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NEUROLOGICAL UPDATE

The neurological update: therapies for cerebellar ataxias in 2020

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Abstract
Cerebellar ataxias (CAs) represent a heterogeneous group of sporadic or inherited disorders. The clinical spectrum of CAs is continuously expanding. Our understanding of the mechanisms leading to the clinical deficits has improved over these last decades, in particular thanks to progress in genetics, neuroimaging and the advent of relevant animal models allowing the identification of the pathophysiological pathways leading to CAs. The rationale behind treatments is now established for most of the CAs encountered during daily practice worldwide. In this update, we will discuss the symptomatic, physical and occupational therapies now being trialled along with individualized exercises, and present key emerging issues on immune-mediated cerebellar ataxias, hereditary cerebellar ataxias. Finally, we will discuss novel therapeutic approaches, including cerebellar non-invasive stimulation and treatments acting on RNA/proteins. So far, no state-of-the art randomized placebo-controlled clinical trial has shown a convincing clinically relevant efficacy of any drug, with the exception of 4-aminopyridine for the symptomatic treatment of episodic ataxia type 2 and downbeat nystagmus (placebo-controlled trials).

Keywords Cerebellum · Ataxias · Therapies · RNA · DNA

Introduction

Cerebellar ataxias (CAs) embarce a group of disorders with heterogeneous clinical presentations [1]. CAs manifest clinically with a pure cerebellar syndrome or combined cerebellar and extra-cerebellar deficits, especially extrapyramidal movement disorders, pyramidal signs, cortical problems (seizures, cognitive impairment/behavioural symptoms), pigmentary retinopathy, and peripheral neuropathy [2]. Loss of balance leading to cerebellar dizziness, lack of coordination, blurred vision due to cerebellar oculor motor disorders, including downbeat nystagmus, and slurred speech are the commonest symptoms. CAs are increasingly being recognized, especially with the advent of novel genetic findings and neuroimaging tools. In addition, the development of relevant animal models has been a key step in establishing the molecular mechanisms behind CAs which has now reached a stage where targeted CAs therapies are being developed. We discuss in this update the major advances of these last years and highlight the therapies which will enter the clinic in the next decade.

General symptomatic therapies

Improvements in our understanding of the pathogenesis of cerebellar ataxias, especially the development of relevant models for human diseases, have led invitably to novel therapeutic strategies. We have now a better knowledge of the natural history of ataxias and several validated clinical scales have been developed [3]. These are key points for rigorous clinical trials. Symptomatic therapy is useful for spasticity, extrapyramidal symptoms, urinary urgency and depression [4]. Amantadine, dopaminergic and anti-cholinergics drugs have been proposed to reduce tremor, bradykinesia, or dystonia in spinocerebellar ataxia type 2 (SCA2) and SCA3. Kinetic tremor may respond to benzodiazepines, primidone, β-blockers, or chronic thalamic stimulation (DBS). Restless

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legs and periodic leg movements in sleep often show a relatively good response to dopaminergic agonists or clonazepam, at least in the early stages. Spasticity is managed with baclofen oral/intrathecal or tizanadine. Botulinum toxin may be used in dystonia and spasticity in SCA3, although small dosages should be used given the muscular atrophy that is seen in SCA3 patients. Urinary urgency is treated with anticholinergic drugs. Neuropathic pain usually responds to gabapentin, pregabalin, anti-depressants and patches of lidocaine. Muscle cramps, which are often present at the onset of the condition in SCAs 2, 3, 7, and DRPLA, are reduced with magnesium, quinine, or mexiletine. Piracetam is given for myoclonus and/or dementia/cognitive decline.

Physical and occupational therapies

Physical and occupational therapies are often offered. Physical therapy interventions aim to maintain or improve the individual's independence in all environmental contexts for as long as possible. Physiotherapy exercises might be complemented with training based on recently developed commercially available videogame technology ("exergames"). Individualized training promotes patient self-empowerment [5]. Some patients benefit from stretching exercises, especially for spasticity. However, there is a need for clear guidelines. Indeed, the available facilities and expertise still vary greatly between centers. Orthotics and physical therapy help maintain joint mobility.

Management of dysarthria and dysphagia includes logopedic treatment to prevent aspiration pneumonia, a common cause of death. Speech therapy is part of daily clinical care. Percutaneous endoscopic gastrostomy is proposed in advanced cases of dysphagia.

Immune-mediated cerebellar ataxias (IMCAs)

IMCAs are a group of neuroimmune disorders including gluten ataxia, primary autoimmune cerebellar ataxia (PACA), GAD65 antibody-associated CA, the cerebellar form of Hashimoto's encephalopathy, paraneoplastic cerebellar degeneration, post-infectious cerebellitis, Miller–Fisher syndrome, opsoclonus myoclonus syndrome (OMS), ataxia associated with systemic lupus erythematosus (SLE), Behçet disease and sarcoidosis [6]. The cerebellum is particularly enriched in antigens implicated in IMCAs [7]. A proportion of IMCAs respond to immunotherapies if they are administered at an early stage when the cerebellar reserve is still sufficient. Depending on the underlying antibodies, specific therapies based on strict avoidance of antigen exposure, oral prednisolone, intravenous methylprednisolone, intravenous immunoglobulins (IVIgs), immunosuppressants, plasma exchange and specific antibodies like ritixumab are now recommended (for Ref. see [8]).

For the rarer paraneoplastic cases (PCD), surgery of the neoplasm should be performed as soon as possible. Depending on the type of cancer, radiotherapy and/or chemotherapy are administered. Various kinds of immunotherapies (e.g., single drug therapy, or combinations of corticosteroids, IV Ig, plasmapheresis, immunosuppressants, and rituximab) are still used, but the response to immunotherapy is often disappointing [8]. Patients positive for anti-Ri antibody exhibit the best response to anti-neoplastic and immune therapies. Patients with anti-Tr antibodies and anti-CV2 antibodies show a long survival time, but they suffer from severe disability. There is a lack of evidence of significant differences in terms of response and prognosis among the various types of immunotherapies, in particular because of a lack of large-scale randomized studies on therapies [8].

Autosomal recessive cerebellar ataxias (ARCAs)

ARCAs are a group of disorders characterized by a high phenotypic heterogeneity and complex phenotypes with salient overlaps [9]. The diseases usually start in childhood or early adulthood. More than 200 genes have been identified as causing ARCA [10] of which the most common is Friedreich's ataxia (FRDA). Except for FRDA, which results from a non-coding repeat expansion in the majority of cases, almost all other ARCA mutations identified so far constitute conventional mutations. Three major mechanisms have been uncovered:

A. ARCAs associated with mitochondrial dysfunction

ROS and oxidative stress (FXN, TTPA)
Impaired metabolism (COQ8A, ANO10)
Impaired DNA maintenance (POLG)
Impaired transcription regulation (APTX)
Defective protein quality control (SPG7)
? (SACS)

B. ARCAs associated with a disorder of DNA repair

Involvement of double-strand break repair (ATM, SETX)
Involvement of single-strand break repair (APTX)
Susceptibility to ionizing radiations

C. ARCAs associated with impaired synaptic morphology or synaptic dysfunction of Purkinje cells

Aberrant morphology of the PC/parallel fiber synapse (ITPR1)
Impaired dendritic architecture (SYNE1)

Friedreich's ataxia (FRDA)

The discovery that frataxin plays a major role in the assembly of iron–sulfur clusters has led to novel therapeutic approaches [11]. FRDA is characterized by iron accumulation which impairs mitochondrial function and makes the cells become vulnerable to oxidative stress. Therapies that have been tried aim to either (1) increase frataxin expression (EPO, interferon gamma, transactivation of transcription TAT, etravirine) or (2) protect against oxidative stress to improve mitochondrial function (antioxidants: idebenone, coenzyme Q10, alpha-tocotrienol quinone; iron chelators: deferiprone). Histone deacetylase inhibitors have also been proposed. There is some hope for gene therapy. However, there is no evidence for clinical efficacy based on RCTs yet using this approach.

Idebenone

A first report has shown a reduction of the left ventricular mass in a small group of patients with FA. This has been confirmed in open trials. Treatment at an early phase of the disease (patients with mild deficits) was associated with an improvement of cerebellar function. The response on the ICARS scale was does-dependent and had no effect on biomarkers of oxidative stress in these patients. However, phase III trials (IONIA: two different doses of idebenone; MICONOS: randomized, double-blind, placebo-controlled trial with three doses of idebenone over 1 year period) were negative. An open-label extension study showed a trend in terms of improvement in neurological function over an 18-month period in young patients. A favourable effect on early-stage cases is not excluded. Still, the results of the studies are considered as inconclusive, i.e., we have so far no evidence for effectiveness [12].

Deferiprone

A detrimental effect on ataxia (worsening of FARS/ICARS scores) was observed with intermediate/high doses of deferiprone, unlike a favourable effect on cardiac hypertrophy (decline of left ventricular mass index as compared to an increase in the placebo-treated patients) [13]. Deferiprone/idebenone has been shown to stabilize neurological status and reduces cardiac hypertrophy. However, the combination of deferiprone/idebenone/riboflavin (triple therapy) showed no neurological or cardiac effects. Overall, the benefits remain uncertain.

Erythropoietin (EPO)

In animals, EPO has been shown to not only upregulate frataxin, but also induce a shift in the iron pool by promoting erythropoiesis. It stimulates mitochondrial biogenesis. In a first open study on a small group of patients (2.000 rhuEPO 3 weeks for 6 months), ataxia was reduced, frataxin levels increased and values of oxidative stress were reduced [14]. Studies using carbamylated erythropoietin (CEPO) were negative in terms of clinical improvement, despite a rise in frataxin levels. Double-blind placebo-controlled studies have not identified any superiority of EPO, so we have no evidence for efficacy with this agent.

Histone deacetylase inhibitors (HDAC inhibitors)

They modify heterochromatin into an active form. Laboratory studies indicate an up-regulation of frataxin expression. A phase I trial demonstrated an increase in frataxin mRNA levels, but possible toxic metabolites were also seen. Vitamin B3 (nicotinamide) acts as an HDAC inhibitor. An increase in FTX levels has been reported in an open study over a short period of 8 weeks. However, no clinical improvement was observed.

Interferon gamma-1b

In pre-clinical studies, interferon gamma-1b increases frataxin expression and exerts positive effects upon motor activities. However, a phase II study found no effect, unlike results from pilot studies. No benefit was found in the recent study of Lynch et al. [15].

Etravirine

The drug increases frataxin levels and restores the activity of iron–sulfur clusters [16]. Clinical trials are anticipated.

N-Acetyl-Cysteine (NAC)

This is a cysteine precursor with a strong antioxidant action making it an appealing drug candidate for the treatment of some cerebellar diseases. NAC exerts its antioxidant effect by providing cysteine to glutathione (GSH). GSH acts as a free radical scavenger, representing a major component of the oxidative stress regulating system. NAC has been used in patients with Friedreich's ataxia, ataxia–telangectasia and multiple system atrophy with some clinical benefits [17].

All in all, at the moment, we have no evidence from any RCT for clinical efficacy of any of the above mentioned pharmacological agents despite a sound rationale for trialling them in patients.

Ataxia with isolated vitamin E deficiency (AVED)

Ataxia with isolated vitamin E deficiency (AVED) occurs worldwide with a higher prevalence in Tunisia and to a lesser extent in the Mediteranean basin. The very low levels of vitamin E cause a progressive neurological syndrome mimicking Friedreich's ataxia. In presymptomatic individuals, the neurological manifestations of AVED are blocked if lifelong oral supplementation of vitamin E is provided. Ataxia improves of the vitamin (40 mg/kg) is administered at an early stage of symptomatic patients. Vitamin E stabilizes the progression if the disease even when it has evolved over several years. Proprioceptive deficits might remain unchanged. Plasma concentrations of vitamin E should be monitored every 6 months and should return to normal range. Meals enriched in fat are recommended. Smoking should be avoided.

Primary coenzyme Q deficiency

The metabolism of CoQ10 (ubiquinone 10) biosynthesis is complex, with eight genes involved in CoQ10 deficiencies. The juvenile ataxic phenotype associated with cerebellar atrophy is due to mutations of ADCK3 (CoQ8). The phenotype is complex. Therapy with CoQ10 supplementation or idebenone gives equivocal results in some patients. For patients with primary CoQ10 deficiency, high-dose oral supplementation (up to 50 mg/kg/day) is recommended [18].

Abetalipoproteinemia

The disorder results in malabsorption of fat and fat-soluble vitamins (vitamins A, E, D and less pronounced vitamin K). The lipoproteins transporting α-tocopherol are missing. The neurological deficits are presumed to be the consequence of vitamin E deficiency. Treatment includes dietary adaptation (low-fat diet improves steatorrhea), with decreased long-chain fatty acids and oral essential fatty acids. Patients receive fat-soluble vitamin supplementation orally (vitamin E 100–300 IU/kg/day, vitamin A 100–400 IU/kg/day, vitamin D 800–1200 IU/kg/day, vitamin K 5–35 mg/week) with regular blood level assessments to adjust daily doses [4]. Other supplementary nutrients like iron and folic acid can also be considered.

Cerebrotendinous xanthomatosis (CTX)

CTX is characterized by the accumulation of bile alcohols, especially cholestanol, in tissues. Chenodeoxycholic acid (15 mg/kg daily) improves the clinical status (cognitive signs, psychiatric manifestations, motor deficits) and reduces cholestanol levels [19]. Every effort should be made to avoid delays in diagnosis since early treatment prevents irreversible neurological deficits. Alternatively, 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors, such as pravastatin, can be administered. Combinations of both drugs are possible. The role of LDL-apheresis is unclear. Symptomatic treatment is recommended for seizures, spasticity and Parkinsonism. Cataracts may require extraction.

Wilson's disease and aceruloplasminemia

The disorder is effectively treated with D-penicillamine (1–2 g/day), trientine (15–20 mg/kg daily) and zinc acetate/sulfate (50–250 mg/day) [20]. Orthotopic liver transplant is reserved for the fulminant form.

Aceruloplasminemia is characterized by a complete ceruloplasmin deficiency, but heterozygotes may show hypoceruloplasminemia. Patients respond to desferrioxamine 500 mg intravenously twice a week.

Refsum's disease

The disease is associated with an accumulation of phytanic acid. Therapy is based on the Westminster-Refsum diet, complemented by apheresis or liver transplantation. Phytanic acid is contained in dairy products, beef and lamb, and fatty fish. Some patients may benefit from cochlear implantation with good audiological outcomes and from orthotopic liver transplantation with improvements of biochemical parameters in the infantile form.

Ataxia–telangiectasia (AT)

A double-blind randomized placebo-controlled crossover study with oral betamethasone (0.1 mg/kg/day) has showed improvement of the ICARS score in this condition [21]. The following factors need to be followed closely: exposure to sun, treatment of infections and exposure to radiations. There is an ongoing multinational rater-blinded phase II clinical trial with acetyl-L-leucine (4 g/day) in the US (NCT03759678) and Europe (EudraCT no. 2018-004407-39) with new primary endpoints: Clinical Impression of Change in Severity (CI-CS) of videos of each patient's change in performance on either the 8 Meter Walk Test (8MWT) or the 9 Hole Peg Test of the Dominant Hand (9HPT-D).

Niemann–Pick type C (NPC) and other lysosomal storage diseases with ataxia

Miglustat is an inhibitor of glucosylceramide synthase which plays a key role in glycosphingolipid synthesis. Miglustat (3×200 mg/day) improves oculomotor deficits, swallowing capacities and reduces the decline in ambulatory capacities in patients with NPC [22]. Based on a case series of 12

patients, there is Class IV evidence that 4 weeks of treatment with acetyl-DL-leucine (5 g/day) may improve cerebellar symptoms and quality of life of NPC patients [23]. These findings are the basis for an ongoing multinational rater-blinded phase II clinical trial in the US (NCT03759639) and Europe (EudraCT no. 2018-004331-71) to evaluate the effects of acetyl-L-leucine (4 g/day) in patients with NPC in terms of symptoms as well as the progression of the disease.

The modified amino-acid acetyl-DL-leucine has been used in France for many years for the symptomatic treatment of vertigo. In an animal model of acute unilateral labyrinthectomy, acetyl-DL-leucine restored the membrane potential of both depolarized and hyperpolarized vestibular neurons, presumably by interacting with membrane phospholipids such as phosphatidylinositol 4,5-bisphosphate [24]. Finally, a similar trial is ongoing for GM2 Ganlgiosidosis (Tay-Sachs and Sandhoff disease) in the US (NCT03759678) and Europe (EudraCT no. 018-004406-25).

Gaucher disease

The disorder is caused by a deficit in glucocerebrosidase (GBA1 mutation). The neuronopathic (acute type 2 and subacute type 3) form of Gaucher disease is characterized by primary CNS involvement. Treatment is based on enzyme replacement therapy and substrate-reduction therapies, often with minimal responses. Ambroxol (expectorant; small molecule chaperone) increases the activity of the enzyme [25]. High-doses show good safety and tolerability, increase lymphocyte glucocerebrosidase activity and reduce glucosylsphingosine levels in the cerebrospinal fluid. Clinically, myoclonic jerks, seizures, pupillary light reflex dysfunction and gross motor function markedly improve [25].

Biotidinase deficiency and SCL19A3 (deficiency of thiamine transporter)

Both disorders are treated with oral supplementation of biotin [26].

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS)

The disorder is characterized by a slowly progressive ataxia leading to severe imbalance and gait disorders. This is due to the combination of bilateral vestibulopathy, sensory polyneuropathy caused by a gangliopathy and cerebellar ataxia [27, 28]. Patients also exhibit dysautonomia [29]. The phenotype is heterogenous. A recessively inherited intronic repeat expansion (AAGGG) in the RFC1 gene has been uncovered recently thanks to novel bioinformatics tools [30, 31]. A specific treatment is not known yet.

Spinocerebellar ataxias (SCAs)

We currently have no drugs for preventing or curing SCAs. Some benefits on cerebellar and extra-cerebellar signs have been observed with pharmacologic treatments.

Slight benefits with acetazolamide and gabapentin have been reported in SCA6. Modest improvement in SARA scores has been reported with riluzole as compared to placebo. Riluzole is the sole drug with a class I evidence in terms of benefits for ataxic symptoms in SCAs [32]. Lithium has been tried in SCAs. No effect was observed in SCA2 and SCA3.

Some improvements have been observed with valproic acid (pan-HDAC inhibitor) 1200 mg/day in SCA3. In SCA38, DHA (docosahexaenoic acid: omega-3 polyunsaturated fatty acid well represented in the cerebellum) at a dose of 600 mg/day improves SARA score and also impacts positively on cerebellar metabolism as studied by FDG-PET [33].

A dysregulation of endocannabinoid signaling, in particular of CB_1 receptors, has been recently demonstrated in SCAs, especially in SCA 3, and, therefore, a pharmacological manipulation of this neuroprotective system represents potentially a promising therapeutic option in these disorders [34]. SCAs are a typical example of progressive diseases and it is thus essential to identify robust clinical, biological or neuroimaging biomarkers of onset and progression.

Episodic ataxias (EAs), cerebellar downbeat nystagmus and cerebellar gait disorders

For the most frequent subtype of EAs—EA2—two treatment options have been described: the carbonic anhydrase inhibitor acetazolamide and 4-aminopyridine. In 1978, acetazolamide was serendipitously discovered to prevent attacks in EA2 patients [35]. However, its efficacy has never been proven in a RCT. Clinical experience has shown that treatment with acetazolamide 250–1000 mg/day prevents or attenuates the attacks. Important to note, many patients discontinue the treatment with acetazolamide due to adverse events (such as paresthesia or nephrocalcinosis) or loss of response.

In 2004, the effects of treating EA2 with the potassium channel blocker 4-aminopyridine (4-AP) were first published in a case series [36]. In 2011, an RCT was published showing a significant effect of 5 mg tid [37]: the median monthly attack frequency decreased significantly with 4-AP (5 mg three times daily) compared to placebo (1.65 under 4-aminopyridine; 6.5 under placebo). In addition, the quality of life improved with 4-AP treatment and the

drug was well tolerated. Aminopyridines improve pacemaking activities in Purkinje cells (PC) and thus diminish the frequency of CA attacks. In a systematic review published in 2018 [32], the American Academy of Neurology recommended 4-AP for the treatment of EA2: "for patients with EA2, 4-AP 15 mg/day probably reduces the frequency of ataxia attacks over a 3-month period (1 class I study)." However, this formulation of 4-AP has no approval for this indication, in contrast to the sustained-release form (SR) of 4-AP (fampiridine), which is approved for the symptomatic treatment of gait disorders in multiple sclerosis (for Ref. see [38]). The SR form of 4-AP (and acetazolamide) is currently being evaluated in a prospective randomized placebo-controlled multi-center trial.

The common mechanism behind the therapeutic influence of aminopyridines in cerebellar disorders lies with their effect on PCs. In vitro studies demonstrate that 4-AP (in therapeutic concentrations) increases the resting discharge rate and excitability of PCs of the guinea pig cerebellum and the precision of pacemaking of PCs in the tottering mouse, an animal model of episodic ataxia type 2 (EA2) [39, 40]. Furthermore, AP normalizes the firing rate and the motor behavior in the ataxin-1 mutant mouse in vivo [41]. Further, animals treated early demonstrated better motor function in the longer term, which may be mediated by a neuroprotective effect due to an enhanced electrical activity of PCs [41].

For the rarer form EA1 carbamazepine, valproic acid and phenytoin are proposed [42].

Downbeat nystagmus (DBN)

This is a frequent form of acquired persisting fixation nystagmus [43], mostly due to cerebellar degeneration leading to a floccular hypofunction [44]. Aminopyridines have been showed to be effective in downbeat nystagmus regarding mean slow phase velocity, visual acuity and also cerebellar downbeat nystagmus [45] as was also shown in an RCT [46] (for Ref. see [47]). The shortage of 4-AP may have been overcome by the sustained relase form of 4-AP (4-AP-sustained release, Fampyra), which has also been shown to be efficient in observational case series [48].

In a retrospective case series, patients with cerebellar gait disorders due to different etiologies also benefitted from 4-AP [49]. The sustained-release form of 4-AP showed modest short-term improvements in a short-term trial with 16 patients with cerebellar ataxia (SAOA, SCA1/3/6, POLG mutation) [50].

Transcranial direct current stimulation

Non-invasive cerebellar stimulation (tDCS, rTMS) aims to modulate the excitability of the cerebellum [51]. Since (1) the cerebellum is heavily connected with the cerebral regions controlling motor, associative, and affective functions and (2) the cerebellum is a brain area easily accessible and highly responsive to neuromodulation for anatomical and electrophysiological reasons. Thus looking at tretaments that noninvasively act on the cerebello-thalamo-cortical pathways represents a promising approach, either alone or in combination with other therapies including medications and neurorehabilitation techniques. TMS is classically used to assess the inhibition of the Purkinje cells over the contralateral M1 through the dentato-thalamo-cortical pathways. A conditioning pulse is applied over the cerebellum (conditioning stimulus: CS, followed by a test pulse over the contralateral M1 (test stimulus; TS). This cerebellum-brain inhibition (CBI) is used as a biomarker of the inhibitory effect exerted by the cerebellar cortex over cerebellar nuclei. Repetitive TMS (rTMS) can be administered at a regular low (1 Hz)/high (25 Hz) frequency or using a theta-burst paradigm TBS (3 pulses at 50 Hz, at a frequency of 1–5 Hz). TBS can be delivered continuously (continuous TBI: cTBI) or using pauses (intermittent TBI: iTBI). Low-frequency rTMS and cTBS exert inhibitory effect, whereas high-frequency rTMS and iTBS reduce inhibition.

tDCS is increasingly being used, including by the patients themselves [52]. The technique is safe and cheap. Patients may complain of a transient itching or burning sensation below the electrodes. tDCS modulates the output of the cerebellar cortex, which exerts a profound inhibitory effect upon cerebellar nuclei, with minor spread around the cerebellum. First, encouraging reports were observed in genetic ataxias [53]. The therapeutic benefits of non-invasive cerebellar stimulation have been subsequently shown in a double-blind, randomized, sham controlled study in 19 ataxic patients [54]. A single session of anodal tDCS transiently improved the SARA score, the ICARS score, and performance on both the 9-holeole peg test and on the 8-meter walking time. In a double-blind, randomized, sham controlled trial with cerebellar tDCS (5 days/week for 2 weeks) in 20 ataxic patients, improvements were observed at 1 month and 3 months [55]. The reduction in SARA score was nearly 3 points at 3 months. Furthermore, the CBI was improved. Cerebello-spinal tDCS (5 days/week for 2 weeks) also improves all the scores [56].

It is likely that both tDCS and rTMS need to be administered at an early phase of the disorder to be effective, at a stage where the cerebellar reserve is still sufficient to respond. Once the cerebellar cortex is severely atrophic

(major loss of Purkinje neurons and interneurons), it is unlikely that these techniques will impact on the CBI to reshape cerebello-cerebral plasticity. Investigators and clinicians need to be cautious in case of history of seizures, brain surgery especially with metallic implants, pacemaker or active skin disorders.

Therapies in development

The current new innovative approach is mainly looking at therapies targeting RNA [57]. Therapies based on gene suppression are also very attractive because RNA pathways are often involved in CAs. RNA interference (RNAi) aims to inhibit the expression of mutated polyglutamine proteins in SCAs caused by expanded polyglutamine mutations. Intracerebellar injection of vectors expressing short hairpin RNAs decreases the expression of mutant proteins and improves disease phenotypes in SCA1 and SCA7 transgenic mice.

Prevention of protein misfolding and aggregation by overexpression of chaperones and by pharmacological treatments are also in the pipeline. Trehalose, which stabilizes polyglutamine-containing protein, reduces gait ataxia and gliosis in SCA17 mice. Chemical compounds that directly target polyQ aggregation without significant cytotoxicity have also been identified in high-throughput screens using cell-free assays or by targeting cellular pathways. Aggregate formation has been successfully targeted with inhibitors of transglutaminase, such as cystamine, which decreases apoptotic cell death and reduces disease features.

Antisense oligonucleotides (ASOs) are another promising therapautic approach. Specific ASOs down-regulate both wild-type and mutant ataxin in SCA2 and SCA3 mouse models, with improved motor function [58, 59]. In SCA2 mice, intrathecal administration of ASOs is associated with motor improvements and a reduction of the levels of ATXN2 proteins is found [58]. Injection in early manifest transgenic SCA3 mice reduces ATXN3 up to 8 weeks after treatment and prevents accumulation of ATXN3 up to at least 14 weeks after therapy [60] as well as rescuing motor impairment and abnormal Purkinje cell firing discharges. Long-term studies are, however, required to establish the chronic effects of ASOs, including on wild-type proteins. For glutamine-expanded proteins resistant to degradation, viral delivery of miRNAs targets the RNAi pathway to remove pathological mRNA [61].

Gene therapy and stem cell grafting approaches are also being considered for treating spinocerebellar neurodegenerations [62]. Delivery of frataxin-expressing AAV (adeno-associated virus) rescues the sensory neuropathy associated with frataxin deficiency in a conditional mouse model with complete frataxin deletion in parvalbumin-positive cells [63]. This is a pre-clinical proof of concept for gene therapy in FRDA. First experimental convincing results were obtained in young conditionally knockout mice, showing that a single administration of AAV9 coding for frataxin improved heart function and doubled the life of animals [64].

In vivo gene editing through the CRISPR/Cas9 technology is an attractive therapeutic strategy, albeit still at early stage of pre-clinical development. Promising results have been obtained in vitro with the excision of the GAA expanded repeat in cells from FA patients using gene-editing technologies. Reprogramming of cells using lentivirus is being assessed in laboratories. Reprogramming of AT fibroblasts is a typical example [65]. Lentiviral vectors rescue cellular defects in mutant AT cells, despite the limitation in terms of cargo capacity of these vectors [66].

Mesenchymal stromal cells (MSCs) are a promising therapeutic strategy for several neurodegenerative disorders [67, 68], because they are easily isolated and they are non tumorigenic [69]. MSCs not only replace the dead cells, but also exert a paracrine effect through production of neurotrophic factors. Cell grafts slow the progression of patients presenting with the cerebellar subtype (MSA-C) of multiple system atrophy [70]. Intrathecal injection of MSCs improves cerebellar morphology and motor behaviour in the transgenic mouse model of SCA1 [71]. Favourable effects have also been observed in the mouse model of SCA3 following multiple systemic injection of MSCs [72].

Conclusions and perspectives

CAs represent an expanding group of disorders characterized by numerous phenotypes. Novel therapies are emerging. Symptomatic improvements, ranging from slight to noticeable in some cases, are now possible in several CAs. Efficacy, however, can only be convincingly demonstrated on the basis of state-of-the-art prospective clinical trials with better clinically meaningful endpoints for symptomatic and disease modifying effects. In this context one has to take into account that many CAs are rare or ultra-rare diseases which requires adjusted study protocols and approval procedures for pharmacological agents. Other therapies targeting the RNA, including ASOs and gene and stem cell therapies in selected cases, are showing some promise. tDCS is safe, easy to administer and could be used in the early stages of CA when the cerebellar reserve in sufficient to obtain a response from the residual cerebellar cortex. Lack of mechanistic understanding and lack of strong biomarkers are drawbacks which require research investments and continuous efforts by the scientific community to improve our management of complex neurological disorders such as CAs.

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Compliance with ethical standards

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