Mitochondrial Ataxias

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ABSTRACT: Mitochondrial disorders (MIDs) are an increasingly recognized condition. The second most frequently affected organ in MIDs is the central nervous system. One of the most prevalent clinical CNS manifestations of MIDs is ataxia. Ataxia may be even the dominant manifestation of a MID. This is why certain MIDs should be included in the classification of heredooxaxies or at least considered as differentials of classical heredooxaxies. MIDs due to mutations of the mitochondrial DNA, which develop ataxia include the MERRF, NARP, MILS, or KSS syndrome. More rarely, ataxia may be a feature of MELAS, LHON, PS, MIDD, or MSL. MIDs due to mutations of the nuclear DNA, which develop ataxia include LS, SANDO, SCAE, AHS, XSLA/A, IOSCA, MIRAS, MEMSA, or LBSL syndrome. More rarely ataxia can be found in AD-CPEO, AR-CPEO, MNGIE, DCMOAD, CoQ-deficiency, ADOAD, DCMA, or PDC-deficiency. MIDs most frequently associated with ataxia are the non-syndromic MIDs. Syndromic and non-syndromic MIDs with ataxia should be delineated from classical heredooxaxies to initiate appropriate symptomatic or supportive treatment.


Hereditary mitochondrial disorders (MIDs) affect the respiratory chain (RC) or oxidative phosphorylation (OXPHOS) in the majority of the cases. Mitochondrial disorders are due to mutations in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) located genes, why transmission of these mutations follows an autosomal dominant (AD), autosomal recessive (AR), X-chromosomal recessive (XL), or maternal trait. Phenotypically, MIDs present in the majority of cases as multi-system disease with onset between birth and senescence, although single-organ affection may dominate at onset of the disease\(^1\). MIDs predominantly manifest in tissues/organs with high-energy requirements\(^2\), such as the peripheral nervous system (PNS), central nervous system (CNS), eyes, inner ears, endocrine glands, heart, intestines, kidneys, or bone marrow\(^3\). Combinations of organ affection constitute mitochondrial syndromes (syndromic MIDs), for which well known acronyms have been adopted (Table 1)\(^2\). In the majority of cases, however, the phenotype does not comply with one of these syndromes (non-syndromic MIDs). The CNS is the second most frequently affected organ in MIDs and ataxia may be a dominant CNS manifestation of MIDs. If ataxia predominates the presentation of MIDs (ataxia neuropathy spectrum)\(^3\), it may be easily mixed up with classical heredooxaxies.

Classical heredooxaxies represent a heterogeneous group of neurological disorders, clinically characterized by a cerebellar syndrome with imbalance, progressive gait and limb un-
coordination, dysarthria, or disturbed eye movements. Heredoataxias are most frequently classified according to the mode of inheritance (AD, AR, or XL). Mitochondrial disorders with ataxia as part of the phenotype may also be inherited via an AD, AR, XL or maternal trait but have gained little attention so far. With the rapidly increasing prevalence of MIDs, however, an increasing number of MIDs with ataxia are reported. This review aims to give an overview of recent advances and current knowledge about the frequency, clinical presentation, genetic background, management, and prognosis of hereditary MIDs associated with sensory, spinal, or cerebellar ataxia.

METHODS

The source of the disorders listed below was a MEDLINE search covering the years 1966 to February 2009 and using the key words: ataxia, sensory ataxia, cerebellar ataxia, mitochondrial respiratory chain, mitochondrial disorder, and all acronyms of syndromic MIDs listed in Table 1.

Definitions

Ataxia was defined as uncoordination and unsteadiness due to cerebral failure to regulate the body’s posture or regulate strength and direction of limb movements. Ataxia is usually a manifestation of a cerebral disorder, particularly of the cerebellum (cerebellar ataxia) or due to a spinal or peripheral lesion (sensory ataxia). Cerebellar and sensory ataxia manifest as uncoordinated movements, or unsteady stance and gait. Additional manifestations of cerebellar ataxia may be nystagmus or dysarthria, which often distinguish central and peripheral ataxia. Sensory ataxia can be compensated by opening the eyes, whereas cerebellar ataxia persists with open or closed eyes.

Frequency of mitochondrial ataxias

No convenient figures are reported about the prevalence of ataxia in MIDs. Only figures about the general prevalence of MIDs are available, estimating that 9/100,000 individuals have a manifest MID. Additionally, 16.5/100,000 children and adults are at risk for the development of a MID. The prevalence of the MERRF mutation 8344A>G in North East England is 0.4/100,000. The most common POLG1 mutation, 467A>T, has been reported to occur in 0.6% of the Belgian population.

Classification of mitochondrial disorders

Most frequently, MIDs are classified according to the type of the mutated gene. A first group of MIDs is due to mutations in mtDNA located genes (Table 2). Mitochondrial disorders due to mtDNA mutations are further classified as MIDs due to point mutations, which are maternally inherited and homoplasmic or exclusively heteroplasmic (Table 2), or as single deletions or duplications, which are sporadic and heteroplasmic. Point mutations may either affect tRNA or rRNA genes (MELAS, MERRF) or genes encoding for RC subunits (LHON, NARP, MILS). Single deletions or duplications are responsible for CPEO, PS, or KSS. The second group of MIDs is due to mutations in nDNA located genes, which are divided into genes encoding for RC subunits (LS, non-syndromic MID), for assembly factors of RC subunits (LS, GRACILE syndrome), for proteins involved in intergenicom signaling, causing breakage syndromes (AD-CPEO, AR-CPEO, SANDO, SCAE, AHS, MNGIE), deletion syndromes (non-syndromic MID, AHS), or translation defects (MLASA), for proteins involved in the CoQ metabolism (LS, non-syndromic MID), for proteins involved in the mitochondrial transport machinery (X-linked DDS (MTS),...
Diagnosis of mitochondrial disorders

The diagnosis of a MID is based on clinical, chemical, electrophysiological, histological, biochemical, and genetic investigations. Phenotypic features suggesting a MID include abnormalities of the PNS (myopathy including ocular muscles, neuropathy, neuromopathy), CNS (epilepsy, migraine, stroke-like episodes, ischemic stroke, ataxia, Parkinsonism, dystonia, optic atrophy, cognitive decline, psychiatric abnormalities, coma), endocrine glands (short stature, pituitary adenoma, pituitary insufficiency, thyroid dysfunction, hypoparathyroidism, diabetes mellitus, hyponatraemia, hypogonadism, hyperhidrosis, osteoporosis), heart (cardiomyopathy, impulse generation or propagation abnormalities), eye (cataract, glaucoma, retinitis pigmentosa), ear (hypoacusis, tinnitus, vertigo), gastrointestinal tract (vomiting, pseudoobstruction, diarrhea, hepatopathy, liver cysts, pancreatitis), kidney (renal failure, renal cysts), bone marrow (anemia, leucopenia, thrombocytopenia, pancytopenia), bones (facial dysmorphism, hypertelorism), or dermis (lipoma, psoriasis, excema). Blood chemical investigations may show
increased creatine-kinase, lactate or pyruvate (at rest or upon exercise). Serum and urine levels of amino acids may be elevated. Organic acids may be elevated in the urine. Lactate and pyruvate may be also elevated in the cerebro-spinal fluid (CSF). Nerve conduction studies may indicate neuropathy or neuronopathy and electromyography may show myogenic, neurogenic or non-specific changes. Neuroimaging may show a variety of abnormalities, including cortical, diffuse, or cerebellar atrophy, basal ganglia calcification, focal or diffuse demyelination, stroke-like lesions, laminar cortical necrosis, lacunas, cysts, or old ischemic lesions. Of paramount diagnostic importance is the detection of a biochemical defect of one of the RC complexes or the OXPHOS in any tissue or the detection of a known or new causative mtDNA or nDNA mutation.

Mitochondrial disorders associated with ataxia

A. Disorders due to mutations in mtDNA genes

Mitochondrial encephalomyopathy, lactacidosis, stroke-like episodes (MELAS)

Ataxia is not a common feature of MELAS syndrome, but has been reported in single patients. In a female with a MELAS phenotype since childhood, cognitive impairment and ataxia developed during the disease course (Table 3)12. In this patient MELAS was due to the 7512T>C tRNAser mutation11. Ataxia has been also reported in a MELAS patient carrying the 3243A>G mutation (Table 4)12.

Myoclonic epilepsy and ragged red fibers (MERRF)

Cerebellar ataxia is a common feature of MERRF syndrome. Nearly all MERRF patients present with cerebellar ataxia13. Cerebellar ataxia may be even the presenting manifestation in quite a number of patients (Table 3)14. In addition, MERRF patients typically present with myoclonic epilepsy, and mitochondrial myopathy with ragged-red fibers15. More rarely patients develop dementia, parkinsonism, hypacusis, optic atrophy, multiple lipomas, or foot deformities in the advanced stages13,16,17. On cerebral magnetic resonance imaging (cMRI) atrophy of the cerebellar peduncles, the cerebellum, or the brainstem can be found14. Histopathological findings include degeneration of the dentate nuclei, globus pallidus, red nuclei, substantia nigra, inferior olivary nuclei, cerebellar cortex, or spinal cord. Particularly the posterior columns, the spino-cerebellar tracts, or Clarke’s columns are affected16. MERRF is most frequently due to point mutations in the tRNAlys gene (Table 4).

Leber’s hereditary optic neuropathy (LHON)

Only in single patients ataxia may be a supplementary feature in addition to optic atrophy (Table 3)18,19. In such patients cMRI may reveal cerebellar atrophy19. LHON is due to homoplasmic mtDNA mutations affecting genes, which encode for subunits of RC complex I, III, IV, or V. Most frequently subunits of RC complex I are mutated in LHON. There are three primary LHON mutations, 3460A>G, 11778A>G, and 14484T>C, which account for >95% of the cases (Table 4)5,20. Only 50% of males and 10% of females, harboring a primary LHON-mutation, actually develop LHON20. The incomplete penetrance and the predominance of males suggest factors other than the primary LHON mutations (secondary LHON mutations, nDNA mutations) play a modifying role.

Neuropathological findings comprise symmetrical lesions in the basal ganglia and brainstem, resembling those of LS23,24. The syndrome is most frequently caused by heteroplasmic point mutations in the ATP6 gene (Table 4)23. The mutation load is particularly high in the cortex, putamen, thalamus, cerebellum, and brainstem24. Irrespective of the mutation load the ATP6 activity is reduced by about half of the normal value25.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Type of ataxia</th>
<th>mtDNA genes</th>
<th>nDNA genes</th>
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<tbody>
<tr>
<td>Ataxia frequent</td>
<td></td>
<td>MERRF</td>
<td>CA</td>
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<td></td>
<td></td>
<td>NARP</td>
<td>SA</td>
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<td></td>
<td></td>
<td>MLS</td>
<td>CA</td>
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<td></td>
<td></td>
<td>KSS</td>
<td>CA</td>
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<tr>
<td>Ataxia infrequent</td>
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<td>MELAS</td>
<td>CA</td>
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<td></td>
<td></td>
<td>LHON</td>
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<td></td>
<td>PS</td>
<td>CA</td>
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<td></td>
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<td>MSL</td>
<td>CA</td>
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<td>MIDD</td>
<td>SA</td>
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<td></td>
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<td>LS</td>
<td>CA</td>
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<td>SANDO</td>
<td>CA, SA</td>
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<td></td>
<td>SCAE</td>
<td>CA, SA</td>
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<td>AHS</td>
<td>CA, SA</td>
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<td></td>
<td>XLSA/A</td>
<td>CA</td>
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<td>IOSCA</td>
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<td>MIRAS</td>
<td>CA, SA</td>
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<td></td>
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<td>MEMSA</td>
<td>SA</td>
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<td></td>
<td>LBSL</td>
<td>CA</td>
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<tr>
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<td>DCMA</td>
<td>CA</td>
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<tr>
<td>Ataxia infrequent</td>
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<td>AD-CPEO</td>
<td>CA</td>
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<td>AR-CPEO</td>
<td>CA, SA</td>
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<td>MNGIE</td>
<td>SA</td>
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<td></td>
<td></td>
<td>ADOAD</td>
<td>SA</td>
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<td></td>
<td>DIDMOAD</td>
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<td></td>
<td></td>
<td>PDC-deficiency</td>
<td>CA</td>
</tr>
</tbody>
</table>

CA: cerebellar ataxia, SA: sensory ataxia
Maternally inherited Leigh syndrome (MILS)

Ataxia is present in nearly all patients with MILS. However, there is broad clinical and genetic heterogeneity. In a family carrying a mitochondrial ATP6 mutation, clinical manifestations ranged from late-onset MILS to NARP. In another patient the 8993T>C mutation caused MILS at early infancy, which disappeared over time, such that he was near normal at age 18 years. Maternally inherited Leigh syndrome with predominant ataxia and neuropathy was diagnosed in a family carrying the 9185T>C mutation in the ATP6 gene with a heteroplasmy rate >90% (Table 3). Other ATP6 mutations may also cause MILS and ataxia may be the only manifestation in mutation carriers. Mito-chondrial genes most frequently mutated in MILS are the ND1-6, ATP6, COXIII, and tRNALys genes (Table 4). The mutation load correlates positively with the severity of the phenotype.

Pearson syndrome (PS)

Pearson syndrome is an uncommon syndromic MID in infants, characterized by pancytopenia. With disease progression, however, patients additionally develop muscle hypotonia, developmental delay, ataxia, tremor, hepatopathy, renal failure, or exocrine pancreatic dysfunction. Later on the phenotype may even turn into KSS or LS. Muscle biopsy may show features of mitochondrial myopathy. So far about 60 cases have been reported in the literature. As with KSS and CPEO, PS is due to single large-scale mtDNA deletions or duplications.

Kearns-Sayre syndrome (KSS)

Typical features of KSS include CPEO, pigmentary retinopathy, and cardiac conduction disturbances. Additional features include short stature, glaucoma, deafness, diabtes, primary amenorrhea, myopathy with ptosis and limb weakness, pyramidal signs, ataxia, and increased CSF protein content (Table 3). In single patients KSS may be dominated by an ataxic syndrome. In accordance with the clinical findings, MRI often shows cerebellar or global atrophy. Additionally, there may be T2-hyperintensities in the deep gray matter nuclei, the cerebellar white matter, or the subcortical white matter. Kearns-Sayre syndrome is due to single large-scale mtDNA deletions or duplications.

Maternally inherited diabetes and deafness (MIDD)

Maternally inherited diabetes and deafness syndrome presents clinically with diabetes and sensorineural hearing loss. There are also families, which additionally present with features of MELAS syndrome, including seizures, migraine, short stature, mental retardation, or stroke-like-episodes. In single cases, ataxia may be a feature of the phenotype. Maternally inherited diabetes and deafness is due to mutations in the tRNAleu or tRNALys gene or due to large-scale tandem duplications or deletions/duplications.

Multiple symmetric lipomatosis (MSL)

Multiple symmetric lipomatosis is a rare condition presenting with CPEO, hypoaucus, cerebellar ataxia, proximal myopathy, and polynuropathy. Muscle biopsy may indicate mitochondrial myopathy. The genetic background is hetero-

Table 4: Mutated genes responsible for syndromic and non-syndromic MIDs with ataxia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Reference</th>
</tr>
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</tr>
<tr>
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<tr>
<td>tRNALeu</td>
<td>MERRF</td>
<td>[14]</td>
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<tr>
<td>tRNALys</td>
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<td>[95]</td>
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<td></td>
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<td>[40]</td>
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<tr>
<td></td>
<td>nsMID</td>
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</tr>
<tr>
<td></td>
<td>ATP6</td>
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<tr>
<td></td>
<td>MILS, NARP</td>
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<td></td>
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<td>MEMSA, ANS</td>
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<td>ANTI</td>
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<td>ADOAD</td>
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<td>TP</td>
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<td>[86]</td>
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<td>Frataxin</td>
<td>FA</td>
<td>[87,88]</td>
</tr>
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</table>

nsMID: non-syndromic MID
ophthalmoparesis syndrome was first reported in 1997.49 Involve othersystems, manifesting as proximal muscule weakness (Table 3).45 Some patients additionally present with dysarthria, severe hearing loss, mental retardation, ptosis, ophthalmoparesis, distal myoclonus, and diabetes mellitus. RC complex I and IV activities were low in the muscle of the affected mother of the index patient41. Ataxia was also a feature in an Italian family with lipomas due to the mtDNA mutation 8365G>A42. Ataxia was also a phenotypic manifestation of the 14680C>A mtDNA mutation in a 14-year-old boy with exercise intolerance, weakness and lactic acidosis, who showed a mosaic pattern of succinate dehydrogenase staining on muscle biopsy43.

**B. MIDs due to nDNA mutations**

**Leigh syndrome (LS)**

Leigh syndrome, also termed subacute, necrotizing encephalopathy, is the most frequent MID in childhood44. It is clinically characterized by a wide variety of abnormalities from severe neurological problems to almost absence of any abnormality. Most frequently the CNS is affected, including psychomotor retardation, seizures, nystagmus, ophthalmoparesis, optic atrophy, ataxia, dystonia, or respiratory failure (Table 3)45. Some patients additionally present with polyneuropathy or myopathy, or non-neurological abnormalities, such as diabetes, short stature, hypertrichosis, cardiomyopathy, anemia, renal failure, vomiting, or diarrhea (Leigh-like syndrome). On MRI, symmetric lesions, particularly in the basal ganglia, thalamus, or brainstem can be found29. Leigh syndrome is the MID with the widest genetic heterogeneity of all MIDs and may be due to mutations in the SURF1, NDUFS1-8, or NDUFV1-2 genes (Table 4)29.

**Autosomal dominant chronic external ophthalmoplegia (AD-CPEO)**

Autosomal dominant chronic external ophthalmoplegia may not only be restricted to the extra-ocular muscles but may also involve other systems, manifesting as proximal muscle weakness and wasting, hearing loss, or cerebellar ataxia (Table 3)46. Multiple mtDNA deletions may be found in the skeletal muscle of these patients46. Responsible for the multiple mtDNA deletions are mutations in the ANT1, C10orf2 (twinkle), or POLG1 genes47.

**Autosomal recessive chronic external ophthalmoplegia (AR-CPEO)**

Rarely, ataxia may be also a feature of AR-CPEO, such as in a family with CPEO, polyneuropathy, sensorineural hearing loss, and affective disorder48. The syndrome was due to two heterozygous missense transitions in the POLG1 gene48.

**Sensory ataxia with neuropathy, dysarthria and ophthalmoparesis (SANDO)**

AR Sensory ataxia with neuropathy, dysarthria and ophthalmoparesis syndrome was first reported in 1997.49 Clinically, it is characterized by the triad of sensory or cerebellar ataxia, dysarthria, and ophthalmoparesis.49 Additionally, there may be dysphagia, neuropathy or myopathy.50 Genotypically, multiple mtDNA deletions due to POLG1 mutations49,50 or more rarely C10orf2 (twinkle) mutations are made responsible for the phenotype51.

**Spino-cerebellar ataxia and epilepsy (SCAE)**

Juvenile-onset SCAE is characterised by a phenotype resembling that of a spinocerebellar ataxia with the difference that SCAE patients also develop seizures52. Most frequently SCAE is due to mutations in the POLG1, C10orf2 (twinkle), or ANT1 genes respectively52. A patient with CPEO and multiple mtDNA deletions additionally developed sensory and cerebellar ataxia peripheral neuropathy, parkinsonism, and depression. The complex phenotype in this patient resembled SCAE and was attributed to mutations in ANT1 and POLG1 genes with deleterious, secondary effects on mtDNA maintenance and integrity52.

**Alpers-Huttenlocher disease (AHS)**

Alpers-Huttenlocher disease starts in the first years of life with sudden onset intractable seizures, developmental delay, psychomotor regression, stroke-like episodes, muscle hypotonia, ataxia, cortical blindness, hepatic failure, fasting hypoglycemia, and death within a short time53,54. Muscle biopsy shows COX-negative fibers55. Neuropathological investigations reveal cortical gliosis and subcortical loss of neurons, particularly in the thalamus55. Alpers-Huttenlocher disease is due to mutations in the POLG1 gene, secondarily causing mtDNA depletion56. The diagnosis is established by liver biopsy, muscle biopsy, or genetic testing. A phenotype similar to AHS, including muscle hypotonia, atetosis, sensory neuropathy, ataxia, hypoacusis, ophthalmoplegia, and intractable epilepsy was caused by C10orf2 (twinkle) mutations, resulting in hepatic mtDNA depletion57.

**Mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE)**

Mitochondrial neuro-gastro-intestinal encephalomyopathy is an AR MID, characterized by nausea, vomiting, diarrhea, ascites, gastrointestinal dysmotility, ophthalmoparesis, neuropathy, and mitochondrial myopathy58. Complementary features include ataxic gait, hearing loss, short stature, facial palsy, dysphonia, dysarthria, sweating, orthostatic hypotension, bladder dysfunction and hepatosplenomegaly58. Mitochondrial neuro-gastro-intestinal encephalomyopathy is due to mutations in the gene encoding for the thymidine-phosphorylase59,60, which plays an important role in the nucleoside metabolism by regulating the availability of thymidine for mitochondrial DNA synthesis61. The mutation secondarily causes mtDNA depletion or multiple mtDNA deletions. Thymidine-phosphorylase is also implicated in angiogenesis and cell trophism62.

**X-linked sideroblastic anemia with ataxia (XLSA/A)**

X-linked sideroblastic anemia with ataxia is a rare syndrome MID, characterized by mild sideroblastic anemia with hypochromia and microcytosis and cerebellar ataxia (Table 3)63-65. Cerebral imaging shows severe cerebellar atrophy. XLSA/A is
due to mutations in the mitochondrial ATP-binding cassette transporter ABC7 gene on chromosome Xq13.64.56.

**Autosomal dominant optic atrophy and deafness (ADOAD)**

Ataxia may be also a feature of ADOAD syndrome, which additionally presents with ataxia, axonal, sensorimotor neuropathy, CPEO, or mitochondrial myopathy (dominant optic atrophy “plus” syndrome)67. Muscle biopsy may show mosaic COX-deficiency48. The syndrome is due to mutations in the OPA1 gene, encoding for a dynamin-related GTPase, involved in mitochondrial fusion, cristae organization, and apoptosis47,69. Affected patients also harbor multiple mtDNA deletions, suggesting that OPA1 is involved in mtDNA stability67. At onset OPA1 mutations may manifest exclusively as optic atrophy but during the disease course most patients develop ADOAD68.

**Infantile-onset spinocerebellar ataxia (IOSCA)**

AR Infantile-onset spinocerebellar ataxia is clinically characterized by cerebellar ataxia, epilepsy, athetosis, hypotonia, hypoacusis, CPEO, hypogonadism, and sensorineural deafness (Table 3)70,71. Cerebral imaging may show progressive atrophy of the cerebellum, brainstem, or spinal cord71. Pathoanatomic studies confirm atrophy of the cerebellum, brainstem and, most severely, spinal cord59. IOSCA is caused by mutations in the C10or2/PEO1 gene leading to an amino acid exchange in the mitochondrial helicase twinkle72. The mutation secondarily results in depletion of mtDNA in the brain and liver, which is why IOSCA is regarded as a depletion syndrome72. Biochemically, there is deficiency of RC complex I and IV72. In children there may be mtDNA depletion without demonstration of any mutation73.

**Mitochondrial autosomal recessive ataxia syndrome (MIRAS)**

Mitochondrial autosomal recessive ataxia syndrome is a common cause of AR juvenile- or adult-onset ataxia74. MIRAS is caused by homozygous or compound heterozygous mutations in the POLG1 gene resulting in multiple mtDNA deletions and to a lesser degree than in IOSCA also to mtDNA depletion72. Multiple mtDNA deletions are particularly present in the brain of these patients72. Biochemically, there is reduced activity of RC complex I and IV. In a study on 27 MIRAS patients they presented with ataxia, peripheral neuropathy, dysarthria, mild cognitive impairment, involuntary movements, psychiatric symptoms, and epileptic seizures75. Because of the high carrier frequency in Finland, the high number of patients in Norway, and an ancient European founder chromosome, MIRAS should be considered as a first-line differential diagnosis of progressive ataxia syndromes in Europe75.

**Myoclonus epilepsy, mitochondrial myopathy, and sensory ataxia (MEMSA)**

Myoclonus epilepsy, mitochondrial myopathy, and sensory ataxia patients present clinically with myoclonus epilepsy, mitochondrial myopathy, and sensory ataxia8. Myoclonus epilepsy, mitochondrial myopathy, and sensory ataxia is due to mutations in the POLG1 gene. In addition to MEMSA, POLG1 mutations cause myo-cerebro-hepato spectrum (MCHS) disorders (SANDO, AHS), ataxia neuropathy spectrum (ANS) disorders (SCAE, MIRAS), AR-CPEO, and AD-CPEO9.

**Leucencephalopathy with brainstem and spinal cord involvement, and lactacidosis (LBSL)**

AR leucencephalopathy with brainstem and spinal cord involvement, and lactacidosis syndrome, a newly described entity, is clinically characterized by slowly progressive cerebellar ataxia, spasticity and dorsal column dysfunction96. Sometimes mild cognitive impairment may additionally develop. There is a highly characteristic constellation of abnormalities on cMRI96. The disorder is caused by mutations in the DARS2 gene, which encodes for the mitochondrial aspartyl-tRNA synthetase96. Though activity of this mitochondrial protein is reduced in affected patients, function of the RC is intact96.

**Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (DIDMOAD)**

Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness or Wolfram syndrome (WFS) is a rare AR neurodegenerative disorder with juvenile onset77. The phenotype is characterized by diabetes and optic atrophy. Other less frequent features comprise psychiatric abnormalities, ataxia, urinary tract atony, limited joint contractures, cardiovascular and gastrointestinal autonomic neuropathy, hyper-gonadotropic hypogonadism, cardiac malformations, or pituitary dysfunction77,78. Wolfram syndrome is due to mutations in the WFS1 gene on chromosome 4p16 or mutations in the WFS2 gene on chromosome 4q22-2479,80. WSF1 and WSF2 mutations secondarily result in single or multiple mtDNA deletions81.

**Coenzyme-Q (CoQ)-deficiency**

Coenzyme-Q (CoQ)-deficiency is a genetically heterogenous disorder, presenting with four distinct phenotypes: a pure myopathic form, a severe infantile neurologic syndrome with nephritis, LS, or an ataxic variant82. Patients with the ataxic form present with epilepsy, weakness, cerebellar ataxia, cerebellar atrophy, migraine, myoglobinuria, or developmental delay83. The ataxic variant is the most common form characterized by cerebellar atrophy and cerebellar ataxia. Biochemically, there is deficiency of CoQ in muscle or fibroblasts. CoQ-deficiency responds well to CoQ-substitution82.

**Pyruvate-dehydrogenase complex (PDC)-deficiency**

The PDC converts pyruvate into acetyl-CoA within the mitochondrion. Mutations in the PDHA1 gene may cause recurrent episodes of isolated ataxia in infancy84. Though patients gain full recovery between the episodes, they later develop severe encephalopathy and die in their twenties84. Ataxia in patients with PDC-deficiency due to mutations in the E1beta subunit (PDHB) is usually less pronounced than in patients carrying PDHA1 mutations85.

**Dilated cardiomyopathy with ataxia (DCMA)**

Dilated cardiomyopathy with ataxia was first described in a family from the Canadian Dariusleut Hutterite population86. Patients presented with early onset dilated cardiomyopathy with
conduction defects, non-progressive cerebellar ataxia, testicular dysgenesis, growth failure, and 3-methylglutaconic aciduria. The causative mutation was the point mutation T1212C in the DNAJC19 gene, encoding a DNAJ domain containing protein. The DNAJC19 protein is located inside mitochondria of cardiomyocytes, and shares sequence and organisational similarity with proteins from several species including the two yeast mitochondrial inner membrane proteins, Mdj2p and Tim14, suggesting that the phenotype of DCMA is the result of defective mitochondrial protein import.

Friedreich ataxia (FA)

AR Friedreich ataxia is clinically characterized by cerebellar ataxia, spasticity, pyramidal signs, hypertrophic cardiomyopathy, and Friedreich’s foot deformity (pes cavus). Additional features may include headache, dysarthria, dysphagia, vertigo, weakness, chorea, or anemia. Scoliosis is found in two thirds of the cases and diabetes mellitus in one third. Friedreich ataxia is the most common of the inherited ataxias. Friedreich ataxia is caused by a homozygous expansion of a GAA triplet repeat (96% of the cases) or point mutations, located within intron 1 of the frataxin gene on chromosome 9q13. Four percent of the patients are compound heterozygous, carrying a GAA expansion on one allele and a point mutation on the other. Frataxin is a widely expressed mitochondrial protein, involved in RNA processing and intra-mitochondrial iron handling and directly involved in mitochondrial iron-binding and detoxification. Frataxin mutations cause frataxin deficiency, which leads to iron accumulation and overload, increased sensitivity to oxidative stress, and deficient RC activity. Frataxin deficiency impairs mitochondrial functions either by a defect of iron/sulphur cluster construction or by the generation of free radicals.

Non-syndromic MID

Non-syndromic MIDs due to mtDNA mutations are the most prevalent group of MIDs and genetically heterogeneous. They comprise all those MIDs, which do not fit into the phenotype of any of the mitochondrial syndromes. As with syndromic MIDs the CNS is frequently involved and ataxia may be a dominant feature.

Among three patients carrying a mutation in the MPV17 gene, resulting in hepato cerebro mitochondrial mtDNA depletion, two had severe, progressive liver disease, and the third patient a milder form but developed progressive ataxia. In a patient simultaneously carrying a POLG1 and ANTI mutation resulting in multiple mtDNA deletions, the phenotype included CPEO, sensory and cerebellar ataxia, neuropathy, parkinsonism and depression. A POLG1 mutation also caused a phenotype with sensory ataxia, myoclonus, epilepsy, cognitive decline, nystagmus, dysarthria, and thalamic and cerebellar white matter lesions on MRI. Another POLG1 mutation caused CPEO, polynuropathy, ataxia, sensorineural hearing loss, and affective disorder. In single cases the common ATP6 mutation R993T>C may not only cause NARP or LS but may also manifest as adult onset ataxia and polyneuropathy. Ataxia was also a phenotypic feature in a patient carrying a rRNA Glu mutation. He additionally presented with exercise intolerance, weakness, and lactide acidosis. Cerebellar ataxia was also a phenotypic feature in a 7-year-old male with CPEO, spasticity, and dystonia attributed to RC complex I deficiency due to a NDUFV1 mutation. This mutation may be also associated with maternally inherited episodic ataxia. In a study on five European MID families ataxia occurred in combination with various other CNS abnormalities. Cerebral MRI showed thalamic and cerebellar white matter lesions and autopsy neuronal loss in gray nuclei. In eight patients the abnormalities could be attributed to AR POLG1 mutations.

DISCUSSION

This review supports the notion that ataxia may be a more or less prominent feature of syndromic or non-syndromic MIDs either due to mutations in mtDNA or nDNA located genes. Mitochondrial disorders are associated with cerebellar ataxia as well as sensory ataxia and both may be present within the same patient or family. Mitochondrial disorders with ataxia are increasingly recognized and should be included in the differential diagnoses or classification of classical heredoataxias. This study also confirms that most MIDs do not nicely fit into one of the original acronyms but rather represent individual phenotypes, which more or less overlap with classical mitochondrial syndromes. Despite limited therapeutic options, neurologists should be aware of ataxia as a feature of MIDs, since it may guide them to the correct diagnosis, particularly if other neurological or non-neurological manifestations of a MID are present. Limitations of this study were that not all papers were accessible, that most studies did not clearly differentiate between cerebellar and sensory ataxia, and that most studies neither quantified the degree of ataxia nor described the course or outcome of the individual phenotypes.

CONCLUSION

This mini review shows that ataxia is a dominant feature of some MIDs with cerebral involvement. Cerebellar ataxia may occur in MID patients and may contribute to the disability in some of these patients. Ataxia is much more frequent in non-syndromic as compared to syndromic MIDs. As soon as ataxia is detected in patients with a phenotype suggesting a MID, they should undergo a comprehensive neurological investigation, including cerebral imaging studies.

LIST OF ABBREVIATIONS

AD Autosomal dominant
ADOAD Autosomal dominant optic atrophy and deafness syndrome
AHS Alpers Huttensolcher syndrome
ANS Ataxia neuropathy spectrum disorders
AR Autosomal recessive
ATP Adenosine-tri-phosphate
ATP6 Subunit of complex V of the RC
CNS Central nervous system
CoQ Coenzyme Q
COX Cytochrome-c-oxidase
CPEO Chronic external ophthalmoplegia
CSF Cerebrospinal fluid
DARS2 Gene, which encodes mitochondrial aspartyl-tRNA synthetase
DIMOAD (WFS) Diabetes insipidus, diabetes mellitus, optic atrophy, deafness syndrome (Wolfram syndrome)
IOSCA Infantile-onset spinocerebellar atrophy
KSS Keans Sayre syndrome
LBSL Leuencephalopathy with brainstem and spinal cord involvement, and lactate elevation
LHON Leber’s hereditary optic neuropathy
LS Leigh syndrome
MCHS Myo-cerebro-hepatop spectrum disorders
MDS Mitochondrial depletion syndrome
MELAS Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes
MEMSA Myoclonus epilepsy, myopathy and sensory ataxia syndrome
MERRF Myoclonic epilepsy and ragged red fibers
MID Mitochondrial disorder
MIDs Mitochondrial disorders
MIDD Mitochondrial diabetes and deafness syndrome
MILS Maternally inherited Leigh syndrome
MIRAS Mitochondrial recessive ataxia syndrome
MNGIE Mitochondrial neuro-gastro-intestinal encephalomyopathy
MPV17 Mitochondrial inner membrane protein
cMRI Cerebral magnetic resonance imaging
mtDNA Mitochondrial DNA
MITS (DDS) Mohr Tranebyjaerg syndrome (deafness dystonia syndrome)
NARP Neurogenic muscle weakness, ataxia, and retinitis pigmentosa
ND1 Subunit of complex I of the RC
nDNA Nuclear DNA
OPA1 Optic atrophy 1 gene
OXPHOS Oxidative phosphorylation
PDC Pyruvate dehydrogenase complex
PDHA1 A1 subunit of the pyruvate dehydrogenase complex
PEO1 Progressive external ophthalmoplegia gene 1
PNS Peripheral nervous system
POLG Polymerase gamma
PS Pearson syndrome
PUS1 Pseudouridine synthase 1
RC Respiratory chain
rRNA Ribosomal ribonucleic acid
SANDO Sensory ataxic neuropathy, dysarthria, ophthalmoplegia syndrome
SCA Spino-cerebellar ataxia and epilepsy
SCAE Juvenile-onset spino-cerebellar ataxia and epilepsy
tRNA Transfer ribonucleic acid
XL X-linked
XLSA/A X-linked sideroblastic anemia with ataxia

REFERENCES


