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CRPD frontiers in movement disorders Therapeutics: From evidence to treatment and applications
Addressing Patients' Needs in the Management of the Ataxias

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ABSTRACT

The genetic ataxias have no cures and no proven ways to delay progression (no disease-modifying therapies). The acquired ataxias may have treatments that address the underlying cause and may slow or stop progression, but will not reverse damage already sustained. The idiopathic ataxias (of unknown genetic or acquired cause) also have no proven disease-modifying therapies. However, for all patients with ataxia of any cause, there is always something that can be done to improve quality of life—treat associated symptoms, provide information and resources, counsel patient and family, help with insurance and disability concerns, be available to listen and answer the many questions they will have.

1. The Patient with a Chronic Progressive Incurable Neurologic Disease: Questions Patients Ask

Over many years of treating patients with ataxia, these are the questions most often asked and typically represent their current and future needs:

- What do I have?
- What is the cause?
- Are my children at risk?
- Can it be cured?
- Will it get worse?
- How bad will it get? How soon?
- Can my symptoms be relieved?
- Is there any research being done?

Table 1. Advances in Diagnosis and Treatment of Ataxia
And these are the things the clinician spends most of the time doing:

- Writing prescriptions for symptomatic medication
- Filling out insurance forms
- Filling out jury duty excuses
- Filling out disability forms
- Signing death certificates
- Recruiting them for teaching exercises in the School of Medicine
- Banking DNA and trying to contribute to the search for new ataxia genes
- And, answering a lot of questions

2. What do i have?

Most ataxic patients by the time they are referred to a neurologist or a movement disorders specialist have had neurological examination and brain imaging done to confirm a cerebellar disorder and screening for other medical illnesses or acquired factors that could cause ataxia [1,2] (Table 2). Other diagnostics (eg. ophthalmological assessment, electronystagmography, electromyography and nerve conduction studies) can help rule in or out other contributors to the ataxia symptoms [3]. Genetic counseling can help with choice of genetic tests and family counseling.

3. What is the cause?

75 % of ataxias can be traced to visible cerebellar lesions [4](injuries, strokes, tumors, demyelinating lesions), other medical illnesses and acquired factors (inflammatory, post-infectious, immune-mediated, paraneoplastic, metabolic and vitamin deficiencies, toxic exposures), or genetic changes. Some can be identified by phenotype as specific degenerative conditions (eg. Multiple system atrophy [5]). The remainder are termed "idiopathic" and still being evaluated for as yet

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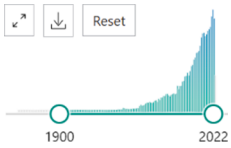
Table 1
Advances in Diagnosis and Treatment of Cerebellar Ataxia.

QUESTION	1977	2002	2022
What do I have?	10 % of causes known	50 % of causes known	75 % of causes known
Can it be cured?	No	No	No
Can it be treated?	No drugs tested Rehabilitation helps	18 drugs tested Rehabilitation helps	251 interventional trials 1 FDA approved drug (for Friedreichs ataxia)[36–38] Rehabilitation helps [9,39–41]
Is there research?	3472 publications	17,512 publications	51,297 publications (PubMed) 
Are my children at risk?	No gene tests available	16 single gene tests available	15 tests available for repeat expansions Whole exome sequencing available Whole genome sequencing available Copy number variation and deletion analysis available Chromosomal analysis available

unknown genetic or acquired causes. In patients with onset of ataxia over the age of 70, the most likely cause is multifactorial.

4. Are my children at risk?

With a known family history of ataxia, questions about risk for the next generation are expected. If the genetic factor is known, single gene predictive testing can be offered to at-risk family members and should be accompanied by consultation with a genetic counselor. At-risk individuals may decline predictive testing as "there is nothing that can be done about it", but it can be helpful for career and family planning. Even without a known family history of ataxia, genetic factors (frequently recessive, X-linked, or mitochondrial) can still be sought and could be found with repeat expansion testing and whole exome sequencing. In one study, clinically relevant genetic information was found in more than 60 % of undiagnosed ataxia patients studied, including diagnostic pathogenic gene variants in 21 % [6,7]. Genetic testing of at-risk family members is usually not offered before the age of 18, unless the individual is symptomatic or an early intervention is available.

5. Can it be cured?

If acquired causes can be identified, there are often treatments that can slow or stop progressive damage [2] (Table 3). Rehabilitation interventions can also improve and possibly stabilize performance [8–11]. There are several research studies ongoing to ferret out the role of aerobic exercise, balance exercise, oculomotor exercise, and vestibular exercise in the management of ataxia (https://clinicaltrials.gov/ Search ataxia and rehabilitation).

Although much research is underway for gene therapies to slow or stop progression of inherited causes of ataxia, none have yet been approved. Pipelines tracking the development of disease-modifying therapies are profiled on the National Ataxia Foundation website (https://www.ataxia.org/pipeline/), the Friedreichs Ataxia Research Alliance website (https://www.curefa.org/research/research-pipeline), and the MSA Coalition website (https://www.multiplesystematrophy.org/msa-research/msa-treatment-pipeline/).

6. Can my symptoms be relieved?

It is fortunate that there are many medications that can be used for the symptoms of ataxic disorders Table 4.

A comprehensive systematic review of the literature [12] noted that in patients with episodic ataxia type 2, 4-aminopyridine 15 mg/d probably reduced ataxia attack frequency over 3 months (1 Class I study). For patients with ataxia of mixed etiology, riluzole probably improved ataxia signs at 8 weeks (1 Class I study). For patients with Friedreich ataxia or spinocerebellar ataxia (SCA), riluzole probably improved ataxia signs at 12 months (1 Class I study).

Multiple other agents have been tried for ataxia without consistent benefit.

But agents in use for tremor [13], nystagmus [14], dizziness [15], and secondary involvement of other neurologic systems (spasticity, rigidity, motor neuron[16], neuropathy, autonomic, sleep disorders [17], mental health issues) may be symptomatically helpful. The co-occurrence of spasticity, rigidity, or neuropathy with cerebellar ataxia can worsen symptoms of imbalance, however the medications used for these symptoms could themselves worsen dizziness, weakness, or imbalance. As an example, spasticity can contribute to pain, fatigue, and worsened gait and quality of life. A standard oral medication for spasticity, baclofen, is associated fatigue and drowsiness and can contribute to increased fatigue and cognitive disturbances in this patient group. Intrathecal baclofen has been tried for symptoms of lower extremity spasticity, to reduce the systemic side effects [18].

Not all symptoms experienced by the ataxia patient are due to the ataxic illness, so the clinician must keep an open mind about any new symptom which could represent a new and unrelated issue (eg. Infection; decompensated medical issue; orthopedic complications).

7. Will it get worse?

Natural history studies have been tracking progression of genetic and non-genetic ataxia. There can be plateaus in disability for short periods of time, but progression is inevitably expected. The genetic ataxias tend to progress slowly over 20–25 years or longer [19–22]. The non-genetic ataxias may progress more rapidly over 5–10 years [23,24].

8. How bad will it get? how soon?

Rate of progression, severity of symptoms, and level of disability have general patterns in the identified forms of ataxia, but can vary between individuals—even in the same family with the same genetic mutation. It is estimated that 50 % of symptom onset and progression are determined by the mutation size in a genetic ataxia, while the rest is a result of other genetic factors (protective or additive), lifestyle factors, and environmental factors[25,26]. Patients are most concerned about when to expect loss of ambulation, loss of ability to care for themselves, loss of speech and swallowing. Palliative Care consultants can be helpful in managing the later stages of most ataxias. Social Work services can help find patient resources, long-term care options, and support for family members and caregivers, and are often part of a multidisciplinary team [27–29].

9. Is there any research being done?

There is extensive basic pre-clinical research in ataxia and some interventional research opportunities for patients with ataxia. Patients will often come to their physician with articles they have read online about research going on in ataxia or in other neurologic disorders that they wonder could also be applied to ataxia. The major research advances have been made in genetic diagnosis [18,30–32] and understanding of the underlying pathophysiology, as well as in clinical trial design [33–35].

Patient should be encouraged to register in one of the registries

Table 2
Diagnostics for Ataxia.

Disease	Initial Tests	Additional Tests	Tests that have been diagnostic markers for genetic disorders but now might be supplanted by Whole Exome Sequencing
General Studies	Complete Blood Count, Basic Chemistry Panel,, Hepatic Function Tests,, uric acid, Sedimentation Rate, Anti-Nuclear Antibody,, Rapid Plasma Reagin,, Thyroid Stimulating Hormone,, Hemoglobin A1c, Vitamin B12, Methylmalonic acid,, Homecysteine,, Folate, Vitamin E, Vitamin D3	Lactate, Pyruvate, Ammonia, Copper, Ceruloplasmin, Angiotensin Converting Enzume (sarcoid), Creatine Kinase, Serum Protein Electrophoresis, Ketones, Fasting Lipids	Plasma Amino Acids
To screen for common acquired factors and to better define the phenotype.	Urine heavy metals	Anti-Sjogrens Syndrome A and B test, Thyroid Peroxidase Antibodies and Thyroglobulin antibodies, Anti-gliadin (non-deamindated), Anti-Glutamic Acid Decarboxylase	Urine Organic Acids
	MRI Brain (w/ and w/o contrast)	Lyme disease antibody test, HTLV I/II test, HIV test	Lysosomal Screen
	Electronystagmography	Hexosaminidase A screening, Very Long Chain Fatty Acid screening, phytanic acid test	———
	Electromyogram/Nerve Conduction Velocity test	Cerebrospinal fluid Studies (Cultures, IgG synthesis, oligoclonal bands, lactate, 14–3-3, other specific tests)	MR Spectroscopy
			Conjunctival Biopsy Bone Marrow Biopsy
Common Adult Genetic Ataxias	Screen for repeat disorders (panel may include testing for SCA1, 2, 3, 6, 7, 8, 10, 17, Friedreich's ataxia, CANVAS, SCA 27B, FXTAS) SPG7[42], SYNE1 mutations are common recessive genetic causes of adult geneti ataxia and are not repeat expansions and are best found with Whole Exome Sequencing.	Whole Exome Sequencing is an appropriate next step when repeat expansion testing is negative. [43]	
Common Pediatric Genetic Ataxias	Ataxia Telangiectasia, Friedreich's ataxia,, Ataxia with Oculomotor Apraxia types 1 and 2 are the most common genetic causes of ataxia before the age of 20. Friedreich's ataxia as a repeat expansion will not be found with Whole Exome Sequencing.	Whole Exome Sequencing [44]	
Other Non Genetic Disorders with Ataxia as a feature			
Multiple Sclerosis	MRI Brain/C-spine	Cerebrospinal Fluid studies (IgG synthesis, oligoclonal bands, Myelin Basic Protein)	
	Visual Evoked Potential testing, Brainstem Auditory Evoked Potential testing,, Somatosensory Evoked Potential testing		
Paraneoplastic disorders	Malignancy workup (CT chest, abdomen, pelvis) Paraneoplastic antibody testing (serum or CSF)		
Parkinson-Plus Syndromes	MRI [45]or dopa-PET [46]may be helpful	Certain genetic ataxic disorders can be phenocopies of MSA (SCA2, 3; CANVAS, POLG1 (MIRAS)	
1. Multiple-System Atrophy (MSA) 2. Progressive Supranuclear Palsy (PSP) 3. Parkinson-Dementia-ALS (PDALS) 4. Corticobasalganglionic Degeneration (CBGD) 5. Diffuse Lewy Body Disease (DLBD)	Diagnosis is clinical[5]		

Table 3
Treatment of Acquired or Metabolic Causes of Ataxia.

Disorder		Agent
Targeted therapy for acquired disorders	Wernicke encephalopathy/chronic alcohol use	Thiamine, 1500 mg, IV daily x 2 d then 250 mg daily x 5 d then 100 mg, PO daily
	Immune-mediated	Screening and providing definitive treatment for underlying cancer where possible.
	Paraneoplastic	Methylprednisolone, 1000 mg, IV x3–5 d + IVIG, plasmapheresis, or Rituximab
	Gluten-associated ataxia	Gluten-free diet
Targeted therapy for inherited disorders	Niemann-Pick type C	Miglustat 200 mg TID
	Abetalipoproteinemia	Vitamin E, 150 mg/kg/d
	GLUT-1 deficiency	Ketogenic diet, avoid fasting
	Cerebrotendinous xanthomatosis	Chenodeoxycholic acid, 250 mg TID

Abbreviations: BID, twice daily; d, day(s); GLUT, glucose transporter; IV, intravenous; IVIG, intravenous immunoglobulins; kg, kilograms; mg, milligrams; TID, three times per day.

Table 4
Symptomatic Therapy for Cerebellar Ataxia (all agents are used off-label).

Symptom	Agent
Ataxia	Riluzole 50 mg po q 12 h Amantadine 200 mg po qd Ceredist (available only in Japan)
Episodic Ataxia type 2	4-aminopyridine 5 mg po tid Acetazolamide 250–1000 mg po qd in divided doses
Nystagmus and Vestibular Dizziness	Acetazolamide, 4-aminopyridine 3,4-diaminopyridine, Baclofen, Clonazepam, Gabapentin, Meclizine and similar agents, Memantine, Ondansetron, Promethazine, Scopolomine transdermal patch, Trihexyphenidyl, Valproate, Venlafaxine, Verapamil, Billed cap, Sunglasses
Tremor	Clonazepam, Gabapentin, Levetiracetam, Primidone, Propranolol, Topiramate, Valproate, Zonisamide. For resting or rubral tremor—dopamineergic agents. Botulinim toxin injections and neural stimulation have also been used.
Fatigue	Treat sleep disturbance Initiate non-fatiguing exercise Amantadine Modafinil, armodafinil, stimulants Energizing anti-depressants Careful use of supplements touted to help fatigue
Non-cerebellar features treated according to standard of care	Symptomatic medication for spasticity, rigidity, neuropathic pain. Medication for mental health issues (depression, anxiety, irritability).

Abbreviations: mg, milligrams; po, oral; tid, three times per day; qd, daily.

available for ataxia (https://research.sanfordhealth.org/rare-disease-registry) or Friedreich's ataxia (https://www.curefa.org/research/patient-registry) and to participate in any one of a number of natural history studies and biomarker studies now running (which can be found through https://clinicaltrials.gov/).

Drugs in the research pipeline may be available for expanded access/compassionate use after a Phase 2 study has demonstrated safety. Physicians can apply for single-subject compassionate access via the FDA website (https://www.fda.gov/drugs/investigational-new-drug-ind-application/physicians-how-request-single-patient-expanded-access-compassionate-use).

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Susan L. Perlman: Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] C.R. Lin, S.H. Kuo, Ataxias: Hereditary, Acquired, and Reversible Etiologies, Semin. Neurol. 43 (1) (2023) 48–64.
[2] S. Radmard, T.A. Zesiewicz, S.H. Kuo, Evaluation of Cerebellar Ataxic Patients, Neurol. Clin. 41 (1) (2023) 21–44.
[3] L.J. Roberts, et al., Overview of the Clinical Approach to Individuals With Cerebellar Ataxia and Neuropathy, Neurol Genet 8 (5) (2022) e200021.
[4] M. Hadjivassiliou, et al., Causes of progressive cerebellar ataxia: prospective evaluation of 1500 patients, J. Neurol. Neurosurg. Psychiatry 88 (4) (2017) 301–309.
[5] G.K. Wenning, et al., The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy, Mov. Disord. 37 (6) (2022) 1131–1148.
[6] H. Lee, et al., Clinical exome sequencing for genetic identification of rare Mendelian disorders, J. Am. Med. Assoc. 312 (18) (2014) 1880–1887.
[7] B.L. Fogel, et al., Exome sequencing in the clinical diagnosis of sporadic or familial cerebellar ataxia, JAMA Neurol. 71 (10) (2014) 1237–1246.
[8] S. Barbuto, S.H. Kuo, J. Stein, Investigating the Clinical Significance and Research Discrepancies of Balance Training in Degenerative Cerebellar Disease: A Systematic Review, Am. J. Phys. Med. Rehabil. 99 (11) (2020) 989–998.
[9] S. Barbuto, et al., Home Aerobic Training for Cerebellar Degenerative Diseases: a Randomized Controlled Trial, Cerebellum 22 (2) (2023) 272–281.
[10] S. Barbuto, et al., Phase I Single-Blinded Randomized Controlled Trial Comparing Balance and Aerobic Training in Degenerative Cerebellar Disease, PM R 13 (4) (2021) 364–371.
[11] S. Barbuto, et al., Phase I randomized single-blinded controlled study investigating the potential benefit of aerobic exercise in degenerative cerebellar disease, Clin. Rehabil. 34 (5) (2020) 584–594.
[12] T.A. Zesiewicz, et al., Comprehensive systematic review summary: Treatment of cerebellar motor dysfunction and ataxia: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology, Neurology 90 (10) (2018) 464–471.
[13] K. Frei, D.D. Truong, Medications used to treat tremors, J. Neurol. Sci. 435 (2022) 120194.
[14] M.J. Thurtell, Treatment of Nystagmus, Semin. Neurol. 35 (5) (2015) 522–526.
[15] A. Zwergal, et al., Cerebellar Dizziness and Vertigo: Etiologies, Diagnostic Assessment, and Treatment, Semin. Neurol. 40 (1) (2020) 87–96.
[16] G. Coarelli, et al., Motor neuron involvement threatens survival in spinocerebellar ataxia type 1, Neuropathol. Appl. Neurobiol. 49 (2) (2023) e12897.
[17] A. Sonni, et al., The effects of sleep dysfunction on cognition, affect, and quality of life in individuals with cerebellar ataxia, J. Clin. Sleep Med. 10 (5) (2014) 535–543.
[18] S.G. Berntsson, et al., Inherited Ataxia and Intrathecal Baclofen for the Treatment of Spasticity and Painful Spasms, Stereotact. Funct. Neurosurg. 97 (1) (2019) 18–23.
[19] T. Ashizawa, et al., Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study, Orphanet J. Rare Dis. 8 (2013) 177.
[20] H. Jacobi, et al., Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study, Lancet Neurol. 14 (11) (2015) 1101–1108.
[21] K. Reetz, et al., Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 4-year cohort study, Lancet Neurol. 20 (5) (2021) 362–372.
[22] S.R. Regner, et al., Friedreich ataxia clinical outcome measures: natural history evaluation in 410 participants, J. Child Neurol. 27 (9) (2012) 1152–1158.
[23] D.J. Lin, K.L. Hermann, J.D. Schmahmann, The Diagnosis and Natural History of Multiple System Atrophy, *Cerebellar Type.* Cerebellum 15 (6) (2016) 663–679.
[24] P.A. Low, et al., Natural history of multiple system atrophy in the USA: a prospective cohort study, Lancet Neurol. 14 (7) (2015) 710–719.
[25] S. Tezenas du Montcel, et al., Modulation of the age at onset in spinocerebellar ataxia by CAG tracts in various genes, Brain 137 (Pt 9) (2014) 2444–2455.
[26] E.P. de Mattos, et al., Age at onset prediction in spinocerebellar ataxia type 3 changes according to population of origin, Eur. J. Neurol. 26 (1) (2019) 113–120.

[27] D.R. Lynch, et al., Friedreich Ataxia: Multidisciplinary Clinical Care, J. Multidiscip. Healthc. 14 (2021) 1645–1658.
[28] S.A. McGrath-Morrow, et al., Multidisciplinary Management of Ataxia Telangiectasia: Current Perspectives, J. Multidiscip. Healthc. 14 (2021) 1637–1644.
[29] R.N. de Silva, et al., Diagnosis and management of progressive ataxia in adults, Pract. Neurol. 19 (3) (2019) 196–207.
[30] A. Schluter, et al., ClinPrior: an algorithm for diagnosis and novel gene discovery by network-based prioritization, Genome Med. 15 (1) (2023) 68.
[31] P. Cunha, et al., Extreme phenotypic heterogeneity in non-expansion spinocerebellar ataxias, Am. J. Hum. Genet. 110 (7) (2023) 1098–1109.
[32] D. Beijer, et al., Standards of NGS Data Sharing and Analysis in Ataxias: Recommendations by the NGS Working Group of the Ataxia Global Initiative, Cerebellum (2023).
[33] A. Traschutz, et al., Responsiveness of the Scale for the Assessment and Rating of Ataxia and Natural History in 884 Recessive and Early Onset Ataxia Patients, Ann. Neurol. 94 (3) (2023) 470–485.
[34] X.N. Shen, et al., Systematic assessment of plasma biomarkers in spinocerebellar ataxia, Neurobiol. Dis. 181 (2023) 106112.
[35] D. Oender, et al., Evolution of Clinical Outcome Measures and Biomarkers in Sporadic Adult-Onset Degenerative Ataxia, Mov. Disord. 38 (4) (2023) 654–664.
[36] V. Profeta, et al., Omaveloxolone: an activator of Nrf2 for the treatment of Friedreich ataxia, Expert Opin. Invest. Drugs 32 (1) (2023) 5–16.
[37] D.R. Lynch, et al., Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data, Ann. Clin. Transl. Neurol. (2023).
[38] D.R. Lynch, et al., Efficacy of Omaveloxolone in Friedreich's Ataxia: Delayed-Start Analysis of the MOXIe Extension, Mov. Disord. 38 (2) (2023) 313–320.
[39] S. Winser, et al., Effects of therapeutic exercise on disease severity, balance, and functional Independence among individuals with cerebellar ataxia: A systematic review with meta-analysis, Physiother. Theory Pract. 39 (7) (2023) 1355–1375.
[40] P. Cabaraux, et al., Consensus Paper: Ataxic Gait, Cerebellum 22 (3) (2023) 394–430.
[41] A. Bogaert, et al., Assessment and tailored physical rehabilitation approaches in persons with cerebellar impairments targeting mobility and walking according to the International Classification of Functioning: a systematic review of case-reports and case-series, Disabil. Rehabil. (2023) 1–23.
[42] G. Pfeffer, et al., SPG7 mutations are a common cause of undiagnosed ataxia, Neurology 84 (11) (2015) 1174–1176.
[43] N. Dragasevic-Miskovic, et al., Autosomal recessive adult onset ataxia, J. Neurol. 269 (1) (2022) 504–533.
[44] M. Beaudin, et al., The Classification of Autosomal Recessive Cerebellar Ataxias: a Consensus Statement from the Society for Research on the Cerebellum and Ataxias Task Force, Cerebellum 18 (6) (2019) 1098–1125.
[45] G. Carre, et al., Brain MRI of multiple system atrophy of cerebellar type: a prospective study with implications for diagnosis criteria, J. Neurol. 267 (5) (2020) 1269–1277.
[46] K.Y. Kwon, et al., Diagnostic value of brain MRI and 18F-FDG PET in the differentiation of Parkinsonian-type multiple system atrophy from Parkinson's disease, Eur. J. Neurol. 15 (10) (2008) 1043–1049.