Neurochemistry and Neuropharmacology of the Cerebellar Ataxias

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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 γ-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.

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 hipothalamus

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-hydroxiindolacetic 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.

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.

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 anhidrase 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-sulfametoxazole (141,145) Serotonergic drugs: buspirone (92), fluoxetin (120), tandospirone (147, 48) Antiepileptic drugs: lamotrigine (146) Antiarrhythmic drugs: mexiletine (148) Riluzole (102)
Episodic ataxia type 1 Episodic ataxia type 2 Episodic ataxia type 3 Episodic ataxia type 4 Episodic ataxia type 5	Acetazolamide, phenytoin (156) Acetazolamide (161) Acetazolamide (164) Dimenhydrinate (166) 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 *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 H^3–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 (^{1}H 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^{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 *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 cardiomyopthy 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 myocardiopathy, who received 5 mg/kg per day of idebenone. The authors concluded that idebenone did not prevent the development of myocardiopathy, 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 in14q32.1, 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 *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 *CACNA1A*, that give rise to truncated α1A 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. Interictal 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 *CACNB4* (2q22-q23), that causes a change of one amino-acid (C104F) in the β4 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 *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.

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