

Autosomal recessive cerebellar ataxias

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Abstract

Autosomal recessive cerebellar ataxias (ARCA) are a heterogeneous group of rare neurological disorders involving both central and peripheral nervous system, and in some cases other systems and organs. The onset is usually early, occurring before the age of 20 years. On the basis of the underlying pathological mechanisms, five main types can be distinguished: congenital ataxias (developmental disorder), degenerative and progressive ataxias, ataxias associated with metabolic disorders, DNA repair defects or other features. The most frequent ARCA in Caucasian population are Friedreich ataxia and Ataxia telangiectasia. Other forms are much less common and include abetalipoproteinemia, ataxia with vitamin E deficiency (AVED), ataxia with oculomotor apraxia (AOA1), cerebrotendinous xanthomatosis, early onset cerebellar ataxia with retained reflexes (EOCARR), Charlevoix-Saguenay spastic ataxia, non-Friedreich spinocerebellar ataxia type 1 (SCAR1), Joubert syndrome, Cockayne syndrome type I (CKN1), Xeroderma pigmentosum (XP). The prevalence of ARCA has been estimated to 7 in 100,000 inhabitants. These diseases are due to mutations in specific genes, some of which have been identified, such as aprataxin in AOA1, frataxin in Friedreich ataxia, Tocopherol alpha transfer protein in AVED. Due to autosomal recessive inheritance, previous familial history of affected individuals is unlikely. ces, pharmacological treatment. Clinical diagnosis must be confirmed by ancillary tests such as neuroimaging (MRI, scanning), eletrophysiological examination and mutation analysis when the causative gene has been identified. Correct clinical and genetic diagnosis is important for appropriate prognosis and genetic counselling and, in some instances, pharmacological treatment. Most of these cerebellar ataxias have no specific treatment with the exception of coenzyme Q₁₀ deficiency and abetalipoproteinemia.

Key-words

Autosomal recessive cerebellar ataxias, early onset cerebellar ataxias, cerebellar ataxias, congenital ataxias, degenerative ataxias, metabolic ataxias, DNA repair ataxias, ataxia genes, genetic counselling

Disease name and synonyms

-Autosomal recessive cerebellar ataxias (ARCA)
 -Early onset cerebellar ataxias (EOCA)

-Autosomal dominant episodic ataxias
 -X-linked recessive ataxias
 -Mitochondrial encephalomyopathies

Definition/Classification

Autosomal recessive cerebellar ataxias (ARCA) are neurological disorders characterized by degeneration or abnormal development of cerebellum and spinal cord, autosomal recessive inheritance and, in most cases, early onset occurring before the age of 20. This group encompasses a large number of rare diseases, the most frequent being Friedreich ataxia. On the basis of the underlying pathological mechanisms, ARCA can be classified into five main groups: 1) congenital; 2) metabolic; 3) DNA repair defects; 4) degenerative; 5) with other features.

Differential diagnosis

A global differential diagnosis for every ARCA will not be reported in this review. However, it is important to establish whether ataxic syndrome belongs to one of the five above-mentioned groups. In addition, Friedreich ataxia, the most prevalent inherited ataxia, especially among early onset cerebellar ataxias, can be excluded in a number of cases since a straight-forward molecular test is available.

Etiology

Autosomal recessive cerebellar ataxias are Mendelian inherited disorders. Every disease belonging to this group is caused by mutations in a specific gene (Table 1).

Excluded diseases

-[Autosomal dominant spinocerebellar ataxias](#)

Table 1: Genetic data on ARCA

Disorder	gene	location	MIM
Friedreich ataxia	Frataxin (FRDA)	9q13	229300
Ataxia telangiectasia	ATM	11q22.3	208900
Ataxia with isolated vitamin E deficiency (AVED)	Alpha-tocopherol transfer protein (α -TTP)	8q13	277460
Abetalipoproteinemia	microsomal trygliceride transfer protein (MTP)	4q22-q24	200100
Cerebrotendinous xanthomatosis	sterol 27-hydroxylase (CYP27)	2q33-qter	213700
Ataxia with oculomotor apraxia 1 (AOA1)	Aprataxin (APTX)	9p13	208920
Oculomotor apraxia – ataxia telangiectasia-like (AOA-ATL/AOA2; SCAR1)		9q34	606002
Charlevoix-Saguenay spastic ataxia	Sacsin (SACS)	13q12	270550
Early onset cerebellar ataxia with retained tendon reflexes (EOCARR)		13q11-12	212895
Infantile onset spinocerebellar ataxia (IOSCA)		10q22.3-q24.1	271245
Marinesco-Sjögren syndrome			248800
Classical MSS		5q32	
MSS with myoglobinuria		18qter	
Spinocerebellar ataxia with axonal neuropathy (SCAN1)	Tyrosyl-DNA phosphodiesterase 1 (TDP1)	14q31	607250
Coenzyme Q ₁₀ deficiency with cerebellar ataxia			607426
Posterior column ataxia and retinitis pigmentosa (PCARP)		1q31	176250
Joubert syndrome		9q34	213300
Cockayne syndrome type I	CKN1	5	216400

Clinical description

For ARCA, which are not described in this review, further information can be obtained from the Orphanet database by clicking on the disease name

Congenital ataxias

Some rare developmental anomalies, such as dysgenesis or agenesis of the vermis, cerebellar hemispheres, or parts of the brainstem, may give rise to congenital ataxias, and most of them are associated with an autosomal recessive inheritance. In the last

years, some congenital ataxia, such as [Joubert syndrome](#), have also been associated with specific chromosomal loci.

Metabolic ataxias

[Abetalipoproteinemia](#)

[Cerebrotendinous xanthomatosis](#)

DNA repair defects

[Ataxia telangiectasia](#)

Cockayne syndrome type I (CKN1)

This disorder is also recognized as Cockayne syndrome type A (CSA). The causative gene *CKN1* has been mapped to chromosome 5. It is characterized by progressive mental retardation, gait imbalance, hydrocephalus, optic atrophy, dwarfism, precocious senility, photosensitivity, hypertension, retinal degeneration and hearing loss. The syndrome may occur in association with features of xeroderma pigmentosum with three different complementation groups: group B (mutations in *ERCC6* or *XPB*; chromosome 10), group D (mutations in *ERCC2* or *XPD*; chromosome 19), and group G (mutations in *ERCC5* or *XPB*; chromosome 13).

Xeroderma pigmentosum (XP)

This is a clinical syndrome with multiple complementation groups and genotypes. Inheritance is autosomal recessive. Six complementation loci, A to G, have been reported and three of them are associated with a Cockayne syndrome (see above). XP is characterized by a variable neurological syndrome (ataxia, choreoathetosis, spasticity, deafness, and progressive mental retardation), skin photosensitivity, early-onset skin cancers, telangiectasia, photophobia, conjunctivitis, keratitis, ectropion and entropion. Defective DNA repair after ultraviolet damage of culture cells is characteristically observed. Genes have been identified for most complementation groups. They correspond to the *excision-repair cross-complementation (ERCC)* genes.

Degenerative and progressive ARCA

[Friedreich ataxia](#)

[Ataxia with isolated vitamin E deficiency](#)

[Charlevoix-Saguenay spastic ataxia](#)

[Ataxia with oculomotor apraxia 1 \(AOA1\)](#)

Oculomotor apraxia – ataxia telangiectasia-like (AOA-ATL/AOA2)

This is a disorder also referred to as non-Friedreich spinocerebellar ataxia type 1 (SCAR1) (MIM 606002) or ataxia-

telangiectasia-like syndrome (MIM 604391). It is characterized by spinocerebellar ataxia with onset between 11 and 22 years, choreoathetosis, dystonic posturing with walking and is occasionally associated with oculomotor apraxia or elevated gamma-globulin, alpha-protein, and creatin kinase (CK). Cerebellar atrophy is observed in some patients. Electrophysiology studies show absence of sensory potentials. The causative gene has been mapped to chromosome 9q34. No evidence of chromosome instability or sensitivity to ionizing radiation has been observed in cells from affected individuals.

[Infantile onset spinocerebellar ataxia \(IOSCA\)](#)

[Marinesco-Sjögren syndrome \(MSS\)](#)

[Early onset cerebellar ataxia with retained tendon reflexes \(EOCARR\)](#)

Spinocerebellar ataxia with axonal neuropathy (SCAN1)

This a disorder characterized by recessive ataxia with peripheral axonal motor and sensory neuropathy, distal muscular atrophy, and pes cavus and stepagge gait as described in Charcot-Marie-Tooth disease. Genetic studies in a large Saudi Arabian family mapped the disease to chromosome 14q31 and identified a homozygous mutation in the gene encoding topoisomerase I-dependent DNA damage repair enzyme (TDP1). Patients had history of seizures, mild brain atrophy, mild hypercholesterolemia and borderline hypoalbuminemia.

Coenzyme Q10 deficiency with CA

This is a syndrome characterized by childhood-onset ataxia and cerebellar atrophy and markedly reduced levels of coenzyme Q₁₀ in muscle biopsies. Patients associate seizures, developmental delay, mental retardation and pyramidal signs. The pattern of inheritance is thought to be autosomal recessive.

Posterior column ataxia and retinitis pigmentosa (PCARP)

It is characterized by early onset in childhood, sensory ataxia with preservation of pain and temperature, absent reflexes, ring scotoma and progressive loss to blindness. The locus *AXPC1* has been mapped to chromosome 1q31.

Diagnostic methods

Natural history and both neurological and systemic examinations help to orientate the diagnosis, which is further confirmed by ancillary tests, such as neuroimaging (MRI, scanning) and electrophysiological examination. Neural imaging is very important to distinguish among developmental disorders and degenerative diseases, and to define neurological structures involved in the pathological process. For metabolic disorders associated with ataxia, specific biochemical tests or measure of enzymatic activities are required. In the last years, isolation of the responsible genes for some ARCA has enabled confirmation of clinical diagnosis by mutation analysis. This approach is not only useful for clinical diagnosis but also for genetic counselling.

Frequency

The prevalence of early onset cerebellar ataxias (Friedreich ataxia and other EOCAs) and congenital ataxias was estimated to 7.2 per 100,000 inhabitants in Cantabria, Spain.

Genetic counselling

Due to the pattern of autosomal recessive inheritance in ARCA, previous familial history is usually not reported. The only exception is when parents are consanguineous or come from a small town or region. As these disorders usually have an early onset, genetic counselling is an important clinical tool for preventing new cases, especially in young couples with a first child affected. Their risk of having an affected child in further pregnancies is 25%. Prenatal diagnosis can be proposed when the disease is well diagnosed and the causative mutation identified. Preimplantation diagnosis is also a new tool but is only available in a few hospital or services in Europe.

Genetic counselling is only relevant in a healthy carrier (*i.e.* patient's sibling) when his or her partner is consanguineous.

Management including treatments

Although most of these cerebellar ataxias have no specific treatment, some may be treated. Coenzyme Q₁₀ deficiency associated with ataxia may be responsive to CoQ₁₀ supplementation (300 to 600 mg/day). Ubidecarenone (CoQ₁₀) has been used in some patients with good clinical and pathological response.

Abetalipoproteinemia, which is associated with severe neurodegenerative complications, belongs to the potentially treatable or preventable conditions associated with vitamin E deficiency, such as ataxia with vitamin deficiency (AVED) caused by mutations in the α -TTP gene. Abetalipoproteinemia treatment is based on a diet with reduced intake of fat and a supplement of oral vitamin E at massive dosage (1,000 mg/day for infants to over 5,000 mg/day for adults) compared with normal requirements. It seems reasonable to start treatment with vitamin E given as an α -tocopherol acetate preparation with a dose of 50 mg/kg/day in three divided doses.

Cerebrotendinous xanthomatosis is currently treated with chenodeoxycholic acid (CDCA) but others inhibitors of the 3-hydroxy-3-methylglutaryl (HMG) CoA reductase also reduce plasma cholestanol levels. CDCA should be administrated at a dosage of 750 mg/day (15 mg/kg/day) in three divided doses.

Unresolved questions

The etiology or the causative gene of many ataxic syndromes remains unknown. Moreover, only few disorders, as indicated in the above paragraph, have palliative treatment. Generation of new drugs or gene and cell therapy approaches require a better understanding of the molecular and pathophysiological mechanisms underlying each disease.

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