s ataxia. FRDA has autosomal recessive inheritance, and an early onset. It is associated with scoliosis, pes cavus, cardiomyopathy, dysarthria, deep tendon areflexia, loss of vibration sense and extensor plantar responses (107). The lesions are located mainly in the spinal cord, where macroscopic atrophy, loss of fibres in the dorsal columns, dorsal and ventral spinocerebellar bundles, and direct and crossed corticospinal tracts, are present. Neuronal loss is found in the gracilis and cuneatus nuclei, Clarke’s dorsal nuclei and in the dorsal root ganglia. The dorsal roots are atrophic, and there is depletion of myelinated fibres in the sensory nerves. Neuronal depopulation and loss of iron in the dentate nuclei, as well as atrophy of the superior cerebellar peduncles are also found, while the cerebellar cortex is preserved (8,97,108). Hypertrophic changes are present in the heart, with increased connective tissue and loss of cardiomyocytes (108).

The genetic anomaly in FRDA is an abnormal expansion of a GAA triplet in the first intron of the \textit{FXN} gene on chromosome 9q13, that inhibits the transcription of the mitochondrial protein frataxin. Its deficiency interferes with the synthesis of iron-sulphur complexes, and with iron transport. These cause an accumulation of reactive iron in the mitochondria, interfere with oxidative phosphorylation and allow the formation of toxic oxygen radicals (109).
Neurochemical studies in FRDA have demonstrated low concentrations of glutamate and glycine in the grey matter of the lumbar cord and of glutamate in the dorsal columns, which reflect the loss of corticospinal and sensory glutamatergic fibres (110,111). There was also a reduction in the concentrations of glutamate and GABA in the vermis and the cerebellar hemispheres (112).

HVA and 5-HIIA CSF levels were reduced in patients with FRDA (85); this was not the case with CSF levels of GABA and homocarnosine (113), nor with the density of BZD receptors in the brain (114).

Pharmacological therapy has only achieved partially favourable results in FRDA. As previously mentioned, the results of trials with L-hydroxytryptophan (40,94), physostigmine (53), TRH (52), vigabatrin (91), riluzole (102) and buspirone (92), in groups that included patients with several types of ataxia, did not permit individualization of the effect of these drugs on FRDA.

Botez et al did not find improvement in ataxia when treating a group of 27 patients with FRDA with amantadine hydrochloride (90). The same result was reported by Filla et al, in a double-blind cross-over trial using amantadine hydrochloride in 12 patients with FRDA (115). No benefit was obtained, either, in an open-label assay of vigabatrin in nine patients with FRDA (116).

Idebenone (a government-supported drug for treatment of FRDA in Canada, among other countries) is a synthetic analogue of coenzyme Q10 with powerful antioxidant properties, whose effectiveness on the ataxia and cardiomyopathy of FRDA is currently being investigated.

A positive effect of idebenone on the cardiomyopathy of FRDA reported in a preliminary trial (117) was confirmed in a randomized placebo-controlled trial with 29 patients, in which a reduction of the thickness of the interventricular septum and posterior wall of the left ventricle, that reached statistical significance, was evidenced by echocardiography (118). Another study found that six (among eight) patients with FRDA exhibited an important reduction of cardiac hypertrophy (119), although no improvement in ataxia was noticed in any of these trials.

In a study with an examination period that ranged from 6 to 84 months, Ribat et al observed that ataxia and cardiac ejection fraction deteriorated in 88 patients with FRDA while receiving 5 mg/kg per day of idebenone (in spite of finding decreased cardiac hypertrophy by echocardiography), as well as in 16 non-treated patients (120). An increase in interventricular septum and left posterior wall thickness was observed in patients without previous myocardial isopathy, who received 5 mg/kg per day of idebenone. The authors concluded that idebenone did not prevent the development of myocardiositis, although no worsening was found in patients with known cardiac disease (121).

The phase 3 Idebenone Effects on Neurological ICARS Assessments (IONIA) study randomized 70 ambulatory FRDA patients aged 8 to 18, with ICARS scores between 10 and 54, to placebo and idebenone at doses of 10-20, and 30-54 mg/kg per day. No improvement in left ventricular hypertrophy or cardiac function could be demonstrated over a six month period (122).
Artuch et al (123) reported a statistically significant amelioration in cerebellar function, compared with baseline evaluation, in paediatric patients with FRDA receiving idebenone.

Recently, emphasis has been placed on the use of high doses of idebenone in an effort to improve ataxia in FRDA (124,125); accordingly, a randomized, double-blind, placebo-controlled phase 2 six-month trial (National Institutes of Health Collaboration with Santhera in Ataxia [NICOSIA]) of this drug at doses of 5, 15 and 45 mg/kg per day, was performed on 48 ambulatory FRDA patients aged between 8 and 18, with ICARS scores between 10 and 54. Increasing doses of idebenone were associated with reductions in ICARS scores in a dose-dependent manner, even though overall statistically significant differences were not obtained; thus concluding that high doses of idebenone might be necessary to attain beneficial effects on neurological function (126).

In contrast, the “neurological” arm of the IONIA trial achieved a minimal mean reduction in ICARS scores, which did not reach statistical significance when compared to placebo (127).

The drug mitoquinone (an antioxidant derived from idebenone), which is active in the mitochondrion though not so in the cytosol, is expected to be an effective therapeutic agent in FRDA (128).

A double-blind study of 5-hydroxytryptophan and placebo in 19 patients with FRDA (129), and of an open-label study of amantadine in 16 (130), only gave slightly positive results. A similar benefit was obtained in a previously mentioned study that used L-acetylcarnitine in 11 patients with FRDA (100).

It was demonstrated recently that human recombinant erythropoietin (rhuEPO) increased frataxin in lymphocytes from patients with FRDA, in vitro; this effect was independent from the EPO receptor (131). Thus, a persistent and significant increase in frataxin levels was found in peripheral blood lymphocytes of seven (among 10) patients with FRDA who received 5,000 units of rhuEPO subcutaneously, three times a week during 8 weeks; reductions in the urinary oxidative stress marker 8-hydroxi-2’-deoxyguanosine excretion, and in SARA scores, were also found (132). The same favourable results (that reached statistical significance) were replicated in a study involving 8 patients with FRDA, who received 2,000 units of rhuEPO three times a week during six months; unfortunately, the design of the trial could not rule out a placebo effect of the drug (133).

More specific therapeutic approaches for FRDA are under investigation, such as the histone deacetylase inhibitors, which impair abnormal DNA transcription in FRDA; peroxisome proliferator-activated receptor gamma agonists, that enhance cell antioxidant activity and frataxin levels; deferiprone (a mitochondrion-specific iron chelator) reduced iron content in the dentate nuclei (as measured by MRI), and improved neuropathy and gait ataxia in the youngest patients among 9 adolescents with FRDA (134); gene-based strategies, as the use of viral vectors that express frataxin, which corrected sensitivity to oxidative stress in FRDA fibroblasts (128,135); and finally, pluripotent stem cells induced from FRDA fibroblasts were able to differentiate into neurons and cardiomyocytes (136).

An isolated deficiency of vitamin E, caused by mutations in the gene that encodes the alpha-tocopherol transfer protein in 8q13, can present with an identical phenotype to FRDA. The neurological manifestations stabilise or may partially revert with administration of vitamin E (137).
7. Degenerations of the dentate nucleus and efferent tracts of the cerebellum

This section deals about about Machado-Joseph disease and dentatorubral-pallidoluysian atrophy (DRPLA).

MJD, also designated SCA3, is caused by an unstable expansion of a CAG triplet in the **ataxin 3** gene in 14q32.1, and exhibits dominant transmission (138). The lesions are found in the dentate nuclei and superior cerebellar peduncles, and respect the cerebellar cortex, striatum, inferior olive and corticospinal tracts. The pontine nuclei are sometimes affected. The dorsal columns, spinocerebellar tracts and Clarke’s dorsal nuclei degenerate in the spinal cord (110). Associated lesions may be present in the anterior horns, oculomotor and subthalamic nuclei, substantia nigra, medial longitudinal fascicle, and peripheral nerves. Among the manifestations of MJD, ataxia is related to lesions in the dentate or pontine nuclei; oculomotor disorders, to those in the brainstem; and parkinsonism, to those in the substantia nigra. The frequent spasticity cannot be explained by the aforementioned findings (138).

Neurochemical abnormalities in MJD consist of a reduced CSF concentration of HVA, even in cases without apparent parkinsonism (85,139). Concentrations of 5-HIAA and MHPG were reduced in CSF in one patient with MJD (136), although these changes were not found in every instance (85,139).

Attempts at pharmacological therapy in MJD are outlined below.

Based on the finding that trimethoprim increased the concentration of tetrahydrobiopterin (THB) in CSF in MJD, Sakai et al administered 1 mg/kg of THB and placebo to five patients for 10 day periods, in a crossover scheme. They reported a statistically significant improvement in the performance of some timed tests of motor function, though deglutition and tendon hypereflexia were not modified (140).

A double-blind, placebo-controlled, crossover trial of trimethoprim-sulfamethoxazole (TS) in 20 patients with SCA3, employed: 1) a clinical scale of ataxia and other non-cerebellar symptoms; 2) posturographic analysis; 3) the Schoppe motor performance test; and 4) achromatic and colour discrimination visual sensitivity tests. After six months of TS administration, none of the patients showed improvement in any of the enumerated tests. No differences were noted in sub-group analysis according to age, sex, duration of illness, phenotype, age at onset, or number of CAG triplets (141). These categorical results contrast with the more favourable outcomes obtained in a study that included eight patients with MJD (142), and with three other reports of individual patients (143-145) that received TS. The reason for the differing results could lie in the absence of molecular diagnosis in the latter studies, or in other methodological differences (141).

An open-label study on the use of the antidepressant drug fluoxetine involved doses of 20 mg per day given to 13 patients with MJD. In spite of a statistically significant improvement according to the Montgomery-Asberg depression rating scale, the EDSS and UPDRS scales showed no differences in motor function. The study concluded that serotonergic stimulation was not effective in the treatment of MJD (146).

Buspirone, at a dose of 60 mg per day, did not improve ataxia in a group of 20 patients that included 4 with SCA 3 (92).
Another open-label study used 10 to 30 mg per day doses of tandospirone. Seven out of 10 patients with MJD had their ICARS scores slightly improved, with additional mitigation of symptoms potentially caused by 5-HT1 receptor dysfunction (insomnia, anorexia, depression and cold lower extremities). The authors concluded that MJD manifested symptoms derived from these receptors, and recommended further tests with tandospirone in this disease (147). An open-label trial of tandospirone in 39 patients (14 with MJD among them) has already been commented on (48).

The antiarrhythmic drug mexiletine was shown to alleviate muscle cramps in MJD, without improving ataxia (148).

Liu et al gave 50 mg/day of lamotrigine to six patients with MJD, and observed improvement in one leg stance and tandem gait. They proposed that this beneficial effect could be due to enhanced expression of ataxin 3, induced by the drug (149).

Dentatorubral-pallidoluysian atrophy is a dominantly transmitted illness caused by an abnormal expansion of a CAG triplet in the atrophyn gene, in 12p13.31, that codifies polyglutamine sequences of abnormal length that exert a toxic action (as in other diseases caused by expansion of CAG triplets) (150). An important neuronal loss in the dentate and red nuclei is found. Less intense degeneration of the subthalamic nuclei and external part of the globus pallidus is also present, while the cerebellar cortex is preserved. Some studies have described spinal cord lesions identical to FRDA in DRPLA, in addition to those described (151); demyelinization in the superior cerebellar peduncles and efferent tracts of the pallidum has been noted, as well. These lesions may be asymmetric (152). Polyglutamine nuclear inclusions have been found in neurons and oligodendrocytes (153).

The clinical manifestations of DRPLA are heterogeneous. Cerebellar ataxia and dementia are considered cardinal signs, accompanied by progressive myoclonic epilepsy in cases with onset before the age of 20, or choreoathetosis and psychiatric symptoms when onset occurs later. It has been determined that there is an inverse correlation between the number of CAG triplets and age at onset of the disease. The differential diagnosis includes Huntington’s disease due to the possible association of chorea and dementia (150).

The neurochemical alterations in DRPLA are centred on a reduction of GABA and substance P in the globus pallidus and substantia nigra, and reduced choline-acetyltransferase activity in the caudate and putamen, in spite of preservation of the small striatal neurons; this result points to cell hypofunction as its cause (154). In CSF, the concentration of GABA was found to be very low in five cases of DRPLA, whilst levels of HVA and 5-HIAA were normal (151).

Recently, an accumulation of 8-hydroxi-2’-deoxyguanosine and 8-hydroxyguanosine, and a reduction of immunoreactivity to Cu/Zn superoxide dismutase, were found in the lentiform and dentate nuclei of DRPLA brains, suggesting the possibility that oxidative stress might play a part in the genesis of this disease (155).

No clinical assay dedicated to the treatment of ataxia caused by DRPLA has been performed to date.

8. Episodic ataxias

Episodic ataxias are transmitted by autosomal dominant inheritance, and are amenable to drug treatment.
Episodic ataxia type 1 (EA1), also known as episodic ataxia with myokymia, has its onset in infancy or early adolescence, and associates interictal myokymia in the face and limbs (identified by electromyography) with brief episodes of unsteadiness, tremor and dysarthria. The attacks are brought about by voluntary movement or startle, and may occur many times every day. They can be prevented with acetazolamide or phenytoin. EA1 is caused by mutations in the \textit{KCNA1} gene in 12p13, which encodes the voltage-dependent potassium channel KCNA1, widely expressed in the cerebellum and peripheral nerve (156-159). It has been demonstrated that the mutated channels increase cellular excitability, and prevent physiological repolarization (160).

Episodic ataxia type 2 (EA2) is caused by mutations in \textit{CACNA1A}, that give rise to truncated \( \alpha \)1A subunits (161). Electrophysiological characterisation of the abnormal proteins has demonstrated reduced channel conductance, causing an abnormally low calcium ingress, with the consequent cell damage (162,163).

EA2 appears in infancy and is associated with crises of ataxia, vertigo and nausea that last hours or days and are precipitated by emotional stress, fatigue or ingestion of coffee or ethanol. Intercital nystagmus, permanent ataxia and atrophy of the cerebellar vermis may coexist. Diagnosis may be difficult, as EA2 may be confused with anxiety or paroxysmal vertigo. The ataxic episodes respond to prophylaxis with acetazolamide (156,161).

Episodic ataxia type 3 (EA3) appears between the age of one year, and forty. It is associated with ataxia, vertigo and tinnitus, frequently headache, diplopia and blurred vision; interictal myokymia is also present. It may be distinguished from EA1 by the presence of vertigo and tinnitus, and from EA2 by the absence of interictal nystagmus and the short duration of the attacks, which are prevented by acetazolamide (164). The responsible gene is located in 1q42 (165).

Episodic ataxia type 4 (EA4), or vestibulocerebellar ataxia, was described by Farmer and Mustian in 1963 and is characterised by vertigo, diplopia, and mild or moderate ataxia that lasts from a few minutes to several weeks. It appears at an average age of 23 years (166). Defects have been found in smooth ocular pursuit and suppression of the vestibulo-ocular reflex, in addition to gaze-evoked nystagmus (167). Some patients develop progressive ataxia (166). EA4 responds to prophylaxis with dimenhydrinate (166) and is genetically distinct from SCA1, 2, 3, 4, 5, EA1, EA2 and DRPLA (168).

Episodic ataxia type 5 (EA5) is caused by a point mutation in \textit{CACNB4} (2q22-q23), that causes a change of one amino-acid (C104F) in the \( \beta \)4 subunit of the VDCC. It was described in patients with French-Canadian ancestry, and its clinical symptoms (ataxia and vertigo) and duration are similar to EA2; there is interictal nystagmus and it responds to prophylaxis with acetazolamide. The main difference is a later age of onset (169).

Episodic ataxia type-6 (EA6) was described in a ten year-old child that exhibited transitory episodes of ataxia and dysarthria in addition to epilepsy, migraine and alternating hemiplegia. A heterozygote mutation was identified in \textit{SLC1A3} (5p13), the gene that encodes the excitatory amino-acid transporter 1 (EAAT1, GLAST1), pointing to abnormal reuptake of synaptic glutamate as the causing factor of the neurological syndrome (170).
9. Conclusions

As may be deduced from the exposed data, pharmacological trials of cerebellar ataxias have been flawed by a number of factors, like the recruitment of very scarce numbers of patients, the predominance of clinical assays which include patients with more than one disease, the lack of an ataxia rating scale of generalized use and that of quantitative means of measuring ataxic symptoms, the absence of standard doses of the drugs under investigation, and probably the most important, the usual lack of application of the available pathophysiological data to the trials performed to date.

The basic neurochemical anomaly in idiopathic CCA consists in a lowering of the cerebellar content of GABA. In OPCA, deficits of glutamate, dopamine, and probably, noradrenaline, are present as well. Glutamate is essentially the deficient neurotransmitter in FRDA. A deficiency of serotonin has not been demonstrated conclusively in degenerative ataxias. The neurotransmitter abnormalities of MJD and DRPLA have not been well defined yet. Thus, it seems obvious that the neurochemical complexity of these disorders is one of the reasons for the lack of effective treatments.

Some tests have shown that the drugs gabapentin, pregabalin and tiagabine are effective in ataxias that associate a predominant deficiency of GABA in the cerebellum, like CCA and OPCA. Presumably, the more selective the deficit of GABA, the more effective the GABAergic substitution.

Agents capable of restoring the physiological action of glutamate (associated with neuroprotective molecules to prevent excitotoxic phenomena) could be useful in disorders like OPCA and FRDA. Conversely, the usefulness of the peptide TRH is conditioned by the risk of hyperthyroidism. Idebenone and other agents used to treat FRDA have to prove their effectiveness on ataxia, in a definite manner. The lack of effectiveness of physostigmine and choline chloride discards them as therapeutic agents for CCA and OPCA. The use of serotonergic agents in the cerebellar ataxias must be considered controversial at least, due to insufficient neurochemical evidence, and that of riluzole should be investigated in depth, as it could benefit patients with multisystem atrophy.

Given the severity of many of the ataxias considered in this work, treatable causes, such as vitamin E deficiency, should be ruled out when faced with phenotypes similar to FRDA. In a similar way, therapeutic trials with acetazolamide should be undertaken in cases with uncertain diagnoses, with the aim of recognising ataxias that respond to this drug.

Research aimed at identifying effective drugs to treat the cerebellar ataxias should, ideally, look for agents able to neutralize the causes of these diseases. However, as this is not possible in most cases, neurochemical evidence might provide useful clues in the search for therapeutic remedies (171,172). The study of animal and experimental models of disease, the use of precise methods for the measurement of ataxia (clinical semi-quantitative scales, quantitative movement analysis, etc) and the recruitment of homogenous study populations (22), are all highly recommended. In this way, the currently exiguous therapeutic panorama of the cerebellar ataxias could be amplified until etiological remedies are found.
10. References

[1] Ottersen OP, Walberg F. Neurotransmitters in the cerebellum. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 38-48.

[2] Mugnaini E. GABAergic inhibition in the cerebellar system. In: Martin DL, Olsen RW, editors. GABA in the Nervous System: the view at fifty years. Philadelphia: Lippincott, Williams & Wilkins, 2000: 383-407.

[3] Ottersen OP. Neurotransmitters in the cerebellum. Rev Neurol (Paris) 1993; 149: 629-636.

[4] Kwong WH, Chan WY, Lee KKH, Fan M, Yew DT. Neurotransmitters, neuropeptides and calcium binding proteins in developing human cerebellum: a review. J Histochem 2000; 32: 521-534.

[5] Colin F, Ris L, Godaux E. Neuroanatomy of the cerebellum. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 6-27.

[6] Bastian AJ, Thach WT. Structure and function of the cerebellum. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 49-66.

[7] Trouillas P. Bases théoriques et propositions pour une neuropharmacologie de l’ataxie cérébelleuse. Rev Neurol (Paris) 1993; 149: 637-646.

[8] Oppenheimer DR. Diseases of the basal ganglia, cerebellum and motor neurons. In: Adams JH, Corsellis JAN, Duchen LW, editors. Greenfield’s Neuropathology. Londres: Edward Arnold, 1982: 699-747.

[9] Kanazawa I, Kwak S, Sasaki H, Mizusawa H, Muramoto O, Yoshizawa K, et al. Studies on neurotransmitter markers and neuronal cell density in the cerebellar system in olivopontocerebellar atrophy and cortical cerebellar atrophy. J Neurol Sci 1985; 71: 193-208.

[10] Ogawa N, Kuroda H, Ota Z, Yamamoto M, Otsuki S. Cerebrospinal fluid gamma-aminobutyric acid variations in cerebellar ataxia. Lancet 1982; 2:215.

[11] Kuroda H, Ogawa N, Yamawaki Y, Nukina I, Ofuji T, Yamamoto M, et al. Cerebrospinal fluid GABA levels in various neurological and psychiatric diseases. J Neurol Neurosurg Psychiatry 1982; 45: 257-260.

[12] Tohgi H, Abe T, Hashiguchi K, Takahashi S, Nozaki Y, Kikuchi T. A significant reduction of putative transmitter amino acids in cerebrospinal fluid of patients with Parkinson’s disease and spinocerebellar degeneraton. Neurosci Letter 1991; 126: 155-158.

[13] Manyam BV, Giacobini E, Ferraro TN, Hare TA. Cerebrospinal fluid as a reflector of central cholinergic and amino neurotransmitter activity in cerebellar ataxia. Arch Neurol 1990; 47: 1194-1199.

[14] Aldo WF, van de Warrenburg BPC, Munneke M, van Geel WJA, Bloem BR, et al. CSF analysis differentiates multiple-system atrophy from idiopathic late-onset cerebellar ataxia. Neurology 2006; 67: 474-479.

[15] Otsuka M, Ichiya Y, Kubawara Y, Hosokawa S, Akashi Y, Yoshida T, et al. Striatal 18F-Dopa uptake and brain glucose metabolism by PET in patients with syndrome of progressive ataxia. J Neurol Sci 1994; 124: 198-203.

[16] Ishida K, Mitoma H, Song S, Uchihara T, Inaba K, Eguchi S, et al. Selective suppression of cerebellar GABAergic transmission by an autoantibody to glutamic acid decarboxylase. Ann Neurol 1999; 46: 263-267.
[17] Saiz A, Arpa J, Sagasta A, Casamitjana R, Zarranz JJ, Tolosa E, et al. Autoantibodies to glutamic acid decarboxylase in three patients with cerebellar ataxia, late-onset diabetes mellitus, and polyendocrine autoimmunity. Neurology 1997; 49: 1026-1030.

[18] Honnorat J, Saiz A, Giometto B, Vincent A, Brieva L, de Andrés C, et al. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies. Arch Neurol 2001; 58: 225-230.

[19] Vulliémoz S, Vanini G, Truffert A, Chizzolini C, Seeck M. Epilepsy and cerebellar ataxia associated anti-glutamic acid decarboxylase antibodies. J Neurol Neurosurg Psychiatry 2007; 78 : 187-189.

[20] Chattopadhyay S, Kriscenski-Perry E, Wenger DA, Pearce DA. An autoantibody to GAD65 in sera of patients with juvenile neuronal ceroid lipofuscinosis. Neurology 2002; 59: 1816-1817.

[21] Walkley SU, Baker HJ, Rattazzi MC, Haskins ME, Wu JY. Neuroaxonal dystrophy in neuronal storage disorders: evidence for major GABAergic neuron involvement. J Neurol Sci 1991; 104: 1-8.

[22] Gazulla J, Benavente I. Gangliosidosis GM2 del adulto: mejoria de la ataxia con fármacos GABAérgicos. Neurología 2002; 17: 157-161.

[23] Massella A, Gusciglio M, D’Intimo G, Sivilia S, Ferraro L, Calzá L, et al. Gabapentin treatment improves motor coordination in a mouse model of progressive ataxia. Brain Res 2009; 1301: 135-142.

[24] Trouillas P, Takayanagi T, Currier RD, Subramony SH, Wessel K, Bryer A, et al. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. J Neurol Sci 1997; 145: 205-211.

[25] Gazulla J, Errea JM, Benavente I, Tordesillas C. Treatment of ataxia in cortical cerebellar atrophy with the GABAergic drug gabapentin. A preliminary study. Eur Neurol 2004; 52: 7-11.

[26] Greenberg DA. Calcium channels in neurological disease. Ann Neurol 1997; 42: 275-282.

[27] Moshé SL. Mechanisms of action of anticonvulsant agents. Neurology 2000; 55 (Suppl 1): S32-S40.

[28] Kuzniecky R, Ho S, Pan J, Martin R, Gilliam F, Faught E, et al. Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults. Neurology 2002; 58: 368-372.

[29] Nakamura K, Yoshida K, Miyakazi D, Morita H, Ikeda S. Spinocerebellar ataxia type 6 (SCA 6): clinical pilot trial with gabapentin. J Neurol Sci 2009; 278: 107-111.

[30] Schmitz-Hübsch T, du Montcel ST, Baliko L, Berciano J, Boesch S, Depondt C, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. Neurology 2006; 66: 1717-1720.

[31] Gazulla J, Benavente I. Single-blind, placebo-controlled pilot study of pregabalin for ataxia in cortical cerebellar atrophy. Acta Neurol Scand. 2007; 116: 235-8.

[32] Vural M, Ozekmekci S, Apaydin H, Altinel A. High-dose piracetam is effective on cerebellar ataxia in patient with cerebellar cortical atrophy. Mov Disord 2003; 18: 457-459.

[33] Ince Gunal D, Agan K, Afsar N, Borucu D, Us O. The effect of piracetam on ataxia: clinical observations in a group of autosomal dominant cerebellar ataxia patients. J Clin Pharm Ther. 2008; 33: 175-8.
[34] Chan-Palay V, Plaitakis A, Nicklas W, Berl S. Autoradiographic demonstration of loss of labeled indoleamine axons in chronic diet-induced thiamine deficiency. Brain Res 1977; 138: 380-384.

[35] Trouillas P. The cerebellar serotonergic system and its possible involvement in cerebellar ataxia. Can J Neurol Sci 1993; 20 (S3): S78-S82.

[36] Lee MA, Strahlendorf JC, Strahlendorf HK. Modulatory action of serotonin on glutamate-induced excitation of cerebellar Purkinje cells. Brain Res 1986; 361: 107-113.

[37] Strahlendorf JC, Lee MA, Strahlendorf HK. Serotonin modulates muscimol- and baclofen-elicited inhibition of cerebellar Purkinje cells. Eur J Pharmacol 1991; 201: 239-242.

[38] Trouillas P, Garde A, Robert JM, Renaud B, Adeleine P, Bard J, et al. Régression du syndrome cérébelleux sous administration a long terme de 5-HTP ou de l’association 5-HTP-bensérazide. 26 observations quantifiées et traitées par ordinateur. Rev Neurol (Paris) 1982; 138: 415-435.

[39] Trouillas P, Brudon F, Adeleine P. Improvement of cerebellar ataxia with levorotatory form of 5-hydroxytryptophan. Arch Neurol 1988; 45: 1217-1222.

[40] Wessel K, Hermsdörfer J, Deger K, Herzog T, Huss GP, Kömpf D, et al. Double-blind crossover study of hydroxytryptophan in patients with degenerative cerebellar diseases. Arch Neurol 1995; 52: 451-455.

[41] Manto M, Hildebrand J, Godaux E, Roland H, Blum S, Jacqy J, et al. Analysis of FRDAst movements in cerebellar cortical atrophy: Failure of L-hydroxytryptophan to improve cerebellar ataxia. Arch Neurol 1997; 54: 1192-1194.

[42] Hurlé MA, Monti J, Flórez J. Fármacos ansiolíticos y sedantes. Farmacología de los trastornos del sueño. In: Flórez J, Armijo JA, Mediavilla A, editors. Farmacología humana. Barcelona: Elsevier Masson SA, 2008: 543-566.

[43] Trouillas P, Xie J, Getenet JC, Adeleine P, Nighoghossian N, Honnorat J, et al. Effet de la buspirone, un agoniste sérotoninergique 5-HT1A sur l’ataxie cérébelleuse: un étude pilote. Rev Neurol (Paris) 1995; 151: 708-713.

[44] Trouillas P, Xie J, Adeleine P. Treatment of cerebellar ataxia with buspirone: a double-blind study. Lancet 1996; 348: 759.

[45] Trouillas P, Xie J, Adeleine P, Michel D, Vighetto A, Honnorat J, et al. Buspirone, a 5-hydroxytryptamine1A agonist, is active in cerebellar ataxia. Results of a double-blind drug placebo study in patients with cerebellar cortical atrophy. Arch Neurol 1997; 54: 749-752.

[46] Lou JS, Goldfarb L, McShane L, Gatev P, Hallett M. Use of buspirone for treatment of cerebellar ataxia. An open-label study. Arch Neurol 1995; 52: 982-988.

[47] Andrade-Filho AS, Passos-Almeida J, Andrade-Souza VM, Sena-Pereira LR. Clorhidrato de buspirona en el tratamiento de la ataxia cerebelosa. Rev Neurol (Barcelona) 2002; 35: 301-305.

[48] Takei A, Hamada S, Homma S, Hamada K, Tashiro K, Hamada T. Difference in the effects of tandospirone on ataxia in various types of spinocerebellar degeneration: an open-label study. Cerebellum 2010; 9: 567-570.

[49] Bier JC, Dethy S, Hildebrand J, Jacqy J, Manto M, Martin JJ, et al. Efectos del preparado oral de ondansetrón sobre la disfunción cerebelosa. Un estudio multicéntrico doble ciego. J Neurol Ed Esp 2003; 1: 90-94.

[50] Berciano J, Pascual J. Farmacoterapia de los síndromes espinocerebelosos. Neurología 1990; 5: 200-204.
[51] Gracia Naya M, Pina Latorre MA. Ensayo terapéutico en una familia con atrofia cerebelosa tardía. Neurologia 1991; 6: 188-189.

[52] Sobue I, Yamamoto H, Konayaga M, Lida M, Takayanegi T. Effect of thyrotropin-releasing hormone on ataxia of spinocerebellar degeneration. Lancet 1980; 1; 418-419.

[53] Wessel K, Langenberger K, Nitschke MF, Kompf D. Double-blind crossover study with phystostigmine in patients with degenerative cerebellar diseases. Arch Neurol 1997; 54: 397-400.

[54] Ogawa M, Shigeto H, Yamamoto T, Oya Y, Wada K, Nishikawa T, et al. D-cycloserine for the treatment of ataxia in spinocerebellar degeneration. J Neurol Sci 2003; 210: 53-56.

[55] Jen JC, Yue Q, Karrim J, Nelson SF, Baloh RW. Spinocerebellar ataxia type 6 with positional vertigo and acetazolamide responsive episodic ataxia. J Neurol Neurosurg Psychiatry 1998; 65: 565-568.

[56] Yabe I, Sasaki H, Yamashita I, Takei A, Tashiro K. Clinical trial of acetazolamide in SCA 6, with assessment using the Ataxia Rating Scale and body stabilometry. Acta Neurol Scand 2001; 104: 44-47.

[57] Manto MU, Jacqy J. Alcohol toxicity in the cerebellum: clinical aspects. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 336-341.

[58] Henson RA, Urich H. Cancer and the nervous system. London: Blackwell Scientific, 1982: 346-367.

[59] Furneaux HM, Rosenblum MK, Dalmau J, Wong E, Woodruff P, Graus F, et al. Selective expression of Purkinje-cell antigens in tumor tissue from patients with paraneoplastic cerebellar degeneration. N Engl J Med 1990; 322: 1844-1851.

[60] Hildebrand J, Balériaux D. Cerebellar disorders in cancer. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 265-287.

[61] Bernal F, Shams‘ili S, Rojas I, Sánchez-Valle R, Saiz A, Dalmau J, et al. Anti-Tr antibodies as markers of paraneoplastic cerebellar degeneration and Hodgkin’s disease. Neurology 2003; 60: 230-234.

[62] Graus F, Lang B, Pozo-Rosich P, Saiz A, Casamitjana R, Vincent A. P/Q type calcium-channel antibodies in paraneoplastic cerebellar degeneration with lung cancer. Neurology 2002; 59: 764-766.

[63] Fukuda T, Motomura M, Nakao Y, Shiraisi H, Yoshimura T, Iwanaga K, et al. Reduction of P/Q-type calcium channels in the postmortem cerebellum of paraneoplastic cerebellar degeneration with Lambert-Eaton myasthenic syndrome. Ann Neurol 2003; 53: 21-28.

[64] Coesmans M, Sillevis Smitt PA, Linden DJ, Shigemoto R, Hirano T, Yamakawa Y, et al. Mechanisms underlying cerebellar motor deficits due to mGluR1-autoantibodies. Ann Neurol 2003; 53: 325-336.

[65] Berciano J. Olivopontocerebellar atrophy. A review of 117 cases. J Neurol Sci 1982; 53: 253-272.

[66] Berciano J, Boesch S, Pérez-Ramos JM, Wenning GK. Olivopontocerebellar atrophy: toward a better nosological definition. Mov Disord 2006; 10: 1607-1613.

[67] Gilman S, Little R, Johanss J, Heumann M, Kluin KJ, Junck L, et al. Evolution of sporadic olivopontocerebellar atrophy into multiple system atrophy. Neurology 2000; 55: 527-532.
[68] Berciano J. Multiple system atrophy and idiopathic late-onset cerebellar ataxia. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 178-197.

[69] Tu P, Galvin JE, Baba M, Giasson B, Tomita T, Leight S, et al. Glial cytoplasmic inclusions in white matter oligodendrocytes of multiple system atrophy brains contain insoluble α-sinuclein. Ann Neurol 1998; 44: 415-422.

[70] Berciano J. La nosología de la atrofia olivopontocerebelosa. Revisión crítica. Arch Neurobiol 1981; 44: 163-181.

[71] Perry TL, Kish SJ, Hansen S, Currier RD. Neurotransmitter amino acids in dominantly inherited cerebellar disorders. Neurology 1981; 31: 237-242.

[72] Kish SJ, Perry TL, Hornykiewicz O. Benzodiazepine receptor binding in cerebellar cortex: observations in olivopontocerebellar atrophy. J Neurochem 1984; 42: 466-469.

[73] Albin RL, Gilman S. Autoradiographic localization of inhibitory and excitatory amino acid neurotransmitter receptors in human normal and olivopontocerebellar atrophy cerebellar cortex. Brain Res 1990; 522: 37-45.

[74] Gilman S, Koeppe RA, Junck L, Kluin KJ, Lohman M, St Laurent RT. Benzodiazepine receptor binding in cerebellar degenerations studied with positron emission tomography. Ann Neurol 1995; 38: 176-185.

[75] Gahring LC, Rogers SW, Twyman RE. Autoantibodies to glutamate receptor subunit GluR2 in nonFRDA mimial olivopontocerebellar degeneration. Neurology 1997; 48: 494-500.

[76] Duvoisin RC, Chokroverty S, Lepore F, Nicklas W. Glutamate dehydrogenase deficiency in patients with olivopontocerebellar atrophy. Neurology 1983; 33: 1322-1326.

[77] Duvoisin RC, Nicklas W, Ritchie V, Sage S, Chokroverty S. Low leukocyte glutamate dehydrogenase activity does not correlate with any particular type of multiple system atrophy. J Neurol Neurosurg Psychiatry 1988; 51: 1508-1511.

[78] Grossman A, Rosenberg RN, Warmoth L. Glutamate and malate dehydrogenase activities in Joseph disease and olivopontocerebellar atrophy. Neurology 1987; 37: 106-111.

[79] Kish SJ, Robitaille Y, El-Awar M, Clark B, Schut L, Ball MJ, et al. Striatal monoamine neurotransmitters and metabolites in dominantly inherited olivopontocerebellar atrophy. Neurology 1992; 42: 1573-1577.

[80] Rinne JO, Burn DJ, Mathias CJ, Quinn NP, Marsden CD, Brooks DJ. Positron emission tomography studies on the dopaminergic system and striatal opioid binding in the olivopontocerebellar atrophy variant of multiple system atrophy. Ann Neurol 1995; 37: 568-573.

[81] Pascual J, Pazos A, del Olmo E, Figols J, Leno C, Berciano J. Presynaptic parkinsonism in olivopontocerebellar atrophy: clinical, pathological, and neurochemical evidence. Ann Neurol 1991; 30: 425-428.

[82] Kish SJ, Schut L, Simmons J, Gilbert J, Chang LJ, Rebbetoy M. Brain acetylcholinesterase activity is markedly reduced in dominantly-inherited olivopontocerebellar atrophy. J Neurol Neurosurg Psychiatry 1988; 51: 544-548.

[83] Whitehouse PJ, Muramoto O, Troncoso JC, Kanazawa I. Neurotransmitter receptors in olivopontocerebellar atrophy: an autoradiographic study. Neurology 1986; 36: 193-197.
[84] Higgins JJ, Harley-White J, Kopin IJ. Low lumbar CSF concentrations of homovanillic acid in the autosomal dominant ataxias. J Neurol Neurosurg Psychiatry 1995; 58: 760.

[85] Botez MI, Young SN. Biogenic amine metabolites and thiamine in cerebrospinal fluid in heredo-degenerative ataxias. Can J Neurol Sci 2001; 28: 134-140.

[86] Orozco G, Estrada R, Perry TL, Araña J, Fernández R, González-Quevedo A, et al. Dominantly inherited olivopontocerebellar atrophy from Eastern Cuba. Clinical, neuropathological, and biochemical findings. J Neurol Sci 1989; 93: 37-50.

[87] ÖZ G, Iltis I, Hutter D, Thomas W, Bushara KO, Gomez CM. Distinct neurochemical profiles of spinocerebellar ataxias 1, 2, 6 and cerebellar multiple system atrophy. Cerebellum 2010; DOI 10.1007/s12311-010-0213-6.

[88] Perry TL, Kish SJ, Hinton D, Hansen S, Becker LE, Gelfand EW. Neurochemical abnormalities in a patient with ataxia-telangiectasia. Neurology 1984; 34: 187-191.

[89] Botez MI, Botez-Marquard T, Elie R, Pedraza OL, Goyette K, Lalone R. Amantadine hydrochloride treatment in heredodegenerative ataxias: a double blind study. J Neurol Neurosurg Psychiatry 1996; 61: 259-264.

[90] Bonnet AM, Esteguy M, Tell G, Schechter PJ, Hardenberg J, Agid Y. A controlled study of oral vigabatrin (γ-vinilGABA) in patients with cerebellar ataxia. Can J Neurol Sci 1986; 13: 331-333.

[91] Currier RD, Collins GM, Subramony SH, Haerer AF. Treatment of hereditary ataxia with the levorotatory form of hydroxytryptophan. Arch Neurol 1995; 52: 440-441.

[92] Assadi M, Campellone JV, Janson CG, Veloski JJ, Schwartzman RJ, Leone P. Treatment of spinocerebellar ataxia with buspirone. J Neurol Sci 2007; 260: 143-146.

[93] Heo JH, Lee ST, Chu K, Kim M. The efficacy of combined estrogen and buspirone treatment in olivopontocerebellar atrophy. J Neurol Sci 2008; 271: 87-90.

[94] Kark RAP, Budelli MAR, Wachsner R. Double-blind, triple-crossover trial of low doses of oral physostigmine in inherited ataxias. Neurology 1981; 31: 188-192.

[95] Finocchiaro G, Di Donato S, Madonna M, Fusi R, Ladinsky H, Consolo S. An approach using lecithin treatment for olivopontoce rebellar atrophies. Eur Neurol 1985; 24: 414-421.

[96] Lawrence CM, Millac P, Stout GS, Ward JW. The use of choline chloride in ataxic disorders. J Neurol Neurosurg Psychiatry 1980; 43: 452-454.

[97] Harding AE. The hereditary ataxias and related disorders. Edinburgh, Churchill Livingstone, 1984.

[98] Pourcher E, Barbeau A. Field testing of an ataxia scoring and staging system. Can J Neurol Sci 1980; 7: 339-344.

[99] Sorbi S, Forleo P, FRDAni C, Piacentini S. Double-blind, crossover, placebo-controlled clinical trial with L-acetylcarnitine in patients with degenerative cerebellar ataxia. Clin Neuropharmacol 2000; 23: 114-118.

[100] Mori M, Adachi Y, Mori N, Kurihara S, Kashiwaya Y, Kusumi M, et al. Double-blind crossover study of branched-chain amino acid therapy in patients with spinocerebellar degeneration. J Neurol Sci 2002; 195: 149-152.

[101] Clauss R, Sathekge M, Nel W. Transient improvement of spinocerebellar ataxia with zolpidem. N Engl J Med 2004; 351: 511-512.

[102] Ristori G, Romano S, Visconti A, Cannoni S, Spadaro M, Frontali M, et al. Riluzole in cerebellar ataxia. A randomized, double-blind, placebo-controlled trial. Neurology 2010; 74: 839-845.
[103] Gazulla J, Benavente I. Mejoría sintomática de la atrofia olivopontocerebelosa con gabapentina. Rev Neurol 2005; 40: 285-288

[104] Duhigg WJ. Effects of propranolol on ataxic syndromes. Arch Neurol 1985; 42: 15.

[105] Buoni S, Zannolli R, Sorrentino L, Fois A. Betamethasone and improvement of neurological symptoms in ataxia-telangiectasia. Arch Neurol 2006; 63: 1479-1482.

[106] Gazulla J, Benavente I, Sarasa M. Ataxia-telangiectasia del adulto. Observación clínica y terapéutica. Neurología 2006; 21: 447-451.

[107] Harding AE. Friedreich’s ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. Brain 1981; 104: 589-620.

[108] Koeppen AH. Neuropathology of the inherited ataxias. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 387-405.

[109] Pandolfo M. The molecular basis of Friedreich ataxia. Neurología 2000; 59: 325-329.

[110] Butterworth RF, Giguere JF. Glutamic acid in spinal-cord gray matter in Friedreich’s ataxia. N Engl J Med 1982; 307: 897.

[111] Butterworth RF, Giguere JF. Amino acids in autopsied human spinal cord. Selective changes in Friedreich’s ataxia. Neurochem Pathol 1984; 2: 7-17.

[112] Huxtable R, Azari J, Reisine T, Johnson P, Yamamura H, Barbeau A. Regional distribution of amino acids in Friedreich’s ataxia brains. Can J Neurol Sci 1979; 6: 255-258.

[113] Bonnet AM, Tell G, Schechter Pj, Grove J, Saint-Hilaire MH, de Smet Y, et al. Cerebrospinal fluid GABA and homocarnosine concentration in patients with Friedreich’s ataxia, Parkinson’s disease, and Huntington’s chorea. Mov Disord 1987; 2: 117-123.

[114] Chavoix C, Samson Y, Pappata S, Prenant C, Maziere M, Seck A, et al. Positron emission tomography study of brain benzodiazepine receptors in Friedreich’s ataxia. Can J Neurol Sci 1990; 17: 404-409.

[115] Filla A, De Michele G, Orefice G, Santorelli F, Trombetta L, Banfi S, et al. A double-blind cross-over trial of amantadine hydrochloride in Friedreich’s ataxia. Can J Neurol Sci 1993; 20: 52-55.

[116] De Smet Y, Mear JY, Tell G, Schechter PH, Lhermitte F, Agid Y. Effect of gamma-vinyl GABA in Friedreich’s ataxia. Can J Neurol Sci 1982; 9: 171-173.

[117] Rustin P, von Kleist-Retzow JC, Chantrel-Groussard K, Sidi D, Munnich A, Rotig A. Effect of idebenone on cardiomyopathy in Friedreich’s ataxia: a preliminary study. Lancet 1999; 354: 477-479.

[118] Mariotti C, Solari A, Torta D, Marano L, Florentini C, Di Donato S. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. Neurology 2003; 60: 1676-1679.

[119] Buyse G, Mertens L, Di Salvo G, Matthijs I, Weidemann F, Eyskens B, et al. Idebenone treatment in Friedreich’s ataxia: neurological, cardiac, and biochemical monitoring. Neurology 2003; 60: 1679-1681.

[120] Ribat P, Pousset F, Tanguy ML, Rivaud-Pechoux S, Le Ber I, Gasparini F, et al. Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up. Arch Neurol 2007; 64: 558-564.

[121] Rinaldi C, Tucci T, Maione S, Giunta A, De Michele G, Filla A. Low-dose idebenone treatment in Friedreich’s ataxia with and without cardiac hypertrophy. J Neurol 2009; 256: 1434-1437.
[122] Lagedrost S, Sutton MSJ, Cohen MS, Satou GM, Kaufman BD, Perlman SL, et al. Idebenone in Friedreich ataxia cardiomyopathy-results from a 6-month phase III study (IONIA). Am Heart J 2011; 161: 639-645.

[123] Artuch R, Aracil A, Mas A, et al. Friedreich’s ataxia: Idebenone treatment in early stage patients. Neuropediatrics 2002; 33: 190-193.

[124] Di Prospero NA, Sumner CJ, Penzak SR, Ravina B, Fischbeck KH, Taylor JP. Safety, tolerability and pharmacokinetics of high-dose idebenone in patients with Friedreich ataxia. Arch Neurol 2007; 64: 803-808.

[125] Schulz JB, Di Prospero NA, Fischbeck K. Clinical experience with high-dose idebenone in Friedreich ataxia. J Neurol 2009; 256 (suppl 1): 42-45.

[126] Di Prospero NA, Baker A, Jeffries N, Fischbeck KH. Neurological effects of high-dose idebenone in patients with Friedreich’s ataxia: a randomized, placebo-controlled trial. Lancet Neurol 2007; 6: 878-886.

[127] Lynch DR, Perlman SL, Meier T. A phase 3, placebo-controlled trial of idebenone in Friedreich ataxia. Arch Neurol 2010; 67: 941-947.

[128] Mancuso M, Orsucci D, Choub A, Siciliano G. Current and emerging treatment options in the management of Friedreich ataxia. Neuropsychiatr Dis Treat 2010; 6: 491-499.

[129] Trouillas P, Serratrice G, Laplane D, Rascol A, Augustin P, Barroche G, et al. Levorotatory form of 5-hydroxytryptophan in Friedreich’s ataxia. Results of a double-blind drug-placebo cooperative study. Arch Neurol 1995; 52: 456-460.

[130] Peterson PL, Saad J, Nigro MA. The treatment of Friedreich’s ataxia with amantadine hydrochloride. Neurology 1988; 38: 1478-1480.

[131] Sturm B, Helminger M, Steinkellner H, Heidai MM, Goldenberg H, Scheiber-Mojdekar B. Carbamylated erythropoietin increases frataxin independent from the erythropoietin receptor. Eur J Clin Invest 2010; 40: 561-565.

[132] Boesch S, Sturm B, Hering S, Goldenberg H, Poewe W, Scheiber-Mojdekar B. Friedreich’s ataxia: clinical pilot trial with recombinant human erythropoietin. Ann Neurol 2007; 62: 521-524.

[133] Boesch S, Sturm B, Hering S, Scheiber-Mojdekar B, Steinkellner H, Goldenberg H, Poewe W. Neurological effects of recombinant human erythropoietin in Friedreich's ataxia: a clinical pilot trial. Mov Disord 2008; 23: 1940-1944.

[134] Boddart N, Le Quan Sang KH, Rötg A, Leroy-Willig A, Gallet S, Brunelle F, Sidi D, et al. Selective iron chelation in Friedreich ataxia: biologic and clinical implications. Blood. 2007; 110: 401-8.

[135] Tsou AY, Friedman LS, Wilson RB, Lynch DR. Pharmacotherapy for Friedreich ataxia. CNS Drugs 2009; 2009: 213-223.

[136] Liu J, Verma PJ, Evans-Galea MV, Delatycki MB, Michalska A, Leung J, et al. Generation of induced pluripotent stem cell lines from Friedreich ataxia patients. Stem Cell Rev 2010; doi: 10.1007/s12275-010-9210-6.

[137] Hammans SR. The inherited ataxias and the new genetics. J Neurol Neurosurg Psychiatry 1996; 61: 327-332.

[138] Subramony SH, Vig PJ. Friedreich ataxia type 3. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 428-439.

[139] Kitamura J, Kubuki Y, Tsuruta K, Kurihara T, Matsukara S. A new FRDA family with Joseph disease in Japan. Homovanillic acid, magnetic resonance, and sleep apnea studies. Arch Neurol 1989; 46: 425-428.
[140] Sakai T, Antoku Y, Matsuishi T, Iwashita H. Tetrahydrobiopterin double-blind crossover trial in Machado-Joseph disease. J Neurol Sci 1996; 136: 71-72.
[141] 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: 1451-1457.
[142] Sakai T, Matsuishi T, Yamada S, Komori H, Iwashita H. Sulfamethoxazole-trimethoprim double-blind, placebo-controlled, crossover trial in Machado-Joseph disease: sulFRDAmethoxazole-trimethoprim increases cerebrospinal fluid level of biopterin. J Neural Transm Gen Sect 1995; 102: 159-172.
[143] Mello KA, Abbott BP. Effect of sulfamethoxazole and trimethoprim on neurologic dysfunction in a patient with Joseph’s disease. Arch Neurol 1988; 45: 210-213.
[144] Sangla S, De Boucker T, Cheron F, Cambier J, Dehen H. Amélioration d’une maladie de Joseph par le sulfaméthoxazole-triméthoprime. Rev Neurol (Paris) 1990; 146: 213-214.
[145] Azulay JP, Blin O, Mestre D, Sangla I, Serratrice G. Contrast sensitivity improvement with sulfamethoxazole and trimethoprim in a patient with Machado-Joseph disease without spasticity. J Neurol Sci 1994; 123: 207-210.
[146] Monte TL, Rieder CRM, Tort AB, Rockennback I, Pereira ML, Silveira I, et al. Use of fluoxetine for treatment of Machado-Joseph disease: an open-label study. Acta Neurol Scand 2003; 107: 95-99.
[147] Takei A, Fukazawa T, Hamada T, Sohma H, Yabe I, Sasaki H, et al. Effects of tandospirone on “5-HTA1 receptor-associated symptoms” in patients with Machado-Joseph disease: an open-label study. Clin Neuropsycharmacol 2004; 27: 9-13.
[148] 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: 965-973.
[149] Liu C-S, Hsu H-M, Cheng W-L, Hsieh M. Clinical and molecular events in patients with Machado-Joseph disease under lamotrigine therapy. Acta Neurol Scand 2005; 111: 385-390.
[150] Tsuji S. Dentatorubral-pallidoluysian atrophy. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 481-490.
[151] Iizuka R, Hirayama K. Dentato-rubro-pallido-luysian atrophy. In: Vynken PJ, Bruyn GW, Klawans HL, editors. Handbook of Clinical Neurology, volume 5 (49). Amsterdam: Elsevier Science Publishers, 1986: 437-443.
[152] Smith JK. Dentatorubropallidoluysian atrophy. In: Vynken PJ, Bruyn GW, editors. Handbook of Clinical Neurology, volume 21. Amsterdam: Elsevier North Holland, 1975: 519-534.
[153] Yamada M, Sato T, Tsuji S, Takahashi H. Oligodendrocytic polyglutamine pathology in dentatorubral-pallidoluysian atrophy. Ann Neurol 2002; 52: 670-674.
[154] Kanazawa I, Sasaki H, Muramoto O, Matsushita M, Mizutani Y, Iwabuchi K, et al. Studies on neurotransmitter markers and striatal neuronal cell density in Huntington’s disease and dentatorubropallidoluysian atrophy. J Neurol Sci 1985; 70: 151-165.
[155] Miyata R, Hayashi M, Tanuma N, Shioda K, Fukatsu R, Mizutani S. Oxidative stress in neurodegeneration in dentatorubral-pallidoluysian atrophy. J Neurol Sci 2008; 264: 133-139.
Berciano J, Infante J, Mateo I, Combarros O. Ataxias y paraplejías hereditarias: revisión clínico-génetica. Neurología 2002; 17: 40-51.

Adelman JP, Bond CT, Pessia M, Maylie J. Episodic ataxia results from voltage-dependent potassium channels with altered functions. Neuron 1995; 15: 1449-1554.

Rajakulendran S, Schorge S, Kullmann DM, Hanna MG. Episodic ataxia type 1: a neuronal potassium channelopathy. Neurotherapeutics 2007; 4: 258-266.

Tomlinson SE, Tan SV, Kullmann DM, Griggs RC, Burke D, Hanna MG, Bostock H. Nerve excitability studies characterize Kv1.1 fast potassium channel dysfunction in patients with episodic ataxia type 1. Brain 2010; 133: 3530-3540.

Brun ER, van Weerden TW. Familial paroxysmal kinesigenic ataxia and continuous myokimia. Brain 1990; 113: 1361-1382.

D’Adamo MC, Imbrici P, Pessia M. Episodic ataxias as ion channel diseases. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge: Cambridge University Press, 2002: 562-572.

Spacey SD, Hildebrand ME, Materek LA, Bird TD, Snutch TP. Functional implications of a novel EA2 mutation in the P/Q-type calcium channel. Ann Neurol 2004; 56: 213-220.

Cuenca-León E, Banchs I, Serra SA, Latorre P, Fernández-Castillo N, Corominas R, et al. Late-onset episodic ataxia type 2 associated with a novel loss-of-function mutation in the CACNA1A gene. J Neuror Sci 2009; 280: 10-14.

Steckley JL, Ebers GC, Cader MZ, McLaclhan RS. An autosomal dominant disorder with episodic ataxia, vertigo, and tinnitus. Neurology 2001; 57: 1499-1502.

Cader MZ, Steckley JL, Dyment DA, McLaclhan RS. A genome-wide screen and linkage mapping for a large pedigree with episodic ataxia. Neurology 2005; 65: 156-158.

Farmer TW, Mustian VM. Vestibulocerebellar ataxia. A newly defined hereditary syndrome with periodic manifestations. Arch Neurol 1963; 8: 21-30.

Small K, Pollock SC. Ocular motility in North Carolina autosomal dominant ataxia. J Neuroophthalmol 1996; 16: 91-95.

Damji KF, Allingham RR, Pollock SC, Small K, Lewis KE, Stajich JM, et al. Periodic vestibulocerebellar ataxia, an autosomal dominant ataxia with defective smooth pursuit, is genetically distinct from other autosomal dominant ataxias. Arch Neurol 1996; 53: 338-344.

Escayg A, De Waard M, Lee DD, Bichet D, Wolf P, Mayer T, et al. Coding and noncoding variation of the human calcium-channel beta(4)-subunit gene CACNB4 in patients with idiopathic generalized epilepsy and episodic ataxia. Am J Hum Genet 2000; 66: 1531-1539.

Jen JC, Wan J, Palos TP, Howard BD, Baloh R. Mutation in the glutamate transporter EAAT1 causes episodic ataxia, hemiplegia, and seizures. Neurology 2005; 65: 529-534.

Matilla-Dueñas A, Sánchez I, Corral-Juan M, Dávalos A, Alvarez R, Latorre P. Cellular and molecular pathways triggering neurodegeneration in the spinocerebellar ataxias. Cerebellum 2010; 9: 148-166.

Schöls L, Bauer P, Schmidt T, Schulte T, Riess O. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. Lancet Neurol 2004; 3: 291-304.
The purpose of this book has been to depict as many biochemical, genetic and molecular advances as possible, in the vast field of the spinocerebellar ataxias.

**How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

José Gazulla, Cristina Andrea Hermoso-Contreras and María Tintoré (2012). Neurochemistry and Neuropharmacology of the Cerebellar Ataxias, Spinocerebellar Ataxia, Dr. José Gazulla (Ed.), ISBN: 978-953-51-0542-8, InTech, Available from: http://www.intechopen.com/books/spinocerebellar-ataxia/neurochemistry-and-neuropharmacology-of-the-cerebellar-ataxias