REVIEW ARTICLE

Degenerative Ataxias: challenges in clinical research

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Abstract

The degenerative ataxias are a very heterogeneous group of disorders that include numerous genetic diseases as well as apparently "sporadic" entities. There has been an explosion of discoveries related to genetic defects and related pathomechanisms that has brought us to the threshold of meaningful therapies in some but not all of these diseases. There also continues to be lack of knowledge of the causation of disease in a sizeable proportion of these patients. The overall rarity of ataxias as a whole and certainly of the individual genetic entities together with slow and variable progression and variable prognosis in juxtaposition with a rapid development of possible therapies in the horizon such as gene replacement and gene knock-down strategies places the ataxias in a unique position distinct from other similar neurodegenerative diseases. The pace of laboratory research seems not matched by the pace of clinical research and clinical trial readiness. This review summarizes the author's views on the various challenges in translational research in ataxias and hopes to stimulate further thought and discussions on how to bring real help to these patients.

Introduction

The degenerative ataxias, particularly the inherited forms, are being elucidated at a molecular genetic level and their cell biologic mechanisms increasingly unraveled. These advances have led us to the threshold of meaningful therapies but there are several issues in the field that impede progress. We review some of the challenges in translational research in the ataxias.

Epidemiological issues

The true prevalence of degenerative ataxias is unknown. Prevalence studies focused on ataxias are summarized in Table 1 and, for the most part, deal with degenerative ataxia.[1–17] The overall prevalence of ataxias ranges from 2.7 to 38.35 per 100,000. Most of these studies are not population based, have used various types of referral resources to ascertain cases, and have dealt with variable groups of patients. In many, sporadic ataxia outnumbers genetic forms. It is likely that most studies underestimate the true prevalence of ataxias. With the generous assumption of 25–30 ataxia cases per 100,000, the US would have

approximately 78,500–94,200 subjects with ataxia, well under the requirements needed for the designation of rare diseases in many parts of the world.

Many studies examine the prevalence of genetically identifiable ataxias based on highly selected referral populations or referral laboratories. Such data have been summarized for the autosomal dominant ataxias (spinocerebellar ataxias or SCAs) by Schols et al.[18] and additional studies have been done in different countries.[19–22] Worldwide, the most common SCA is SCA 3 (21%), followed by SCA 6 and SCA 2 (15% each), but these figures vary widely from region to region often due to founder effects. Worldwide, about 30% of patients and families with SCAs cannot be classified based on available gene tests. Friedreich's ataxia (FA) is the most frequent autosomal recessive (AR) ataxia but is confined to Indo-Caucasian populations, estimated to occur with a frequency of 1 in 50,000.[23] Among a large cohort of patients with AR ataxias referred to a genetic laboratory, fully 47% could not be precisely diagnosed[24]; two-thirds of those in whom a molecular diagnosis could be established had FA. Another study from Algeria found mutations in 110 out 166 patients with AR ataxia with FA and AVED being the most common.[25] In contrast, in a

Table 1. Prevalence of ataxias.

Reference	Country	Methodology	Diagnoses	Prevalence per 100,000
Sridharan et al. 1985	Libya	Referral clinic	HA	2.7
Brignolo 1986	Italy	Hospital based	HA	4.8
Leone 1990	Italy	Multiple sources	FA	1.2
Polo 1991	Spain	Hospital based	HA	10.6
Filla 1992	Italy	Mail/phone	HA	4.8
Leone 1995	Italy	Referral clinic	HA	10.5
Silva 1997	Portugal	Population based	HA	4.4
Sasaki 2003	Japan	Nationwide survey	HA, SA	15.7 (30% HA)
Tsuji 2008	Japan	National registry	HA, SA	18.5 (33% HA)
Shibata-Hamaguchi 2009	Japan	Referral clinics	HA, SA	40.4% HA, 38% SA
Muzaimi 2008	Wales	Multiple sources	HA, SA	10.2 (17% HA)
Erichsen 2009	Norway	Multiple sources	HA	6.5
Tallaway 2010, Farghaly 2011	Egypt	Population based	All ataxia	38.35
Coutinho 2013	Portugal	Multiple sources	HA	8.9
Kourstis	Greece	Reference lab	FA, SCA 1,2	FA 0.87, SCA 0.68
Musselman 2014	Europe	Literature survey	Children	26

HA, hereditary ataxia; SA, sporadic ataxia; FA, Friedreich ataxia; SCA, spinocerebellar ataxia.

population-based study of chronic childhood ataxia in Manitoba, the most common diagnoses were Angelman syndrome, ataxia telangiectasia, and mitochondrial disease, followed by Friedreich's ataxia, vascular lesions, and other familial ataxias.[26] There is variation in specific etiological diagnoses in different populations reflecting founder effects and other genetic factors such as consanguinity rates.

Patients with AR ataxias often present to the clinician as "singletons". The absence of a family history together with onset of disease in late adult life is likely to indicate a disorder that does not have a monogenic basis, but there is no absolute cutoff to define late onset. Thus, the definition of truly "sporadic" ataxia is not clear. Many patients seeking consultation for progressive degenerative ataxias at even specialized centers have no specific diagnosis; additionally, many disorders that have ataxia as a major feature are not classified as an "ataxia" and are not included in epidemiological studies. The online Mendelian Inheritance database identifies more than 900 entries with ataxia. Newborn screening may be useful in defining the true prevalence of various gene mutations identified to cause ataxia but needs considerations of expense, ethics, and utility.

Whole-genome and exome sequencing are already proving useful in identifying known as also novel gene defects,[27–29] but questions remain as to the technical capabilities and interpretation of these. For clinical research, these data point to the need for intense collaborative efforts. More precise epidemiological data may be possible using registries and other web-based methods. Repositories of biologic samples and cooperative efforts with genetic laboratories may lead to identification of causative mutations in many families and patients.

Progression rates, sample sizes

Neurological rating scales have been developed to quantify ataxic diseases. The scale for assessment and rating of ataxia (SARA) was developed and validated by a cooperative study among many European centers. Following up on the original 2-year follow up, the EUROSCA investigators have recently reported their data on long-term follow up of their large cohort of SCA subjects.[30] Progression rate as assessed by annual change in the SARA score appeared linear and was fastest in SCA 1 at 2.11 (SE 0.12). SCA 2 and SCA 3 had an intermediate progression rate of 1.49 (SE 0.07) and 1.56 (SE 0.08), respectively. Factors such as age at inclusion, age at onset, repeat size, and baseline SARA score influenced progression rate but in a variable way across the SCAs studied. Sample size estimates for a 50% reduction in progression rate over 1 year in a double-blind placebo controlled study were 142 for SCA 1, 172 for SCA 2, 202 for SCA 3, and 602 for SCA 6. Other studies have reported somewhat similar progression rates and confirmed a faster rate of progression in SCA 1.[31–33] SCA subjects from Taiwan have been reported to have a faster progression rate.[34] Large studies of SCA 3 from Brazil have used other rating scales such as ICARS and NESSCA and note similar progression rates by extrapolation but cannot be compared to studies using SARA.[35,36] The Spinocerebellar Ataxia Functional Index, a composite of timed walk, timed peg board test, and timed syllables was developed as an objective measure of ataxia.[37] Effect size, estimated by standardized response means, was however, comparable to that of SARA and sample size estimates were not improved. The Composite Cerebellar Functional Severity Score (CCFS) used timed

tasks such as writing, tapping, peg board, and a "click test" (alternate tapping on two keys set apart by a standard distance); a composite of the peg board time and the click test time in the dominant hand best reflected the cerebellar deficits in SCAs.[38] The longitudinal properties of CCFS have been recently reported in a limited number of subjects[31]; worsening in CCFS over 2 years was seen in SCA 1, 2, and 3 but not in SCA 6 and this was also the case with their SARA scores.

In FA, Friedman et al. noted a decline of the Friedreich's ataxia rating scale (FARS) score by 3.55 and 5.51 by years 1 and 2 in a large cohort of subjects.[39] For a 1-year trial with a 50% reduction in disease progression, FARS would require 133 patients per arm. For a 2-year trial, a composite of timed walk, 9HPT, and low-contrast vision testing would require 100 patients per arm and FARS, 52. Thus, performance measures were not more sensitive than clinical scores but were more linear. Further longitudinal analysis and a cross-sectional study using SARA have pointed out that younger subjects and subjects with longer GAA repeat sizes progress faster and may be more suitable for clinical trials.[40,41] A limitation of FA natural history studies has been the limited number of children in the studies.

There is need for more sensitive and unbiased measures of disease progression. The validity and responsiveness of automated measures such as gait monitors, smartphone-based measures of static and dynamic stability, posturography, and gait analysis using pressure-sensitive carpets or video cameras are undetermined and their expense in money and time and relative unavailability pose impediments to large-scale use. Thus, more work needs to be done to develop and validate relatively inexpensive, unbiased measures of disease including patient-reported outcome data that can be performed both in the clinic and in home-based settings which may serve as surrogate markers of disease progression. Additional strategies include access to large sample sizes by nationwide and international collaboration, implementation of disease registries, longer follow ups, more frequent collection of outcome measures that may mitigate against day to day fluctuations, and identification and control of variables that may affect such measures. Additionally, interventions that may be applicable to more than one type of ataxia may have greater success in accessing larger study populations.

The difficulties of clinical trials in rare diseases have been recently reviewed.[42] This publication provides suggestions for minimizing sample sizes such as focusing on high-risk subjects, using genetic data to minimize subject variability and using continuous outcome variables; maximizing on-treatment participants such as cross-over designs; advanced methods for dealing with confounding and statistical design among others.

Biomarkers

Biomarkers are objectively measured characteristics that serve as indicators of normal biological processes, pathogenic process, or response interventions. Surrogate markers serve as a substitute for a clinically meaningful change in a therapeutic intervention. Diagnostic biomarkers serve as independent tools for confirming the diagnosis of specific diseases and there is a need for such biomarkers in sporadic neurodegenerative diseases including "sporadic" ataxia. In addition, biomarkers for disease pathogenesis and progression will be extremely useful. Biomarkers may be clinical, imaging, or biochemical measures.

Gene expression profiling has been used to identify biochemical signatures of disease states, but the experience in ataxia remains limited. Both data-driven approach which is unbiased and global in nature and knowledge-driven approach based on current understanding of disease process have been used.[43–45] Coppola et al. noted an overrepresentation of genes involved in cell cycle regulation, cell death, and mitochondrial localization among those differentially expressed in FA. Haugen et al. noted alterations in many gene categories including downregulation of genes related to transcription, RNA biosynthetic pathways, posttranslational protein modifications, and intracellular signaling cascade. Frataxin immunoassays have been developed as biomarkers for FA and may be useful for diagnosis, but their use as markers of treatment response will be confined to those interventions that are expected to improve frataxin deficiency.[46] Similarly, accurate measurements of various ataxin levels may be useful for treatment strategies aimed at "knocking down" the gene. Others have reported on plasma protein profiling, oxidative markers, and microRNAs.[47–49]

Imaging studies have also been used to monitor disease status in the ataxias as reviewed recently.[50] Quantitative techniques are needed for monitoring disease progression. Both 3D volumetry requiring some observer interaction and the unbiased voxel-based morphometry have been used to study SCAs.[51–53] In addition, brain structure evaluation using diffusion studies, metabolite estimation using spectroscopy and functional MRI are also being used. Such studies have provided conflicting results, perhaps related to small number of patients studied, lack of correlations with clinical rating scales, and lack of longitudinal data among other reasons. Recent quantitative imaging studies are summarized in Table S1, including three longitudinal studies.[54–62] In the largest of these, MRI measures were shown to have larger effect size than SARA.[55] There are also reports of longitudinal imaging findings in FA suggesting that alterations in structures other than cerebellum may correlate with progression of disease.[63]MR spectroscopy demonstrates changes such as reduced N-acetylaspartic acid

and choline and increase in myoinositol reflecting neuronal loss and gliosis and may show differential patterns in different ataxias.[64–66] In a longitudinal study of SCAs with studies done 3–4 years apart, MRS measures did not change significantly while the SARA scores did.[65] Problems with imaging have included cost, availability of technical expertize, and need for uniform technology.

There has been little exploration of clinical neurophysiological measures for estimating longitudinal progression of disease in the SCAs. There is an involvement of peripheral nerves and the corticospinal tract in many ataxias and these are amenable to monitoring by physiological techniques; other physiological techniques such as oculomotor recordings and evoked potentials may also be useful.[67] Other measures that have been looked at in small groups of subjects include optical coherence tomography of the retina and auditory processing deficits.[68,69] The drawback of these techniques is that they reflect pathology in limited regions of the nervous system and may not reflect clinically relevant changes.

Treatment of ataxia

The potential for neuroprotective treatment, based on pathogenic mechanisms, such as gene knock down or gene enhancement is beyond the scope of this review. Symptomatic therapy of ataxia has been disappointing. Earlier reviews have summarized the limited effects with many drugs that influence neurotransmitter functions. More recent studies of symptomatic therapies are summarized in Table 2.[70–77] Better understanding of the physiological underpinnings of ataxia may lead to better therapies.[78] In many animal models of inherited ataxias, symptoms occur even in the absence of overt loss of Purkinje (PKJ) cells suggesting an opportunity for symptomatic treatment. The spontaneous firing of Purkinje cells at about 40 Hz is modified by the input from parallel fibers and by the complex spikes generated by climbing fiber input. Pathology in the PKJ cells is likely to lead to over activity of the deep cerebellar nuclei (DCN). Mouse models of episodic ataxia reveal impaired precision of PKJ cell firing[79]; mice lacking fibroblast growth factor 14 (FGF 14), related to SCA 27, have impaired expression of sodium channels (Nav1.6) on PKJ cells and the PKJ cells do not fire spontaneously or in response to depolarizing currents.[80] Simple spike duration is doubled in duration in mice with potassium channel (Kv3) knockout because of impaired repolarization[81]; this channel is mutated in SCA 13. In SCA 3 mouse model, PKJ cells have increased excitability and undergo depolarization block leading to inability to sustain repetitive firing; an activator of the SK potassium channel leads to partial correction of these abnormalities and improved motor function.[82] In SCA 1, altered PKJ cell firing has been related to alterations in the expression of several ion channels.[83] In general, restoring the right pattern of DCN firing may be expected to alleviate ataxia. There has been limited experience with deep brain stimulation to treat the tremor often associated with certain ataxic syndromes, but in general, ataxia has not been reversed. External stimulation of the cerebellum as well as motor cortex using different stimulation paradigms as a therapy have been reported in a limited fashion.[84] Better understanding of the neural circuitry abnormalities related to the generation of ataxia may allow better identification of targets and modes of stimulation. There has been increasing interest in rehabilitation techniques, but more studies are needed in this regard together with investigations into neural plasticity mechanisms involved.[85]

Presymptomatic subjects

One of the advantages of genetically determined ataxias is the ability to identify at-risk individuals by targeted gene testing based on family history. It is tempting to speculate

Table 2. Recent trials of drugs for symptomatic improvement of ataxia.

Study	Patients, (number)	Drug, daily dose	Design	Duration	Results
Tsunemi et al. 2010	Mixed,(15)	3,4 DAP, 40 mg	OL	1 week	Improved DBN by oculomotor studies, no change in sway or ICARS score
Ristori et al. 2010	Mixed, (40)	Riluzole 100 mg	RDBPC	8 weeks	Significant improvement in ICARS by 7 points
Velasquez-Perez et al. 2011	SCA 2, (36)	Zinc 50 mg	RDBPC	6 months	No significant improvement in SARA
Schinepp 2012	Mixed, (31)	4-AP, 15 mg	Observational	2–4 h	Improved gait speed and gait variability using gait recording
Zesiewicz et al. 2012	SCA 3, (20)	Varenicline, 2 mg	RDBPC	4 weeks	Significant improvement in SARA
Strupp et al. 2013	Mixed,(13)	Acetyl-DL-Leucine 5 gm	OL	1 week	Improved SARA by over 3 points, SCAFI
Giordano 2013	Mixed,(16)	4-AP-SR	Observational	2 weeks	Some improvement in gait, speech
Romano et al. 2015	SCA, FA, (55)	Riluzole 100 mg	RDBPC	12 months	More improved SARA score in treated group; improved SARA score

SARA, scale for assessment and rating of ataxia; ICARS, International Cooperative Ataxia Rating Scale. OL, open label; RDBPC, randomized double blind placebo-controlled; SCA, spinocerebellar ataxia; FA, Friedreich's ataxia.

that therapy at this stage will postpone conversion into a symptomatic phase or altogether avoid development of disease but regulatory perspective is that this population is not acceptable for drug efficacy studies. Such therapy will have to use "presymptomatic" markers of progressive neural dysfunction. Clinical, imaging, and physiological studies done in Huntington's disease, which may serve as a model, indicate the large sample sizes needed for any therapeutic study using such measures. Jacobi et al. have reported on a cohort of subjects at risk for SCA 1, 2, 3 or 6 from Europe with estimated age time to onset ranging from 8 to 18 years for various diseases.[86] Clinical assessment with SARA and performance measures showed significant but modest differences between mutation carriers and mutation-negative individuals in SCA 1 and SCA 2. Imaging studies in a subset of subjects showed significant gray matter loss in brainstem and cerebellum by VBM only in SCA 1 and SCA 2 mutation carriers. Another study examined 21 mutation carriers of the SCA 2 expansion prospectively for many years and noted that muscle cramps and sensory deficits frequently preceded onset of ataxic symptoms as did a decline in sensory nerve action potential amplitudes.[87] These studies need to be extended and other simple but reliable methodologies identified to quantitatively evaluate neural function in persons at risk for different ataxias in the hope that these may serve as outcome measures in treatment trials.

Prevention

Primary prevention of disease is the target for medical research in many fields and is usually thought to be more cost effective than either secondary prevention or treatment after the disease is well established. The idea that we need to be paying more attention to prevention of many of the genetic ataxias has been eloquently expressed by Bushara recently.[88] Preimplantation genetic diagnosis (PGD) has been facilitated by the ability to detect mutations using PCR in single cells; this combined with in vitro fertilization allows implantation of unaffected embryos 3–5 days after fertilization essentially eliminating an autosomal dominant disorder from future generations. Of course, de novo mutations are likely to keep many such diseases around, especially in repeat expansion disorders which may originate by expansion into the pathogenic range from a pool of "large" normal alleles. Cost and access remain issues for such techniques as also ethical issues posed by societal and religious concerns. In addition, utilization of such techniques, even when available may be less than expected because of "future discounting of genetic risk" due to the time-distance to risk for children, hope for cures in the near future, and the costs involved.[89] Putting into place better education of families with such diseases and better expertize and access to such

technologies may be useful. The need for careful thought regarding counseling and information sharing and possibilities for ethical breaches has to be carefully examined.[90]

Conclusions

While it is gratifying to note the tremendous success in disease gene identification and unraveling pathogenic cascades in the degenerative ataxias, there still remain many obstacles to bring these advances to the bedside. Some of the issues in this regard are discussed above and hopefully will stimulate further discussion and work.

Conflicts of Interest

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Recent imaging studies in spinocerebellar ataxias.