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Movement Disorders (A Videnovich, Section Editor)

The Comprehensive Management of Cerebellar Ataxia in Adults

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Abstract

Purpose of review In this review, we present the multidisciplinary approach to the management of the many neurological, medical, social, and emotional issues facing patients with cerebellar ataxia.

Recent findings Our holistic approach to treatment, developed over the past 25 years in the Massachusetts General Hospital Ataxia Unit, is centered on the compassionate care of the patient and their family, empowering them through engagement, and including the families as partners in the healing process. We present the management of ataxia in adults, beginning with establishing an accurate diagnosis, followed by treatment of the multiple symptoms seen in cerebellar disorders, with a view to maximizing quality of life and effectively living with the consequences of ataxia. We discuss the importance of a multidisciplinary approach to the management of ataxia, including medical and non-medical management and the evidence base that supports these interventions. We address the pharmacological treatment of ataxia, tremor, and other associated movement disorders; ophthalmological symptoms; bowel, bladder, and sexual symptoms; orthostatic hypotension; psychiatric and cognitive symptoms; neuromodulation, including deep brain stimulation; rehabilitation including physical therapy, occupational therapy and speech and language pathology and, as necessary, involving urology, psychiatry, and pain medicine. We discuss the role of palliative care in late-stage disease.

Summary The management of adults with ataxia is complex and a team-based approach is essential.

Introduction

Cerebellar dysfunction can be due to many causes, from primary cerebellar diseases such as degenerative and genetic ataxias, to secondary causes of cerebellar dysfunction due to strokes, tumors, demyelinating disorders such as multiple sclerosis (MS), autoimmune/paraneoplastic syndromes, and toxic/metabolic etiologies. Symptoms include the cardinal features of the cerebellar motor syndrome (dysarthria, eye movement abnormalities, appendicular dysmetria, and gait ataxia), which are frequently debilitating. However, the management of ataxic disorders is often very challenging, due to considerable heterogeneity and the presence of symptoms spanning several different domains. Such non-ataxia symptoms include other movement disorders, spasticity, cramps, dysphagia, weakness, ophthalmological symptoms (reduced visual acuity, diplopia, nystagmus), peripheral neuropathy with neuropathic pain, autonomic dysfunction (notably in multiple system atrophy (MSA)), REM sleep behavior disorder and other sleep disorders, bladder and bowel symptoms, cognitive dysfunction, and psychiatric illness, often as part of the cerebellar cognitive affective syndrome (CCAS) [1]. There is currently no cure or disease-modifying treatment for ataxia, and there are no FDA approved treatments for the cerebellar motor syndrome.

The first step informing treatment is making the correct diagnosis, followed by treatment of the multiple symptoms seen in cerebellar disorders, with a view to maximizing quality of life and effectively living with the consequences of ataxia. Treatment should be multidisciplinary and includes medical and non-medical management, physical therapy (PT), occupational therapy (OT), speech and language pathology (SLP), and, as necessary, involving urology, psychiatry, and pain medicine and consideration of palliative care in the later stages of disease.

In this review, we present the multidisciplinary approach to the management of the many neurological, medical, social, and emotional issues facing patients with cerebellar ataxia. Our holistic approach to treatment, developed over the past 25 years in the Massachusetts General Hospital Ataxia Unit, is centered on the compassionate care of the patient and their family, empowering them through engagement, and including the families as partners in the healing process.

Making the diagnosis

To determine appropriate treatment in a patient with cerebellar disease, one must first establish the correct diagnosis. This involves taking a careful history, including a detailed family history, social history, presence of drug and alcohol use, occupational or other exposures, and other pertinent medical problems. In addition, the tempo of progression is often critical in establishing an etiology. A comprehensive neurological examination can determine whether a patient has a pure cerebellar syndrome or whether there are other extra-cerebellar manifestations, such as other movement disorders, spasticity, peripheral neuropathy, or autonomic features, which may point to a particular diagnosis. MRI imaging is essential and may indicate a certain diagnosis, such as pontocerebellar atrophy or the pontine "hot cross bun sign" associated with (but not exclusive to) MSA, the middle cerebellar peduncle sign in Fragile X Tremor Ataxia Syndrome (FXTAS), or other pathognomonic changes. Targeted laboratory testing may detect potentially treatable causes of ataxia, and testing can include vitamin E, coenzyme Q10, vitamin B12, TSH, and anti-TPO antibodies, with additional testing of paraneoplastic antibodies, or others where indicated. A lumbar puncture may be appropriate in certain cases, particularly if there is concern for an autoimmune, infectious (including prion disease), neoplastic/paraneoplastic or other systemic cause. Toxic etiologies are important to exclude, including excess alcohol, lithium, exposure to mercury, drugs of abuse-like heroin and organic solvents, and side effects of medications such as anticonvulsants, methotrexate, and metronidazole. If a genetic diagnosis is suspected, genetic testing is critical for management, genetic counseling, and satisfying the "need to know imperative". We start with evaluation for the triplet repeat disorders, because these are the most common genetic causes of ataxia and current exome sequencing does not detect repeat expansions. These include the spinocerebellar ataxias (SCA) (SCA1, 2, 3, 6, 7, 8, 10, 12, 17 ± DRPLA), as well as FXN (Friedreich's ataxia (FA)) and the fragile X expansion premutation as necessary. If this proves unrevealing, this can be followed by exome sequencing, potentially including sequencing of the mitochondrial DNA, to look for other known, rare, and novel genetic causes of ataxia. As technical advancements in genetic testing develop and costs continue to decrease, it is likely that we will modify this approach accordingly.

General pharmacological treatment of ataxia

It is important to identify potentially treatable ataxias and institute treatment as soon as possible. Primary vitamin deficiencies, such as ataxia with vitamin E deficiency [2], Wernicke's encephalopathy [3], or coenzyme Q10 deficiency [4] should be promptly treated. In addition, other ataxias may respond to coenzyme-Q10 supplementation, including those without documented coenzyme Q10 deficiency [5] and those harboring the ANO10 mutation (autosomal recessive cerebellar ataxia type 3) [6]. As such, we therefore advocate starting all patients on an antioxidant cocktail including, vitamin B complex, vitamin E 400 units/day, vitamin C 1000 mg/day, and coenzyme Q10 1200 mg/day.

A recent American Academy of Neurology (AAN) comprehensive systematic review has addressed the evidence for various treatment options in the ataxias [7••]. In a pilot randomized, double-blind, placebo-controlled trial in a mixed ataxia cohort, riluzole (50 mg 2 times/day) was felt to probably improve signs

of clinical ataxia at 8 weeks [8]. In a larger follow-up study in 60 patients (2:1 SCA:FA), there was improvement in ataxia rating scores in the treated group compared with placebo at 12 months [9••]. Given the rare risks of leukopenia and hepatic dysfunction [10], laboratory monitoring is recommended [7••]. A similar drug, troriluzole, is currently being studied in a large, multi-center clinical trial in SCA patients [11]. We therefore recommend considering riluzole in patients with ataxia, being mindful to monitor for potential laboratory and other side effects. In episodic ataxia type 2, acetazolamide (125 mg/day to 500 mg 2 times/day) may reduce frequency of attacks and attack severity [12•]. Furthermore, 4-aminopyridine (5–10 mg 3 times/day) may reduce frequency and severity of attacks [13], as well as avoidance of triggers. The AAN task-force review [7••] cited weak or insufficient evidence of efficacy for several other medications, some of which we use, including amantadine and serotonin reuptake inhibitors which may have modest benefit. Muscle cramps can be disabling in some of the SCAs and, in our experience, often respond to salt repletion, magnesium supplementation, gabapentin, and diazepam. Quinine is effective but its side effect profile (arrhythmia, thrombocytopenia) led to its prohibition for this purpose by the FDA in 2007.

Immune-mediated cerebellar ataxias are also potentially treatable and include primary autoimmune ataxias (Miller Fisher syndrome [14], anti-GAD65 Ab-associated ataxia [15], Hashimoto's encephalopathy [16], and gluten ataxia [17]), ataxia as part of an immune-mediated paraneoplastic syndrome [18] or in the setting of another inflammatory disorder, such as MS or systemic lupus erythematosus [19], and post-infectious cerebellitis [20].

Such autoimmune ataxias are often distinguished by a rapid progression and the presence of specific autoantibodies and may respond to typical immunomodulatory therapy. If suspected, antibody testing should be instituted and in the case of suspected paraneoplastic disease, the search for occult malignancy includes whole-body PET-CT [21]. Management is similar to other autoimmune disorders, with corticosteroids and consideration of intravenous immunoglobulin or plasmapheresis as first-line treatment, and rituximab, cyclophosphamide, or other agents employed in treatment-refractory cases [22•]. Subacute onset of a cerebellar syndrome may represent the cerebellar form of Creutzfeldt-Jakob disease, which at this time is not curable [23].

Pharmacological treatment of tremor and other movement disorders in the ataxias

Genetic ataxias may have mixed movement disorders other than ataxia, including dystonia, parkinsonism, chorea, and myoclonus, as well as sometimes debilitating tremor, including palatal tremor [24••].

The main evidence for treatment of postural and action tremor in cerebellar disorders comes from the treatment of other conditions, such as essential tremor [25]. Such strategies may be beneficial in the treatment of the tremor in FXTAS [26], and there is limited evidence for other causes of cerebellar tremor. Beta blockers, such as propranolol, are a common first-line treatment and are generally well tolerated. Other options include the anticonvulsants primidone (starting 25–50 mg/night) or topiramate (starting 100 mg/day) and

trihexyphenidyl (starting 2 mg 1–2 times/day) [25]. There was possible efficacy for levetiracetam in an open-label study of levetiracetam in MS patients with cerebellar tremor [27] Given a strong association with anxiety and tremor, benzodiazepines, such as clonazepam can also be effective. Botulinum toxin injections may be considered in medically refractory cases [28].

Dystonia may complicate several SCAs, and there are reports of levodopa-responsiveness in SCA 2, SCA 3, and SCA 6 [29–33]. There may not always be a sustained benefit to carbidopa/levodopa; however, rare cases may have dramatic improvement of dystonia [34]. We therefore suggest a trial of carbidopa/levodopa in patients with significant or troublesome dystonia in the setting of ataxia. Trihexyphenidyl may also provide symptomatic benefit. Botulinum toxin injections have established benefit in the treatment of focal dystonias [35] and have been used in the setting of ataxia [36, 37] and with baclofen, may also be useful in the treatment of spasticity [38].

Parkinsonism, including parkinsonian resting tremor in the SCAs may be carbidopa/levodopa responsive [39–42] and complications may include the development of dyskinesias [43]. This may also treat concurrent parkinsonism in MSA-C [44•].

Deep brain stimulation in ataxia

There is a growing body of literature on the application of deep brain stimulation (DBS) for the treatment of ancillary symptoms in ataxia, including tremor and dystonia.

There is increasing evidence for the use of DBS for the treatment of tremor associated with underlying ataxia syndromes. It may be challenging to disentangle ataxic dysmetria from tremor and in the case of disabling dysmetria being the major component, the potential efficacy of DBS is much less certain. Artusi et al. performed a systematic review on the use of DBS for uncommon causes of tremor [45••], including ten patients with FXTAS. Targets included the ventral intermediate nucleus (Vim) of the thalamus in 8/10 [45••], one also targeting the posterior subthalamic area (PSA) and another with additional bilateral subthalamic nucleus (STN) DBS [46–51]. There was tremor improvement in all patents and ≥ 50% reduction in 5/8 [45••]. Notably, four patients also reported improvement in ataxia symptoms [45••]. Adverse events in 5/8 included worsening ataxia and speech, as well as slight worsening of cognition [45••]. One patient underwent ventralis oralis posterior/zona incerta (VOP/ZI-DBS), with a descriptive improvement in tremor and ataxia [52] and another had PSA-DBS alone, with > 50% tremor improvement [53].

There is also evidence of efficacy of DBS in the treatment of medically refractory tremor in other ataxias, with substantial tremor improvement in two patients with SCA2, using Vim-DBS [54••] and STN-DBS [55]. Hashimoto et al. also reported efficacy of Vim-DBS in five SCA patients (two SCA6, SCA31 and two sporadic) and noted similar tremor improvement in the SCA cases to those with essential tremor (ET) (although the SCA cases required higher voltages), with significant functional improvement, despite no improvement in ataxia [56]. There is one case report of contralateral dentate nucleus DBS resulting in improvement of tremor and ataxia after a unilateral cerebellar stroke [57]. We therefore suggest that DBS could therefore be considered for the

treatment of medically refractory tremor associated with ataxia, although being mindful of reports of worsening gait [54••].

Targeting the globus pallidus interna (GPi) is a standard strategy for the treatment of generalized and some focal cases of dystonia [58]; however, there is very limited literature for its use in the setting of ataxia. Dystonic involvement is most common in SCA1, 2, 3, and 17 [24••]. There are reports of successful treatment using bilateral GPi-DBS, with near-complete resolution of generalized dystonia in SCA1 [59], improvement in dystonia and dystonic tremor in SCA17 [54••], improvement in dystonic tremor and myoclonus in SETX-associated ataxia [54••], and improvement of right arm segmental dystonia with unilateral GPi-DBS in a patient with EA2 [60]. We would therefore recommend the consideration of GPi-DBS for ataxia patients with prominent or disabling dystonia, as efficacy may be similar to that of primary dystonias.

França et al. in their systematic review of cerebellar neuromodulation suggest that this may be beneficial in ataxia patients [61]. Shiga et al. in a large placebo-controlled study of transcranial magnetic stimulation (TMS) in a mixed cohort of spinocerebellar degeneration patients (MSA and SCAs) appeared to demonstrate improvement in truncal ataxia, 10-m walk time, tandem steps, and standing capacity, although there was a clear placebo effect of the sham stimulation [62]. The AAN taskforce therefore concluded that cerebellar TMS possibly improves symptoms of ataxia [7••], although this treatment is limited by availability of centers and insurance coverage.

Neuropathic pain management in ataxia

Patients with ataxia and neuropathic pain may benefit from medications used in other cases with neuropathic pain, such as gabapentin, pregabalin (starting 75 mg 2 times/day), amitriptyline/nortiptyline (starting 10 mg/night), and duloxetine (starting 30–60 mg/day) or topical lidocaine patches [63•]. We have had some success with the use of topical desipramine cream. Opioids should be avoided if possible. Some patients may benefit from referral to a specialist pain clinic.

Physical therapy in ataxia

Cerebellar disease leads to specific gait abnormalities leading to gait instability, which can be a challenge to physical therapists (PT). Quantitative analysis reveals a wide-base gait with variable gait parameters. Gait changes included slower steps, variable foot placement, as well as step timing and amplitude, resulting in irregular gait speed and foot trajectory [64, 65], with a subsequent high fall risk [66].

Ilg et al. performed an open-label, 4-week intensive outpatient physical therapy program in patients with degenerative ataxia, involving three sessions per week involving static and dynamic balance, whole body movements, fall strategies, and fall and contracture prevention [67•]. There was significant improvement in ataxia symptoms and balance, quantitative motor performance, and activities of daily living (ADLs) [67•]. Furthermore, after transitioning to a home exercise program, the improvements persisted at 1-year follow-up [68]. A study of daily inpatient physical and occupational therapy

resulted in improved ataxia and functioning after the 4-week intervention, with > 50% having some sustained improvement [69•].

Choosing the correct walking aid is important, and there is a choice of canes and walkers which should be appropriate to the height of the patient, including those with a heavy base of support (to prevent falls from retropulsion) and consideration of the new all-terrain walkers, which can facilitate walking outdoors. Additional strategies may include wearing a weighted vest for truncal loading [70], which may benefit some patients. Service/walker dogs can provide stability as well as companionship and have been transformative in the care of some of our adults and children with ataxia. A PT who knows how to employ ataxia-specific expertise is essential, providing strategies for a more stable and safer gait, teaching how to prevent falls or how to fall more safely. This can reduce the risks of injury associated with falling and provide patients with improved function, as well as greater confidence and independence.

Occupational therapy in ataxia

There is limited literature on the use of occupational therapy (OT) in the treatment of ataxia patients. An uncontrolled study of OT in SCA3 revealed stability in disability score but improvement of depressive symptoms [71]. Ataxia-specific dysfunctions include abnormalities of motor control, including appendicular dysmetria, dysdiadochokinesia, dyssynergia, tone alterations, tremor, or other movement disorders and visual dysfunction [72•]. Having an occupational therapist who specializes in working with patients with neurological diagnoses can be useful in treatment of improving performance in ADLs and instrumental activities of daily living (IADLs). Treatment is commonly focused on using task specific training and teaching environmental strategies and adaptive movement techniques to maximize safety and independence with ADLs and IADLs.

Gillen provides a comprehensive overview of the complexities of OT treatment in ataxia and can be useful as a guide for OTs [73••]. The goal of therapy is to identify limitations and to provide strategies to integrate movement into the most effective and efficient manner possible. OT interventions can include the use of orthotics (i.e., wrist brace) and/or environment adaptations (i.e., support forearms on table, ensure sitting in chair with supportive back rest) [74] for increased support of limb and trunk to increase stability, motor control retraining to decrease degrees of freedom required to participate in tasks and training using adaptive equipment. In addition, exploring the use of weighted devices [75], such as dampening the computer mouse and assistive technology modifications for computer use, may help compensate for action tremor [76] and assist with improving performance of ADL and IADL tasks [77, 78]. Relaxation techniques and biofeedback may help with anticipatory anxiety prior to manual tasks [79].

Driving and ataxia

Symptoms of ataxia may make safe driving more difficult. Important physical aspects involved in driving include vision, cognition, physical functioning such as reaction time and manual dexterity, as well as mobility and the complex

interaction of these components, all of which may be impaired in the setting of cerebellar disorders. Patients should be counseled that if they have concern regarding their driving or are having accidents, they should not drive. Family members may also voice concerns and should be heard. If the patient and family are unsure regarding their driving ability, specialized programs exist, which involve a standardized on and off-road driving assessments, typically completed by an occupational therapist [80•,81]. In the event of a patient being deemed unsafe to drive, transportation alternatives can allow continued independence.

Speech, language, and swallowing in ataxia

Dysphagia, dysarthria, and cognitive-linguistic deficits are common in ataxia and have a significant impact on a patient's health and well-being. Therefore, the speech and language pathologist (SLP) plays an essential role in the multidisciplinary treatment team.

Patients presenting with ataxic dysarthria exhibit a scanning pattern of speech, disturbed articulation of both consonants and vowels, and abnormal voice quality [82•], often requiring multiple treatment approaches [83]. The SLP conducts a comprehensive assessment of a patient's respiration, phonation, resonance, articulation, and prosody to properly diagnose ataxic dysarthria [82•] and identifies appropriate treatment goals for each of these areas. Therapy is conducted in this hierarchical order, as suggested by the principals of motor learning [84]. Treatment approaches that emphasize methods to increase willingness and independence, internal cueing, self-evaluation, and self-correction are essential for motor speech treatment of both cognitively normal and cognitively impaired patients [85]. Unfortunately, no medications have yet been shown to improve speech in ataxia [86•].

Patients with ataxia experience breakdown in swallowing physiology [87•]. Video fluoroscopic swallowing study is the gold standard for assessment of swallowing physiology and evaluation of benefit from postural compensatory strategies. A recent Cochrane Systematic Review describes the benefits from direct (i.e., Valsalva) and indirect interventions (oral motor exercises), as well compensations (diet modifications) to maximize safe and efficient swallowing in the ataxic patient [87•]. Excess salivation and drooling can be troublesome in the later stages of the ataxias and usually improves with glycopyrrolate by mouth, scopolamine patch every 3 days, and atropine 1% ophthalmic drops administered sublingually. Botulinum toxin injection into salivary glands may be required in severe cases [88]. Safe swallowing and appropriate dietary modification may help prevent aspiration and its sequelae, including aspiration pneumonia, which may be life-threatening but a gastrostomy tube may be required.

Ophthalmological symptoms in ataxia

The cerebellum is involved in the mediation of most categories of eye movements. The dorsal motor vermis and fastigial nuclei mediate saccadic initiation and termination [89•]. The flocculus and nodule subserve gaze-holding, smooth pursuit, and modulation of vestibular-mediated eye movements [90].

Vergence tone is subserved by the emboliform, globose, and fastigial nuclei [91]. Improper regulation of these efferent visual functions results in predictable symptoms. Saccadic abnormalities produced by cerebellar dysfunction (e.g., saccadic hypermetria and hypometria) are typically asymptomatic owing to suppression of afferent visual signals during saccades [92]. Conversely, the slow eye movements which define nystagmus tend to be highly symptomatic. Abnormalities of vergence may result in diplopia if marked enough and may require monocular occlusion, prism therapy, or strabismus surgery when the ocular misalignment is too large to manage with prisms and is stable over time.

Downbeat nystagmus and upbeat nystagmus arise from dysregulation of the vestibular-driven maintenance of the vertical set-point of vision leading to a slow vertical ocular drift followed by a corrective saccade [93]. These result in oscillopsia and degradation of visual acuity when present in primary position. Treatments include 4-aminopyridine (10 mg/day) [94, 95], 3,4-diaminopyridine (20 mg up to 4 times/day) [96], clonazepam [97], and baclofen (5 mg 3 times/day) [98].

Periodic alternating nystagmus (PAN) is characterized by a spontaneous, horizontal, jerk nystagmus, which reverses direction every 90 s with 5–10 s of rest between directions. When acquired, PAN typically implicates damage to the nodulus or uvula, thought to disinhibit vestibular networks which demonstrate periodicity [99, 100]. Baclofen may be effective [101].

Oculopalatal myoclonus (OPM), constituted by palatal myoclonus and vertical pendular nystagmus, results from disruption of the triangle of Guillain-Mollaret [102]. Gabapentin and memantine may be helpful and retro-orbital botulinum toxin injections have been tried [103].

Bladder, bowel, and sexual symptoms in ataxia

Bladder and bowel symptoms are frequent and underappreciated in patients with ataxia and are a frequent source of morbidity [104•]. In a large case series of patients with MSA and in patients with MSA-C, constipation was present in 45.8% and urinary symptoms in 90.6% [104•]. Studies also report high levels of lower urinary tract symptoms (LUTS) in FA, frequently associated with a worse quality of life [105], with many not treated, despite significant symptoms [106•].

Management of neurogenic lower urinary tract dysfunction (NLUTD) associated with ataxias aims to improve symptoms and quality of life. A video-urodynamic study (VUDS) is essential in order to understand the nature of the NLUTD and its management. Occasionally, VUDS may indicate upper urinary tract pathology, which should be addressed, or other systemic diseases causing LUTS. Management of LUTS is usually conservative. Neurogenic detrusor overactivity (NDO) is usually managed with peripherally acting antimuscarinics as monotherapy (oxybutynin 5-10 mg/day, tolterodine 4 mg/day, trospium 20 mg 2 times/day, solifenacin 5–10 mg/day, etc.) or in combination with a beta-3 agonist (mirabegron 50 mg/day) [44•]. The role of intravesical botulinum toxin injections for NDO in the ataxias has yet to be established. Neurogenic detrusor underactivity is usually managed with alpha-blockers (tamsulosin 0.4–0.8 mg/day, alfuzosin 10 mg/day, silodosin 4–8 mg/day, terazosin 2–10 mg/day). Occasionally, a cholinomimetic (bethanechol

50–200 mg/day) is efficacious, though there is no evidence-based data to support its use. Clean, intermittent, straight catheterization is always a consideration, as is permanent drainage with a suprapubic catheter.

Constipation is a frequent sign of autonomic dysfunction and is common and often severe in the setting of MSA [107]. Treatment is symptomatic and should start with high fluid and fiber intake, prune juice, psyllium, and senna, followed by PRN and regular laxatives, such as, polyethylene glycol and sodium docusate [44•].If severe, linaclitide may be considered, generally under the supervision of gastroenterology [108].

In a study of FA by Lad et al., 25% reported sexual dysfunction and was associated with urinary or bowel symptoms [106•]. Sildenafil [109] and intracavernosal injections may be beneficial [44•].

Autonomic symptoms in ataxia: orthostatic hypotension

Autonomic symptoms are frequently severe and disabling in MSA-C and may complicate other ataxias. They include symptoms of orthostatic hypotension, ranging from mild postural lightheadedness to syncope, as well as bowel and bladder symptoms and erectile dysfunction addressed above. Diagnosis is frequently clinical, with demonstration of a > 20 mmHg systolic or > 10 mmHg diastolic blood pressure drop from lying for 5 min to standing for at least 2 min [110]. Autonomic/tilt-table testing may be required to confirm the diagnosis in less obvious cases. Treatment involves the careful balance of elevating standing and sitting blood pressure to avoid orthostatic symptoms and syncope which can lead to falls and other untoward sequelae with the risk of supine hypertension, which can be severe. We recommend starting with pyridostigmine (starting 30–60 mg 2–3 times/day), which has a modest effect but has the benefit of not worsening supine hypertension. Other options include fludrocortisone (starting 0.1 mg/day) and midodrine (starting 2.5–5 mg 2–3 times/day) or the newer agent droxidopa (starting 100 mg 3 times/day) [111, 112]. Increasing salt and fluid intake or wearing compression stockings may be beneficial [113]. Practical suggestions include positioning a commode at the bedside to avoid unnecessary ambulation overnight and some patients may require a catheter placement if the act of micturition results in exacerbation of autonomic dysfunction.

Psychiatric and cognitive symptoms in ataxia

Early recognition of psychiatric symptoms in ataxia is very important, as this can have a significant bearing on quality of life. Psychiatric symptoms, including depression and anxiety, often accompany neurogenetic and other ataxias and can involve all stages of disease. This may be due to their role as part of the cerebellar cognitive affective syndrome, which may include impairment of executive functions, visual-spatial organization and memory, and affective domains of attention control, emotion control, autism spectrum, psychosis spectrum, and social skill set [1]. Another aspect is the adaptive emotional response to living with a degenerative disease and the dealing with the uncertainty surrounding progressive debility.

In the large study of Lo et al., depression was common, present in 26% of a large cohort of SCA patients [114•] and in 40–62% of MSA patients [115, 116], with worse symptoms correlating with more severe physical symptoms. Depression had a negative impact on functional status and quality of life in the SCAs, independent of disease progression [114•].

Various treatment options are available for psychiatric disorders and are outside the scope of this review; however, selective serotonin reuptake inhibitors (SSRIs; particularly sertraline, citalopram, and escitalopram) have a generally lower side-effect profile and may be valuable for the treatment of both depressive symptoms and anxiety [63•]. Duloxetine may have an added advantage by its role in the concurrent treatment of neuropathic pain. Treatment with a therapist and/or a psychiatrist may be indicated in more severe symptoms. Suicidal ideation is not infrequent in the SCAs [114•] and its presence may require psychiatric assessment or hospitalization.

There is little evidence in the literature pertaining to the treatment of cognitive dysfunction in ataxia and clinicians' use off-label treatments used in Alzheimer's disease and other degenerative dementias [117]. Pharmacological treatments include the cholinesterase inhibitors donepezil, galantamine, and rivastigmine and the NMDA receptor antagonist memantine [117]. The benefit of these medications in the ataxias is uncertain.

Alternative treatments in ataxia

Alternative treatments, such as tai chi in Parkinson's disease, may improve balance and reduce falls [118•] and may be beneficial in ataxia patients. Furthermore, high intensity treadmill exercise may slow progression of Parkinson's disease [119]. We recommend that ataxia patients continue to regularly exercise, while safe to do so. There are anecdotal reports of acupuncture helping some ataxia patients and reports in the Chinese literature of potential benefit [120]; however, further research is needed to make any definite assertions.

Palliative care and end-of-life issues in the ataxias

Palliative care is an important component of care for many of the ataxias and other degenerative disorders [121••]. Palliative care is specialized medical care aimed at improving quality of life for patients with serious illness. Palliative care can be delivered alongside curative and supportive therapies and focuses on relieving both the physical and emotional toll illness can have on patients and their families. Neurologists and their teams provide the first level of palliative care, termed "primary palliative care" [122]. Patients with more intensive needs may benefit from referral to a palliative care specialist.

Palliative care symptoms include physical, emotional, and spiritual symptoms. The care of the physical symptoms of the ataxias is described above and include both the motor and non-motor symptoms. Addressing the emotional symptoms and loss experienced in the progressive ataxias is an important aspect of care.

Serious illness conversations are another key component of palliative care for patients. A serious illness conversation is a discussion between the patient and provider about their goals, values, and understanding of their illness.

During these discussions, clinicians can better ascertain patients' prognostic awareness and support medical decisions that align with patient's goals [123]. Advance care planning is one component of these conversations and encourages early discussions about medical decision making such as discussion regarding placement of a gastrostomy tube, designation of health care proxy and power of attorney, and discussions about advance directives. Research in non-neurology populations has shown that patients who have serious illness conversations with providers report higher quality of life and are more likely to have their wishes followed [124, 125]. Additionally, surviving relatives of patients who had advance care planning report significantly less stress and depression than those who had not had facilitated discussions [126]. The optimal timing of these discussions in patients with neurodegenerative disease has not been established, though one proposed model for patients with MSA suggests several symptom-based triggers for serious illness conversations, such as frequent falls, development of dysphagia, and severe orthostatic changes [127].

In addition to patients' needs, caregivers' needs require careful assessment. Caregiver burden is high in patients with neurodegenerative illness. One study estimated that 63% of caregivers of patients with MSA report depression [128]. Caregivers may be at risk for poor health and mortality compared to age-matched controls [129]. More research is needed to better assess caregivers' needs in the ataxias and to develop an appropriate care plan.

For patients with advanced illness, hospice may be helpful. Hospice is a philosophy of care appropriate for patients who are no longer seeking curative treatment and who are estimated to be in the last 6 months of life. Hospice can be provided in the home, in a nursing facility, or in a hospice-designated facility. Neurologists can continue to provide longitudinal care to their patients throughout their illness, including after enrollment in hospice [130].

Furthermore, another important end-of-life issue involves discussion regarding the important subject of brain donation. This should be done when appropriate but does not necessarily need to be done at the end stages of disease. Brain donation allows families to better understand what happened to their loved one and also to help others through better understanding of disease through research [131].

Conclusion

The treatment of ataxic disorders is complex and requires a multi-disciplinary approach. Identifying the cause of the ataxia is the first step and subsequent treatment is directed towards the many different symptomatic domains seen in patents with cerebellar disease. Providing a holistic care for the whole patient is important, as is addressing psychiatric symptoms, which may be overlooked. Referral for palliative consultation and hospice care may be beneficial in late-stage disease, with a focus on maximizing quality of life.

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Compliance with Ethical Standards

Conflict of Interest

Kate Brizzi, Marc Bouffard, Pablo Gomery, Stacey Sullivan, Julie Mello, and Julie MacLean declare no potential conflicts of interest. Jeremy Schmahmann reports personal fees from Bayer, personal fees from Biogen, personal fees from Biohaven, personal fees from Cadent, personal fees from Pfizer, outside the submitted work; in addition, Dr. Schmahmann has a Brief Ataxia Rating Scale licensed to Schmahmann and the General Hospital Corporation, a Cerebellar Neuropsychiatric Rating Scale pending to Schmahmann and the General Hospital Corporation, and a Cerebellar Cognitive Affective syndrome/Schmahmann Scale pending to Schmahmann and the General Hospital Corporation, and Royalties from Elsevier, MacKeith, Oxford, Springer; Grants from National Ataxia Foundation, Ataxia-Telangiectasia Children's Project, MINDlink Foundation. Christopher D. Stephen has been paid for work as an investigator as part of a multi-center US trial of troriluzole in the ataxias.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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