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Review

Main inherited neurodegenerative cerebellar ataxias, how to recognize them using magnetic resonance imaging?

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ABSTRACT

Ataxia is a neurodegenerative disease resulting from brainstem, cerebellar, and/or spinocerebellar tracts impairments. Symptoms onset could vary widely from childhood to late-adulthood. Autosomal cerebellar ataxias are considered as one of the most complex group in neurogenetics. In addition to their genetic heterogeneity, there is an important phenotypic variability in the expression of cerebellar impairment, complicating the genetic mutation research. A pattern recognition approach using brain MRI measures of atrophy, hyperintensities and iron-induced hypointensity of the dentate nuclei, could be therefore helpful in guiding genetic research. This review will discuss a pattern recognition approach that, associated with the age at disease onset, and clinical manifestations, may help neuroradiologists differentiate the most frequent profiles of ataxia.

Introduction

Ataxia can be a neurodegenerative disease resulting from brainstem, cerebellar, and/or spinocerebellar tracts impairments. It is characterized by the inability of the patient to coordinate voluntary muscle movements leading to gait-limb ataxia, frequent falls, dysarthria and oculomotor abnormalities such as nystagmus or saccadic dysmetria. Symptoms onset could vary widely from childhood to late-adulthood. Patterns of inheritance have been previously described in hereditary cerebellar ataxia [1–4]. A specific diagnosis is important for accurate genetic counseling. Indeed, many of the disorders are inherited as autosomic recessive traits [5]. Autosomal cerebellar ataxias are considered as one of the most complex group in neurogenetics with more than 20 different clinical entities and at least 30 associated genes/loci [6]. In addition to the genetic heterogeneity of this group, there is an important phenotypic variability in the expression of cerebellar impairment, complicating the genetic mutation research. A pattern recognition approach using brain magnetic resonance imaging (MRI) could be therefore helpful in guiding genetic research.

In this following review, we describe the most typical autosomal recessive cerebellar ataxias namely, Friedreich ataxia (FRDA), ataxia-telangiectasia (AT), spastic ataxia of Charlevoix-Saguenay (ARSACS), ataxia with oculomotor apraxia type 1 (AOA1) and type 2 (AOA2), ataxia with isolated vitamin E deficiency (AVED), two of the most frequent autosomal dominant cerebellar ataxias, the Spinocerebellar ataxia type 3 (SCA3) and type 6 (SCA6), which together account for almost half of the SCAs, and the Fragile X-associated tremor/ataxia syndrome (FXTAS) (Table 1). We start our review by a brief cerebellar anatomy overview.

Cerebellar involvement in inherited neurodegenerative cerebellar ataxias

To determine which part of the cerebellum is most affected in inherited neurodegenerative cerebellar ataxias, we reviewed the

Abbreviations: AOA1, Ataxia with Oculomotor Apraxia Type 1; AOA2, Ataxia with Oculomotor Apraxia Type 2; AT, Ataxia-Telangiectasia; ARSACS, Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; AVED, Ataxia with Vitamin E Deficiency; FLAIR, Fluid Attenuated Inversion Recovery; FRDA, Freidreich ataxia; FXTAS, Fragile X-associated Tremor/Ataxia Syndrome; MRI, Magnetic Resonance Imaging; SCA3, SpinoCerebellar Ataxia Type 3; SCA6, SpinoCerebellar Ataxia Type 6; SWI, Susceptibility Weighted Imaging.

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Table 1
Characteristics of the different types of ataxias.

	Transmission type	Gene	Age at onset
FRDA	AR	*FXN*	2nd decade
AT	AR	*ATM*	2nd year of life
ARSACS	AR	*SACS*	First 2 decades
AVED	AR	*TTPA*	From 4 to 17
AOA1	AR	*APTX*	Around 4 years old
AOA2	AR	*SETX*	Mean age: twenty
SCA3	AD	*ATXN3*	Mean age: forty
SCA6	AD	*CACNA1A*	Mean age: sixty
FXTAS	X-associated	*FMR1*	Mean age: sixty

AOA1: Ataxia with Oculomotor Apraxia Type 1; AOA2: Ataxia with Oculomotor Apraxia Type 2; AT: Ataxia-Telangiectasia; ARSACS: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; AVED: Ataxia with Vitamin E Deficiency; FRDA: Freidreich ataxia; FXTAS: Fragile X-associated Tremor/Ataxia Syndrome; SCA3: SpinoCerebellar Ataxia Type 3; SCA6: SpinoCerebellar Ataxia Type 6.

literature of every pathology and its MRIs and showed the following: In FRDA, we noticed a preservation of the cerebellum volume or mild upper vermis atrophy associated with smaller dentate nuclei as well as increased iron accumulation. In AT, there is a predominant vermian atrophy, oftenly isolated in young children, and for some patients, an involvement of the lateral hemispheres. In ARSACS, we observed cerebellar atrophy with a predominance in the superior vermis (not always observed) and thickening of the middle cerebellar peduncle. In AOA1 and AOA2, the iron-induced signal normally observed in dentate nuclei disappears, and diffuse cerebellar atrophy that predominates the anterior vermis is observed. In AVED, cerebellar atrophy or MRI anomalies are absent. In SCA3, we noted a mild atrophy of the vermis and the cerebellum, a volume reduction of the dentate nuclei and an atrophy of the middle cerebellar peduncle. In SCA6, a marked atrophy of the vermis and cerebellar hemispheres was observed but no atrophy of middle cerebellar peduncle was reported. In FXTAS, we observed moderate to severe generalized atrophy and bilateral T2/FLAIR hyperintensities of middle cerebellar peduncles (Table 2). Thus, it appears that the region most affected by inherited neurodegenerative cerebellar ataxia is the vermis and more particularly the upper vermis.

Table 2
Cerebellar regions most affected by each inherited neurodegenerative cerebellar ataxia discussed in this review.

Inherited cerebellar ataxia	Cerebellar region most affected
FRDA	± Upper vermis
AT	Vermis atrophy ± cerebellar hemispheres
ARSACS	Atrophy with predominance in upper vermis, thickening ± hypersignal of middle cerebellar peduncles
AVED	None
AOA1	Atrophy that predominates on the anterior vermis, disappearance of SWI hyposignal of dentate nuclei
AOA2	Atrophy that predominates on the anterior vermis, disappearance of SWI hyposignal of dentate nuclei
SCA3	Atrophy of middle cerebellar peduncles, mild upper vermis and hemispheres atrophy, atrophy of middle cerebellar peduncles
SCA6	Marked atrophy of the vermis and the cerebellum,
FXTAS	T2/FLAIR hyperintensities of middle cerebellar peduncles and generalized atrophy

AOA1: Ataxia with Oculomotor Apraxia Type 1; AOA2: Ataxia with Oculomotor Apraxia Type 2; AT: Ataxia-Telangiectasia; ARSACS: Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; AVED: Ataxia with Vitamin E Deficiency; FRDA: Freidreich ataxia; FXTAS: Fragile X-associated Tremor/Ataxia Syndrome; SCA3: SpinoCerebellar Ataxia Type 3; SCA6: SpinoCerebellar Ataxia Type 6.

Friedreich ataxia (FRDA)

FRDA is the most known genetic cerebellar ataxia. It is a rare autosomal recessive hereditary disorder that affects approximately 1 in 50,000 Caucasians. It is caused by insufficient levels of Frataxin (FXN) gene expression, induced by a hyperexpanded tract of repeated GAA (Glucosidase Alpha, Acid) triplets in the first intron of the *FXN* gene [7]. Initial symptoms of the disease usually appear around the beginning of the second decade of the patient's life. In addition to neuropathological disabilities such as ataxia, sensory loss, and muscle weakness, common signs are scoliosis, foot deformity, and hypertrophic cardiomyopathy [8].

Typical MRI pattern of FRDA includes (Fig. 1):

- preservation of the cerebellum volume [9] or mild upper vermis atrophy [10];
- smaller dentate nuclei [9] with increased iron accumulation [11] than in general population, well detected with susceptibility weighted imaging (SWI);
- decrease of the anteroposterior diameter of the spinal cord and the medulla oblongata [9,12,13];
- abnormal signal in the posterior or lateral columns of the spinal cord [12,14].

The involvement of the spinal cord and the medulla oblongata, associated with preservation of the cerebellum volume makes FRDA one of the easiest hereditary ataxia to diagnose.

Ataxia-telangiectasia (AT)

AT is the most common form of infantile onset cerebellar ataxia, with symptoms of gait instability beginning typically in the second year of life, followed shortly by other cerebellar abnormalities including cerebellar degeneration. This pathology should not to be confused with hereditary hemorrhagic telangiectasia [15]. AT prevalence is estimated at 1-2.5 per 100,000. AT is a systemic condition in which the underlying cellular abnormality is related to defective DNA repair, resulting in oculocutaneous telangiectasia, immunological incompetence, and increased risk of malignancy, typically lymphoreticular malignancy, germ cell tumours in childhood, and adenocarcinoma as adults. Recurrent sino-pulmonary and cutaneous infections, such as impetigo, are often antecedent to neurological abnormalities. The differential diagnosis includes other sporadic, recessively or dominantly inherited forms of progressive ataxia with onset in this age range. The gene responsible for AT encodes a protein, ATM (ataxia telangiectasia mutated), localized mainly in the nucleus. At least 70 different ATM gene mutations associated with loss of function have been found in patients with AT [16].

MRI pattern is not specific unless highlighting telangiectasia. It includes (Fig. 2):

- predominantly vermian atrophy, often isolated in young children [17–19], and involvement of the lateral hemispheres for some patients [20];
- possibly associated ischemic-hemorrhagic complications and white matter involvement in older children and adults [17,18];
- capillary telangiectasia observed in some but not all patients (small foci of hypointensity on SWI and T2*, suggesting hemosiderin deposits) [19].

The radio-clinical association of vermian atrophy and oculocutaneous telangiectasias is thereby highly suggestive of AT.

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