Clinical features and molecular genetics of autosomal recessive cerebellar ataxias

Brent L Fogel, Susan Perlman

Among the hereditary ataxias, autosomal recessive spinocerebellar ataxias comprise a diverse group of neurodegenerative disorders. Clinical phenotypes vary from predominantly cerebellar syndromes to sensorimotor neuropathy, ophthalmological disturbances, involuntary movements, seizures, cognitive dysfunction, skeletal anomalies, and cutaneous disorders, among others. Molecular pathogenesis also ranges from disorders of mitochondrial or cellular metabolism to impairments of DNA repair or RNA processing functions. Diagnosis can be improved by a systematic approach to the categorisation of these disorders, which is used to direct further, more specific, biochemical and genetic investigations. In this Review, we discuss the clinical characteristics and molecular genetics of the more common autosomal recessive ataxias and provide a framework for assessment and differential diagnosis of patients with these disorders.

Clinical features of autosomal recessive ataxias

Insidious loss of balance and coordination can be debilitating for patients and a diagnostic dilemma for clinicians. The phenotype of progressive cerebellar ataxia can result from both acquired and hereditary disorders. For these reasons, a systematic approach to the diagnosis of patients with ataxia is essential. Hereditary ataxias can be divided into autosomal dominant, autosomal recessive, X-linked, and mitochondrial on the basis of mode of inheritance. This Review will focus on the clinical and genetic aspects, as well as the molecular basis for pathogenesis, of the more common autosomal recessive ataxias.

When assessing a patient with ataxia, the clinician may initially be unable to differentiate autosomal recessive ataxia from other forms unless the patient can disclose a characteristic family history of affected relatives. What factors should influence physicians to add this class of ataxic disorders to patients’ differential diagnoses?

Most autosomal recessive ataxias are early onset, which traditional classification systems define as before age 20 years.1 Although useful, such a distinction is not universally applicable, as age at onset can be quite diverse, with typical early-onset, recessively inherited disorders, such as Friedreich’s ataxia and Tay-Sachs disease, presenting in adulthood. Phenotype can, therefore, be a more reliable means of identification.

The key feature in all these disorders is spinocerebellar ataxia, involving the cerebellum, brainstem, or spinocerebellar long tracts, typically characterised by poor balance with falls, imprecise hand coordination, postural or kinetic tremor of the extremities or trunk, dysarthria, dysphagia, vertigo, and diplopia.2 Autosomal dominant spinocerebellar ataxias may also have diverse associated neurological features including retinopathy, optic atrophy, extrapyramidal or pyramidal signs, peripheral neuropathy, cognitive impairment, or epilepsy.3 Autosomal recessive ataxias, by contrast, are generally associated with peripheral sensorimotor neuropathy, most notably with loss of proprioception and vibration sense as seen in the prototypical disorder, Friedreich’s ataxia.4,3 The presence or absence of deep tendon reflexes can also be a useful examination finding,5 as areflexia is more common in autosomal recessive ataxias. In further contrast to the autosomal dominant ataxias, autosomal recessive ataxias tend to have involvement outside the nervous system.5,3

From a diagnostic viewpoint, categorisation of autosomal recessive ataxias as either resembling a Friedreich’s ataxia phenotype or as having an early-onset phenotype with cerebellar atrophy is useful (table 1). Due to the heterogeneity among these disorders, further differentiation will generally require detailed assessment of the phenotype, as well as additional diagnostic studies, particularly neuroimaging, because the presence of cerebellar atrophy is a useful distinguishing feature. As many of the autosomal recessive ataxias now have identifiable gene mutations, the goal of this assessment is to provide a focus for genetic testing.

In this Review, we present an overview of the most common autosomal recessive ataxias and discuss strategies for clinical differentiation. Many autosomal recessive disorders, particularly those of metabolic, storage, or mitochondrial function, may include ataxia as an associated or occasional feature; however, only diseases with ataxia as a defining component of the clinical phenotype are covered. Although the molecular genetic causes behind the most common autosomal recessive disorders are known, there are several rare disorders described in single families or a few patients that are not yet understood molecularly and are therefore not mentioned here.

Friedreich’s ataxia and phenotypically related disorders

Friedreich’s ataxia is an important consideration in all assessments of autosomal recessive ataxic syndromes. However, several other ataxic disorders strongly mimic this phenotype. Therefore, the initial characterisation of a patient as having Friedreich’s ataxia phenotype is a useful first step in differentiation. Despite their clinical similarity, these disorders are easily differentiated by...
laboratory testing and, ultimately, through genetic analysis.

**Friedreich’s ataxia**

Friedreich’s ataxia is the most common of the autosomal recessive ataxias and the most common hereditary ataxia overall with a prevalence of approximately one person in 30 000 to one in 50 000 in most populations and a carrier frequency of approximately one in 85 in white people.7–10 Age at onset is typically age 5–25 years. Clinically, Friedreich’s ataxia is characterised by early-onset progressive gait and limb ataxia, dysarthria, loss of vibration and proprioceptive sense, areflexia, abnormal eye movements (such as fixation instability), and pyramidal weakness of the feet with upgoing toes.11–13 Cardiomyopathy, diabetes, scoliosis, and pes cavus are other common systemic complications.11–13 Large sensory neurons in the dorsal root ganglia are lost initially, with subsequent deterioration of the spinocerebellar tract, pyramidal tract, and dorsal columns.14 Neuroimaging does not show progressive cerebellar degeneration (figure 1),11 unlike the autosomal-dominant hereditary ataxias.

Although the phenotype is well-described and detailed, there are various atypical phenotypes, including late-onset presentations after age 25 years, which are commonly associated with lower limb spasticity, retained reflexes, and mild cerebellar vermian atrophy.15 Friedreich’s ataxia should be considered in all patients with sporadic or recessive ataxia, with the exception of those with severe olivopontocerebellar atrophy on neuroimaging.16

In about 98% of patients, the disease is caused by a triplet GAA expansion within the first intron of the frataxin gene found on chromosome 9q13.17 The increased number of GAA repeats may allow the formation of a “sticky” triplex DNA structure that impedes transcription of the gene and limits protein production.18–21 The inverse correlation of age at onset, severity of the disease, and associated systemic symptoms with the size of the repeat expansions, which can range from 70–90 repeats (normal less than 40) to over 1000, is likely caused by residual protein expression from the alleles with smaller GAA expansions.7,8,10,22,23 Point mutations, although rare (about 2–4% of patients), can cause the disorder7,8,10,23 and must be considered when assessing a new patient with ataxia, as routine testing may only screen for repeat expansions and may misidentify a compound heterozygote. Some point mutations result in a more severe phenotype and others in a milder phenotype.7,8,23 Tissue mosaicism may also contribute to the observed phenotype seeming disparate relative to the GAA repeat lengths.24,25

Frataxin is a mitochondrial protein.26 Current evidence suggests that loss of frataxin impairs mitochondrial iron handling and respiratory chain function and contributes to increased oxidative stress and cellular damage.26–29 Studies of mutants in the yeast homologue Yfh1p have shown inhibition of oxidative phosphorylation and accumulation of iron29 as well as an inability to detoxify...
iron, resulting in hypersensitivity to oxidative stress. This phenotype can be rescued by the human frataxin protein, demonstrating a functional similarity. A murine knockout model of frataxin is lethal during embryogenesis, and this too can be rescued by the human protein. Neuron-specific and striated-muscle-specific knockout mice demonstrate a phenotype of ataxia and proprioceptive loss as well as cardiac hypertrophy and a deficiency in respiratory-chain complexes, suggesting the usefulness of this system as a model for studying Friedreich’s ataxia. On the basis of these studies, oxidative damage within the mitochondria seems to have a key role in the disease phenotype.

Given the current knowledge of the pathogenesis of Friedreich’s ataxia, treatment options have been directed at antioxidant protection. A recent uncontrolled, open-label, 4 year pilot study of ten patients on a combination of coenzyme Q₁₀ and vitamin E reported improvement in cardiac function and suggested possible stabilisation or reduced decline in certain neurological symptoms. Studies of low-dose idebenone, a synthetic analogue of coenzyme Q₁₀, seem to show reduction of cardiac hypertrophy but no improvement in neurological symptoms. Consistent with these clinical studies, idebenone also seems to be cardioprotective in the FRDA mouse model. No drugs have led to any improvement in ataxia or other associated neurological features in patients, and treatment for this disease remains symptomatic.

**Ataxia with vitamin E deficiency**

This disorder presents with a clinically similar phenotype to Friedreich’s ataxia, but serum concentrations of vitamin E are low. Most patients are from North Africa where its incidence may be as common as that of Friedreich’s ataxia, but many have been reported elsewhere including Europe, North America, and Japan. Like Friedreich’s ataxia, age at onset is before 20 years but, by contrast, decreased visual acuity or retinitis pigmentosa may be an early finding. Cardiomyopathy is the most common systemic finding but seems to be less common than in Friedreich’s ataxia. Patients also tend to have more head titubation as well as less neuropathy and a slower disease course. The disease is caused by mutation of the α-tocopherol transfer protein on chromosome 8q13. The α-tocopherol transfer protein mediates the incorporation of vitamin E into circulating lipoproteins, and the mutations presumably reduce delivery to the CNS. Mutations are varied, including missense, nonsense, frameshift, and splice-site mutations, and may affect the severity of the disease, presumably via residual protein activity with certain mutations. Supplementation with vitamin E seems to stop progression of the disease and can mildly improve cerebellar ataxia. A mouse model has been developed that shows late-onset head tremor, ataxia, and retinal degeneration, the neurological aspects of which resolve with supplementation of vitamin E. As is suspected for Friedreich’s ataxia, the mechanism underlying this pathogenesis seems to be increased oxidative stress.

**Abetalipoproteinaemia**

This disease is caused by mutations in the gene for the large subunit of microsomal triglyceride transfer protein, located on chromosome 4q22–24, which functions in the assembly of apolipoprotein-B containing very low-density lipoproteins and chylomicrons. The neurological phenotype presents before age 20 years and is similar to Friedreich’s ataxia, but is generally also associated with lipid malabsorption, hypocholesterolaemia, acanthocytosis, and retinitis pigmentosa. Patients become deficient in the lipid-soluble vitamins, especially vitamin E, the loss of which likely has neurological and ophthalmological complications. Treatment involves dietary modification and vitamin replacement, which
may prevent neurological complications if begun early.54 MTP knockout mice have an embryonic lethal phenotype; however, conditional knockouts have abnormalities in plasma lipoproteins.55

Refsum’s disease

Refsum’s disease is clinically characterised by cerebellar ataxia, peripheral polyneuropathy, sensorineural deafness, retinitis pigmentosa, and anosmia, with skeletal abnormalities, ichthyosis, renal failure, and cardiac myopathy or arrhythmias as additional associated features.5–18 The disease is primarily caused by mutation of the gene for the peroxisomal enzyme phytanoyl-CoA hydroxylase, PHYH, on chromosome 10pter–11.2.56–18 Less commonly, mutation of PEX7 on chromosome 6q21–22.2, which encodes the peroxin 7 receptor protein needed for peroxisomal importation of proteins containing a type 2 peroxisomal targeting signal, can produce an identical phenotype due to impaired importation of proteins into the peroxisome, including phytanoyl-CoA hydroxylase.56–18

PEX7 mutations can also cause the more complex syndrome of rhizomelic chondrodysplasia punctata type 1,56–18 and other disorders of peroxisome biogenesis can cause the severe phenotypes of neonatal adrenoleukodystrophy and Zellweger’s syndrome.56 Therefore, clinical diagnosis of disorders involving ataxia, polyneuropathy, and retinitis pigmentosa may need a full screen of peroxisomal function, a search for mitochondrial disorders, or consideration of a glycosylation defect.19–41

Onset of Refsum’s disease is typically before age 20 years but can be much later.56–70 Because of impaired branched-chain fatty acid α-oxidation, pythanic acid, found primarily in dairy products, meat, and fish, accumulates to high levels in body fat.56–58 This accumulation within myelinated neurons is likely pathogenic, although the precise mechanism remains unclear.56–58 Stressful conditions, such as rapid weight loss or illness, can result in mobilisation of pythanic acid from fat stores, which can cause sudden worsening of symptoms or even an acute presentation similar to Guillain-Barré syndrome.56–58 Dietary restriction halts disease progression,56–58 so early identification of this disorder is essential so that treatment may be started. Plasmapheresis could be considered in patients presenting in an acutely ill state to rapidly reduce plasma concentrations of pythanic acid.56

Friedreich’s ataxia phenotype with cerebellar atrophy

As with the disorders described above, the following disorders can mimic the Friedreich’s ataxia phenotype; however, they can be readily distinguished by the presence of cerebellar atrophy or other findings on neuroimaging. Furthermore, the presence of clinical neurological findings not typically seen in Friedreich’s ataxia, such as epilepsy or cognitive or psychiatric symptoms, should also alert physicians to consider these disorders in the differential diagnosis.

Late-onset Tay-Sachs disease

Tay-Sachs disease is a G_{M2}-gangliosidosis caused by a deficiency of the enzyme β-hexosaminidase A, the gene for which, HEXA, is on chromosome 15q23–24.62–63 This is typically a severe infantile disorder associated with developmental delay, hypotonia, mental retardation, seizures, and blindness with the presence of a cherry-red spot on fundoscopy, resulting in death by age 3 years.64 In contrast, the late-onset phenotype presents as either a childhood-onset or adult-onset disease characterised by cerebellar dysfunction, areflexia, proximal muscle weakness with subsequent muscle atrophy and fasciculations, and psychiatric or behavioural problems.64 The juvenile-onset form can also include spasticity, seizures, and dementia.64 These differences in phenotype seem to arise because of genotypic variations, with the severe infantile form resulting from two inactive alleles, whereas the later onset forms retain at least one allele with a less severe mutation resulting in residual enzyme activity.64,65 It is important to consider this cause in the differential diagnosis of autosomal recessive ataxia, as the later onset form can present as a Friedreich’s ataxia phenotype. An important distinction is the presence of notable cerebellar atrophy on MRI.64 The disease is typically seen in Ashkenazi Jewish populations, but has also been reported in non-Jewish people.64,65

Knockout mouse models seem to most closely mimic the late-onset phenotype, primarily due to murine metabolic differences that prevent early ganglioside accumulation.65–66 Progressive CNS inflammation has been suggested as a potential mediator of disease pathogenesis.57 Although the available mouse models offer insight into the biology of this disease, there are no effective treatment options.62 Substrate reduction therapy56 and gene therapy69 are being explored for this and other gangliosidoses.

Cerebrotendinous xanthomatosis

This disorder is caused by mutation of CYP27 on chromosome 2, which encodes the mitochondrial enzyme sterol 27-hydroxylase, part of the hepatic bile-acid-synthesis pathway, resulting in increases of serum cholesterol and bile alcohols.70–72 Deposition of these metabolites in CNS tissues probably causes the clinical phenotype.72 Although generally thought of as a rare disorder, it may be seen in diverse ethnic populations,72 and recent studies have suggested prevalence may be as high as one per 50 000 white people for certain mutations.70 Neurological symptoms generally start around age 20 years and can include ataxia with pyramidal or extrapyramidal signs, sensorimotor peripheral neuropathy, seizures, psychiatric problems, and dementia; although the phenotype can be quite diverse.70–72 Associated features include juvenile cataracts,
tendon xanthomas, early atherosclerosis, osteoporosis, and chronic diarrhoea.\(^{70-72}\) Signs on neuroimaging include generalised cerebral and cerebellar atrophy as well as diffuse white-matter hyperintense lesions on MRI.\(^{73,74}\) Early diagnosis is important because the disease is treatable by bile-acid replacement therapy with chenodeoxycholic acid.\(^{75,77}\)

**DNA polymerase γ disorders including mitochondrial recessive ataxia syndrome**

Several neurodegenerative disorders are associated with mutation of POLG, the catalytic subunit of mitochondrial DNA polymerase γ, including progressive external ophthalmoplegia\(^{75-76}\) and the severe hepatocerebral disturbances seen in Alpers' syndrome.\(^{73,75}\) Additionally, several POLG mutations produce ataxic syndromes in an autosomal recessive manner.\(^{75-80}\) Several of these patients present with ataxia due to sensory neuropathy,\(^{76}\) including SANDO syndrome (sensory ataxic neuropathy, dysarthria, and ophthalmoplegia),\(^{76}\) and therefore will not be considered here. Six Norwegian patients from at least three different families have a syndrome consisting of cerebellar ataxia, ophthalmoplegia, sensorimotor neuropathy with prominent dorsal column involvement and areflexia, myoclonus, impaired cognition, epilepsy, and migraine headaches with onset before age 23 years.\(^77\) MRI in these patients showed hyperintensities in the thalamus, occipital lobes, brainstem, and cerebellum, as well as cerebellar atrophy in one patient.\(^{77}\) Four of the patients were homozygous for the same missense mutation, Ala467Thr.\(^{77}\) A similar phenotype has been reported in three members of a Finnish family with onset around age 30 years,\(^{79}\) who have mutations within POLG.\(^{77}\) Further genetic analysis of a large group of Finnish patients with ataxia identified several additional patients with these mutations; 27 patients from 15 different families were identified, all of whom were homozygous for two missense mutations (Trp748Ser and a known polymorphism Glu1143Gly) in \(\text{POLG}\).\(^{79}\) These patients had a variable age at onset, from childhood to adulthood with a median at 28 years.\(^{79}\) Clinically they demonstrated progressive cerebellar ataxia, sensorimotor peripheral neuropathy with involvement of the dorsal columns and leg areflexia, and about half of all patients had various combinations of mild cognitive impairment, psychiatric features, epilepsy, or myoclonus or other involuntary movements.\(^{79}\) MRI showed bilateral white-matter hyperintensities in the cerebellum and mild vermian atrophy, with occasional signal changes in the thalamus.\(^{79}\) Carrier prevalence was estimated as one per 125 making this disorder, which the authors called mitochondrial recessive ataxia syndrome (MIRAS), the most prevalent late-onset ataxia in Finland.\(^{79}\) A more recent study of primarily Norwegian patients with either homozygous Ala467Thr, homozygous Trp748Ser (Glu1143Gly), or heterozygous Ala467Thr/Trp748Ser(Glu1143Gly) showed the syndromes to be clinically identical with a mean age at onset of 14-5 years.\(^{79}\) The results of this study also suggest that liver failure is a commonly associated feature.\(^{79}\) Epilepsy was common and was the presenting symptom in many cases,\(^{79}\) thus clinically distinguishing this disorder from other Friedreich’s ataxia phenotypes.

\(\text{POLG}\) is located on chromosome 15q22–26,\(^{77}\) and the product is the only DNA polymerase found in mitochondria, and therefore functions in both the replication and repair of the mitochondrial genome.\(^{73}\) Disruption of the enzyme’s proofreading function or a catalytic polymerase defect with a resultant increase in mitochondrial mutations may be responsible for the disease phenotypes;\(^{77}\) however, how these specific mutations affect POLG function and contribute to the precise pathogenesis of this ataxic syndrome is unknown.

**Spinocerebellar ataxia with axonal neuropathy**

This childhood-onset disorder, found in Saudi Arabia, is characterised by cerebellar ataxia with atrophy, peripheral axonal sensorimotor neuropathy, distal amyotrophy, and pes cavus.\(^{71}\) The gene, \(\text{TDPL}\), is found on chromosome 14q31–32 and encodes tyrosyl-DNA phosphodiesterase 1, which is likely involved in repair of DNA-topoisomerase I complexes during transcription and replication in dividing cells\(^{72}\) and topoisomerase I-related single-stand break repair in postmitotic neurons.\(^{72,80}\) Oxidative stress and transcription may lead to single-stand breaks in the nervous system DNA, which become persistent in patients with spinocerebellar ataxia with axonal neuropathy, resulting in the neurodegenerative phenotype.\(^{72,81}\)

**Early-onset ataxia with cerebellar atrophy**

This final class of disorders differs from those previous in that the age at onset is typically much younger than seen in Friedreich’s ataxia and phenotypically similar disorders. Cerebellar atrophy is also a prominent feature. Ataxia telangiectasia is the prototypical disorder in this group. Although they may present in the teenage years, ataxia with oculomotor apraxia types 1 and 2 are also included in this category due to their notable similarities to ataxia telangiectasia. This category is defined solely by the clinical phenotype of the included disorders and is therefore distinct from the early-onset cerebellar ataxia classification originally defined by Harding for disorders of unknown cause.\(^{14}\)

**Ataxia telangiectasia**

In patients with ataxia telangiectasia, onset of cerebellar dysfunction begins by age 2–3 years and is severely progressive.\(^{82-86}\) Assessment of eye movement will commonly show oculomotor apraxia.\(^{88}\) There is notable clinical variability, however, and symptoms can present much later in life.\(^{86}\) Cerebellar atrophy is typically seen on MRI (figure 1), but may not be present early.\(^{85-88}\) Associated
features include oculocutaneous telangiectasias, variable degrees of immunodeficiency, and an increased risk for various cancers, especially leukaemia or lymphoma.85–87

Prevalence is variable but is estimated to be as high as one per 40 000 in the USA.85,86 High concentrations of serum α fetoprotein is a typical laboratory finding and patients are also radiosensitive.85,86,88

Ataxia telangiectasia results from mutation of the AT-mutated gene, ATM, on chromosome 11q22–23.85–87 The protein is a serine/threonine protein kinase involved in the DNA damage response pathway.85–87 ATM is initially involved in the signal transduction cascade triggered by DNA damage, particularly double-stranded DNA breaks.87,90,91 Loss of protein function seems to disrupt pathways leading to either cell-cycle checkpoint regulation or apoptosis, resulting in a syndrome of cellular genomic instability,87,90,91 which likely gives rise to the clinical features of the disease. Phenotype can vary in severity depending on whether or not there is a complete absence of ATM protein.85,86,88

There are several other disorders with clinical and biochemical similarities to ataxia telangiectasia, including ataxia telangiectasia-like disorder (ATLD) and Nijmegen breakage syndrome (NBS).86,88 Clinically, ATLD is very similar to ataxia telangiectasia but has later onset with slower progression; patients lack telangiectasias and do not have raised concentrations of serum α fetoprotein.85,86,88 NBS, in contrast, differs from ataxia telangiectasia in that patients have microcephaly and growth retardation with decreased intelligence and they lack telangiectasias, elevated α fetoprotein, and ataxia.86,88,92 ATLD is caused by mutation in the meiotic recombination 11 gene, MRE11, whereas NBS is caused by mutation of the nibrin gene, NBS1.86,88 Both of these proteins are components of the meiotic recombination complex that is rapidly recruited to sites of DNA damage and participates in the initiation of the DNA damage response pathway, including the activation of ATM.86,91 Although ATM knockout mice are viable,91 both NBS1 and MRE11 knockouts die during embryogenesis.86,91 Although ATM-deficient mice show phenotypic similarities to ataxia telangiectasia, they do not seem to have gross histological changes in the cerebellum or overt ataxia.91–93 Recently developed NBS1 hypomorphic (gene function partly reduced) mice have phenotypes similar to both human ataxia telangiectasia and NBS including cerebellar degeneration and ataxia86 and may be useful to elucidate further the pathogenesis and role of these proteins in the CNS. In human beings, NBS and ataxia telangiectasia do not overlap clinically—except perhaps in the Fresno phenotype of the latter, which clinically seems to be a combination of both disorders, but only shows mutations in ATM genetically.86 In the case of ataxia telangiectasia and ATLD, the availability of genetic testing is the quickest means of providing a definitive diagnosis. Treatment for all these disorders is primarily symptomatic.

Ataxia with oculomotor apraxia

Another ataxic syndrome, very similar to ataxia telangiectasia, has been recently determined to be two distinct disorders. Ataxia with oculomotor apraxia type 1, reported in patients from Europe, Japan, and north Africa,86,87 presents later than ataxia telangiectasia, at about age 7 years86,90,91 and sometimes even much older.86 Patients have cerebellar gait and limb ataxia; sensorimotor neuropathy with notable dorsal column involvement and areflexia; eye movement abnormalities including nystagmus, fixation instability, and variable oculomotor apraxia; extrapyramidal signs; and mild cognitive impairment.86,87 MRI shows cerebellar atrophy, especially of the vermis.86–88 Laboratory studies show hypoalbuminaemia, hypercholesterolaemia, and normal serum α fetoprotein.86,90 The disease is caused by mutation of the aprataxin gene, APTX, on chromosome 9p13.86,87,90 The protein likely plays a part in DNA repair, particularly single-strand DNA breaks.103–105 Although other additional roles are possible, such as in RNA processing.86,87 How the protein affects pathogenesis and contributes to the phenotypic distinctions from other DNA repair disorders is unknown.

Ataxia with oculomotor apraxia type 2 presents with a similar phenotype as type 1, but at age onset is in the early teens and there is perhaps a lesser degree of certain features, such as oculomotor apraxia, extrapyramidal signs, or cognitive changes in some populations.105–107 In further contrast to type 1, laboratory studies show normal albumin and high serum α fetoprotein concentrations, although MRI again shows cerebellar, particularly vermian, atrophy (figure 1).105–107 Ataxia with oculomotor apraxia type 2 could be the second most common autosomal recessive ataxia after Friedreich’s ataxia in the European population.105 Type 2 is caused by mutation in the gene for senataxin, SETX, on chromosome 9q34.105–107 The senataxin protein contains a DNA/RNA helicase domain and, in cultured cells, is localised to the cytoplasm and the nucleolus, possibly in a cell-cycle-dependent manner.105 Although the functional role of human senataxin is unknown, its yeast orthologue, SenIp,107 is implicated in DNA transcription, DNA repair, and the processing of non-coding RNAs.105–107 Interestingly, specific missense mutations in the senataxin gene, similar but distinct from those found in ataxia with oculomotor apraxia type 2, cause an autosomal dominant form of juvenile ataxic lateral sclerosis (ALS4), a disorder not seen in heterozygous carriers of type 2 mutations.105–107 One possible explanation for this dichotomy is that the ataxic lateral sclerosis mutations produce a specific gain-of-function phenotype whereas the ataxia mutations produce a diffuse loss-of-function phenotype.106–107 However, further study of senataxin will be necessary to determine precisely which functions are affected and how they contribute to pathogenesis.
Autosomal-recessive spastic ataxia of Charlevoix-Saguenay

Characterised primarily by progressive cerebellar dysfunction, pyramidal signs such as spasticity with hyperreflexia, and peripheral sensorimotor neuropathy with amyotrophy, autosomal recessive spastic ataxia of Charlevoix-Saguenay was first identified in northeast Canada. More recently, the disorder has been described in Europe, Eurasia, north Africa, and Japan. Hypermyelinated retinal fibres seen on fundoscopy have been described in many patients, predominantly those from Canada, but is not typical of cases seen elsewhere. Onset is typically between age 1–5 years, but has been reported in the teens in some families. MRI shows cerebellar vermal atrophy. The gene implicated in this disorder, SACS, is on chromosome 13q11. This gene contains one of the largest known exons in the human genome, at about 13 kb in size. The protein, known as sacsin, is predicted to have a chaperone role in protein-folding. The cellular role of sacsin and the mechanism by which loss of sacsin function contributes to the pathogenesis of autosomal recessive spastic ataxia of Charlevoix-Saguenay remains unknown.

Infantile-onset spinocerebellar ataxia

This disorder, seen in Finland, is a severe ataxic syndrome with onset before age 2 years. Infants present with a progressive course that includes cerebellar ataxia, hypotonia, sensory neuropathy with areflexia, optic atrophy, ophthalmoplegia, hearing loss, involuntary movements, and epilepsy. Female hypogonadism is an associated feature. MRI shows atrophy of the cerebellum, brainstem, and spinal cord with corresponding atrophic changes seen on pathology. The gene C10orf2 on chromosome 10q24 is implicated in this disorder; it encodes the proteins twinkle, a mitochondrial helicase involved in DNA replication, and twinky whose current function is unknown. Similar to POLG, twinkle mutations also cause progressive external ophthalmoplegia.

Table 2: Clinical characterisation of the autosomal recessive ataxias

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The typical or most common clinical features of the various autosomal recessive ataxic disorders are shown. Due to profound variability in clinical presentation, not all patients will present with all the features listed and, in some cases, notable deviations may also be observed. + = Feature may be present. − = Feature not present, uncommon, or not reported. ↓ = Reduced or absent. ↑ = Increased. * = Clinical features useful for differential diagnosis. FRDA = Friedreich’s ataxia. AVED = ataxia with vitamin E deficiency. ABL = abetalipoproteinaemia. RD = Refsum’s disease. LOTS = late-onset Tay-Sachs disease. CTX = cerebrotendinous xanthomatosi. MIRAS = mitochondrial recessive ataxia syndrome. SCAN1 = spinocerebellar ataxia with axonal neuropathy. AT = ataxia telangiectasia. ATLD = ataxia telangiectasia-like disorder. AOA1 = ataxia with oculomotor apraxia, type 1. AOA2 = ataxia with oculomotor apraxia, type 2. ARSACS = autosomal recessive ataxia of Charlevoix-Saguenay. IOSCA = infantile-onset spinocerebellar ataxia. CA = Cayman ataxia. MSS = Marinesco-Sjögren syndrome.
plegia. This suggests that similar pathogenetic mechanisms may cause both infantile-onset spinocerebellar ataxia and the POLG related ataxic disorders, although why the former is much more severe is unknown.

Cayman ataxia

This rare childhood-onset disorder is found in an isolated inbred population from Grand Cayman Island in the Caribbean and is characterised by cerebellar ataxia with atrophy of the cerebellum on neuroimaging, hypotonia, and psychomotor retardation. The gene, ATCAY, is located on chromosome 19p13.3 and encodes the protein caytaxin. Caytaxin contains a binding domain similar to that of the α-tocopherol transfer protein, which is mutated in ataxia with vitamin E deficiency, but likely binds a different

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Clinical findings associated with the various autosomal recessive ataxias are shown along with key laboratory and other diagnostic test results. + = feature may be present. — = feature not present, uncommon, or not reported. *Features useful for differential diagnosis: an = anosmia. bl = blindness. cd = chronic diarrhoea. f = fasciculations. i = ichthyosis. isr = increased startle response. op = osteoporosis. pa = premature atherosclerosis. sh = short stature. AS = axonal sensory neuropathy. ASM = axonal sensorimotor neuropathy. DSM = demyelinating sensorimotor neuropathy. FRDA = Friedrich’s ataxia. AVED = ataxia with vitamin E deficiency. ABL = abetalipoproteinemia. RD = Refsum’s disease. LOTS = late-onset Tay-Sachs disease. CTX = cerebrotendinous xanthomatosis. MIRAS = mitochondrial recessive ataxia syndrome. SCAN1 = spinocerebellar ataxia with axonal neuropathy. AT = ataxia telangiectasia. ATLD = ataxia telangiectasia-like disorder. AOA1 = ataxia with oculomotor apraxia, type 1. AOA2 = ataxia with oculomotor apraxia, type 2. ARSACS = autosomal recessive ataxia of Charlevoix-Saguenay. IOSCA = infantile onset spinocerebellar ataxia. CA = Cayman ataxia. MSS = Marinesco-Sjögren syndrome.

Table 3: Phenotypic and diagnostic characterisation of the autosomal recessive ataxias
Abnormal Cerebellar atrophy†

Marinesco-Sjögren syndrome

This rare infantile-onset or childhood-onset syndrome is characterised by cerebellar ataxia, cataracts, mental retardation, and short stature associated with hypogonadotropic hypogonadism, and skeletal deformities.127–129 Patients may also present with variable degrees of myopathy involving hypotonia, muscle weakness, and atrophy, as well as peripheral neuropathy or epilepsy.127–129 MRI may show cerebellar atrophy.127 The causative gene, SIL1, is located on chromosome 5q31 and encodes a nucleotide exchange factor for heat-shock protein 70 family member HSPA5, which functions as a molecular chaperone during nascent protein folding and transport.128,129 Because SIL1 is ubiquitously expressed,128 it is unclear why its impairment causes the specific features seen in the Marinesco-Sjögren phenotype.

Conclusion

Among the hereditary ataxias, those with autosomal recessive inheritance form a heterogeneous population. The major disorders can be effectively grouped into three categories. The first two of these are best represented clinically by Friedreich’s ataxia, while the last category is exemplified by ataxia telangiectasia. Although additional clinical assessment can aid in further differentiation within these categories (table 2), ancillary testing with simple laboratory studies and neuroimaging can be quite helpful in many cases, particularly for disorders that resemble Friedreich’s ataxia (table 3). Armed with this information, directed genetic testing can then be done to definitively establish the diagnosis (figure 2). Because of its prevalence and variability of presentation, almost all patients should be screened initially for Friedreich’s ataxia. Subsequently, clinical phenotype can direct further diagnostic biochemical testing, if available, and suggest relevant genetic testing when appropriate for management or when a molecular diagnosis is desired. Genetic testing can be expensive, currently ranging, on average, from US$300 for repeat expansion or specific mutation screening to US$1000 or more for sequencing of an entire gene and therefore focused testing is recommended when a genetic diagnosis is clinically warranted.

Although many advances have occurred in our understanding of the molecular and cellular pathogenesis underlying many of these disorders, particularly Friedreich’s ataxia, further study is needed to better understand the biology of these disorders. Why global metabolic changes involving the mitochondria, lipid biochemistry, or other fundamental cellular processes unknown ligand.125 In rodents, the protein seems to interact with kidney-type glutaminase and mutations are speculated to affect glutamate synthesis at synapses, potentially causing abnormal neuron growth or neurotoxicity.125

[Figure 2: Diagnostic assessment of a patient with a suspected autosomal recessive hereditary ataxia. Blue boxes represent clinical or diagnostic considerations; red boxes indicate points requiring further clinical or diagnostic assessment; points for establishing a definitive diagnosis are indicated on the basis of type of test as green (genetic), purple (serum), or yellow (radiosensitivity) boxes. Note that ataxic disorders characterised by cerebellar atrophy may present with normal neuroimaging early in their course; therefore these conditions should also be investigated in patients with normal imaging if clinically warranted (blue star). Further considerations may include focused genetic testing if a molecular diagnosis is desired. *=if clinically indicated. †=or white-matter changes. ‡=or other POLG cerebellar ataxic disorder. FRDA=Friedreich’s ataxia. AVED=ataxia with vitamin E deficiency. ABL=abetalipoproteinaemia. RD=Refsum’s disease. LOT5=late-onset Tay-Sachs disease. CTX=cerebrotendinous xanthomatosis. MIRAS=mitochondrial recessive ataxia syndrome. SCAN1=spinocerebellar ataxia with axonal neuropathy. AT=ataxia telangiectasia. AOA1=ataxia with oculomotor apraxia, type 1. AOA2=ataxia with oculomotor apraxia, type 2. ARSACS=autosomal recessive ataxia of Charlevoix-Saguenay. IOSCA=infantile-onset spinocerebellar ataxia. CA=Cayman ataxia. MSS=Marinesco-Sjögren syndrome.]
such as DNA repair, protein folding, or RNA processing so profoundly and specifically affect the cerebellum and spinocerebellar pathways is an important area for further investigation (figure 3). The effects of oxidative stress, metabolic complications leading to premature cell death, and genetic instability appear to be key underlying mechanisms in several of these disorders and may ultimately aid in the development of effective treatment strategies. Current treatments are unfortunately limited primarily to symptomatic management but, with continued research, hopefully physicians will be able to provide more options to their recessive ataxia patients in the future.

Search strategy and selection criteria

References for this review were identified by searches of PubMed from 1966 until June 2006 with the terms “cerebellar ataxia”, “recessive cerebellar ataxia”, “Friedreich ataxia”, “AVED”, “abetalipoproteinemia”, “Refsum disease”, “late onset Tay-Sachs”, “cerebrotendinous xanthomatosis”, “POLG ataxia”, “SCAN1”, “ataxia telangiectasia”, “AOA1”, “AOA2”, “ARSACS”, “IOSCA”, “Cayman ataxia”, and “Marinesco-Sjögren”. Due to space limitations, emphasis was placed on comprehensive reviews and primary articles published after 1996. Articles were also identified through searches of the authors’ own files and references from relevant articles. Only papers published in English were reviewed.

Contributors

BF contributed to the concept, design, literature search, writing, and critical review of this review. SP contributed to the concept, design, literature search, writing, and supervision of this review. Both authors have seen and approved the final version.

Conflicts of interest

We have no conflicts of interest.

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