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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.

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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.

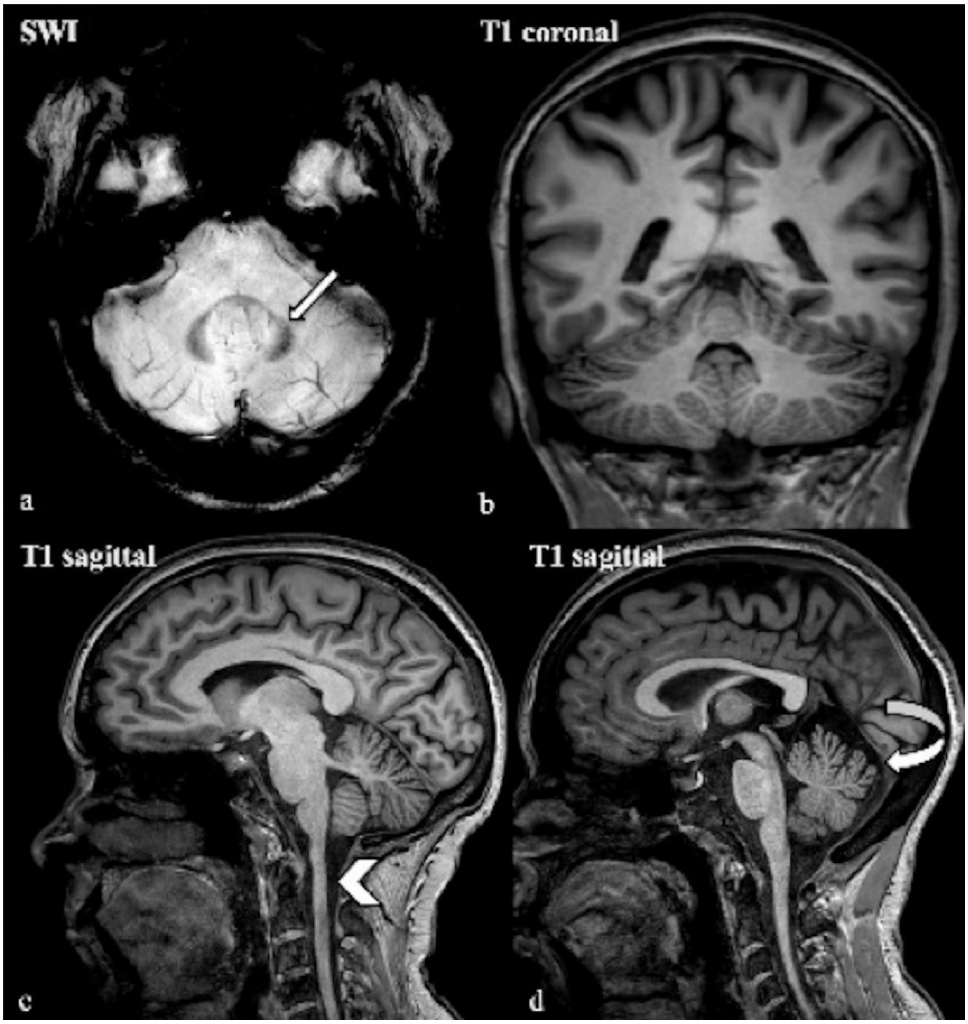

Fig. 1. Freidreich ataxia in a 55-year-old female: a) Small dentate nuclei with increased hyposignal (straight arrow); b) Preservation of the cerebellum hemispheres volume; c) Decrease of the anteroposterior diameter of the cervical spinal cord (chevron); d) Decrease of the anteroposterior diameter of the medulla oblongata. Mild upper vermis atrophy (curved arrow).

Autosomal recessive spastic ataxia of Charlevoix Saguenay (ARSACS)

ARSACS is a frequent cause of autosomal recessive early onset ataxia around the world. It was long regarded as a subtype of early onset ataxia restricted to the Quebec region. After cloning of the responsible gene, *SACS*, it became evident that ARSACS is not limited to Quebec. More than 100 different pathogenic mutations have so far been identified worldwide [21]. Most ARSACS patients show a typical triad of early-onset cerebellar ataxia, lower limb spasticity and peripheral neuropathy. However, the classical triad might not be exclusive to all patients. Indeed, some ARSACS might be underdiagnosed in patients with atypical phenotypes [22–24]. Additionally, urinary urge incontinence is also frequent [25].

Typical MRI pattern of ARSACS includes [25] (Fig. 3):

- cerebellar atrophy with predominance in the superior vermis (not always observed);
- linear pontine FLAIR and T2 hypointensities;
- bilateral FLAIR and T2 hyperintensities of the lateral pons when merging into the middle cerebellar peduncle;
- thickening of the middle cerebellar peduncle;
- arachnoidal cyst in the posterior fossa is a frequent association;
- arsacs patients may also present a bilateral parietal cerebral atrophy and a short-stretched thinning of the posterior mid-body of the corpus callosum.

Ataxia with oculomotor apraxia type 1 (AOA1)

AOA1 is an autosomal recessive cerebellar ataxia, caused by *APTX* gene mutations [3], associated with oculomotor apraxia, hypoalbuminaemia and hypercholesterolaemia [26]. It is characterized by a childhood onset of slowly progressive cerebellar ataxia, followed by an oculomotor apraxia and a severe primary motor peripheral axonal motor neuropathy. The first manifestation is progressive gait imbalance (mean age of onset: 4.3 years; range: 2–10 years), followed by dysarthria, and upper-limb dysmetria with mild intention tremor. Oculomotor apraxia, usually noticed a few years after the onset of ataxia, progresses to external ophthalmoplegia. All affected individuals have generalized areflexia followed by a peripheral neuropathy and quadriplegia with loss of ambulation about seven to ten years after onset [27].

Typical MRI pattern of AOA1 includes (Fig. 4):

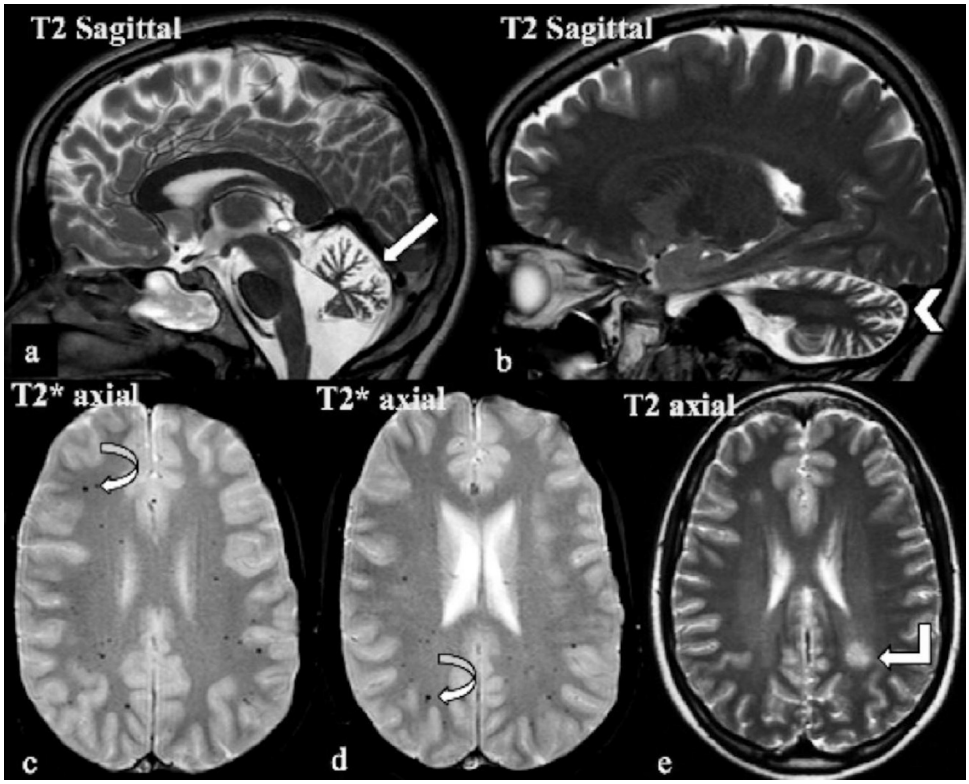

Fig. 2. Ataxia-Telangiectasia in a 19-year-old female: a) Diffuse vermian atrophy (straight arrow); b) Atrophy of cerebellar hemispheres on this particular patient (chevron); c) and d) Multiple capillary telangiectasias appearing as black dots on T2 gradient echo sequences (curved arrow); e) White matter involvement in an older patient (angled arrow). (*With courtesy and permission of Dr Griffiths, Sheffield University, England).*

- disappearance of the iron-induced signal normally observed in the dentate nucleus [28], only found in AOA1 and AOA2;
- diffuse cerebellar atrophy that predominates on the anterior vermis [28];
- an almost vertical tentorium cerebelli.

AOA1 is easily diagnosed when associating the loss of the dentate nuclei SWI hyposignal with a disease onset inferior to ten years.

Ataxia with oculomotor apraxia type 2 (AOA2)

AOA2 is an autosomic recessive disease caused by the mutation of the *SETX* gene. It is characterized by a wide range in age of onset, between ages of 3 and 30 (mean approximately 20 years), progressive gait and truncal ataxia, tremor, dysarthria, severe peripheral sensory and motor neuropathy manifesting as hypo- or areflexia, distal sensory loss, distal amyotrophy, and pes cavus deformity and scoliosis. Nystagmus and impaired visual pursuits are common, but only one-half or fewer of AOA2 patients have oculomotor apraxia. Some patients exhibit dystonic posturing of the hands, choreiform movements, and titubation or postural tremor. Mild mental decline in the fifties has been reported. AOA2 has a slow progression rate, however patients eventually become bound to a wheelchair. Most patients have elevated serum α-fetoprotein (AFP) levels, which should highlight the diagnosis [28–31].

Typical MRI pattern of AOA2 includes (Fig. 5):

- disappearance of the iron-induced signal normally observed in the dentate nucleus [28], only found in AOA1 and AOA2;
- diffuse cerebellar atrophy that predominates on the anterior vermis [28,32].

AOA2 is easily diagnosed when associating the loss of the dentate nuclei SWI hyposignal with a disease onset inferior to ten years and elevated AFP levels.

Ataxia with vitamin E deficiency (AVED)

AVED is an autosomic recessive disease caused by the mutation of the *TTPA* gene. Common characteristics of AVED include progressive ataxia, clumsiness of the hands, loss of proprioception (especially of vibration and joint position sense), and areflexia. Other oftenly observed features are dysdiadochokinesia, positive Romberg sign, head titubation, decreased visual acuity, and positive Babinski sign. Phenotype and disease severity vary widely among families with different mutations; age of onset and disease course are more uniform within a given family, but symptoms and disease severity can vary even among siblings [33].

MRI is typically normal in AVED or may show mild cerebellar and vermian atrophy [4] (Fig. 6).

Spinocerebellar ataxia type 3 (SCA3)

SCA3 is the most common SCA worldwide [34]. It is an autosomal dominant neurodegenerative disease caused by an expansion of a poly-CAG sequence in the *ATXN3* gene coding for the protein ataxin-3 [35,36]. SCA3 symptoms onset is commonly in the third to sixth decade of the patient's life. Most frequently, SCA3 is presented as "ataxia plus" syndrome. It often begins with ataxia accompanied by dysarthria, bulging eyes caused by lid retraction ("staring eyes"), oculomotor impairments, rigidity and dystonia. Small CAG-repeats are associated with late-onset ataxia combined with peripheral neuropathy, medium-sized expansions

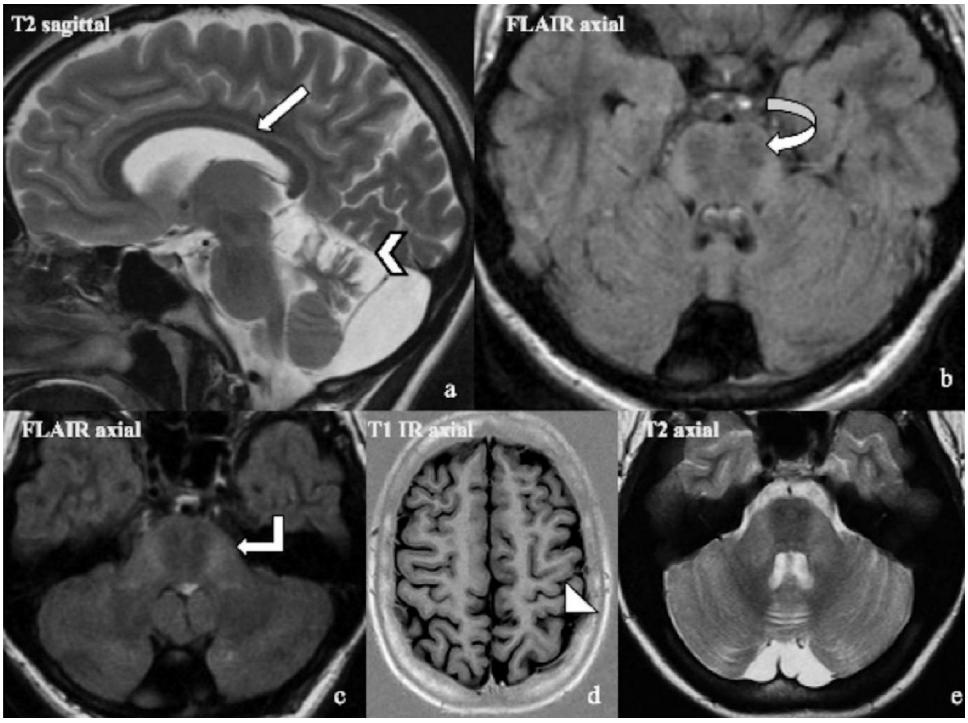

Fig. 3. Autosomic recessive spastic ataxia of Charlevoix-Saguenay: a) Thinning of the posterior mid-body of the corpus callosum (straight arrow), arachnoid cyst. Upper vermis atrophy (chevron); b) Linear pontine FLAIR hypointensity (curved arrow); c) Bilateral FLAIR hyperintensity of the lateral pons and thickening of the middle cerebellar peduncle (angled arrow); d) Bilateral parietal atrophy (arrow head); e) Linear pontine T2 hypointensity, bilateral T2 hyperintensity of the lateral pons and thickening of the middle cerebellar peduncles. (*With courtesy and permission of Dr Synofzik, Tübingen University, Germany*).

Fig. 4. Ataxia with oculomotor apraxia type 1 in a 42-year-old female: a) Iron-induced SWI loss of dentate nuclei hyposignal (straight arrow); b) Predominant atrophy in the anterior vermis and almost vertical tentorium cerebelli (chevron); c) Diffuse cerebellar atrophy (curved arrow).

Fig. 5. Ataxia with oculomotor apraxia type 2 in a 27-year-old female: a) Iron-induced SWI loss of dentate nuclei hyposignal (straight arrow); b) Predominant atrophy in the anterior vermis (chevron); c) Diffuse cerebellar atrophy (curved arrow).

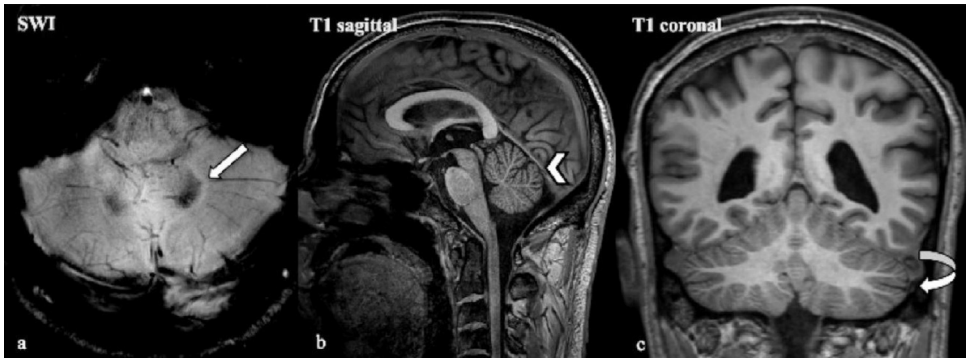

Fig. 6. Ataxia with vitamin E deficiency in a 50-year-old female: a) Normal iron-induced SWI hyposignal in the dentate nuclei (straight arrow); b) No significant vermian atrophy (chevron); c) No significant cerebellar atrophy (curved arrow).

with adult-onset ataxia, and large expansions with early-onset of rigidity and dystonia. SCA3 symptoms may also include: dysphagia, bradykinesia, intentional tremor, pyramidal signs, L-dopa responsive Parkinsonism, sensory deficits, amyotrophy, autonomic dysfunctions, sleep disturbances, depressive symptoms and neuropsychological abnormalities [37,38].

Typical MRI pattern of SCA3 includes [10,39,40] (Fig. 7):

- mild atrophy of the vermis and the cerebellum;
- atrophy of the brainstem, responsible of an enlargement of the fourth ventricle;
- volume reduction of dentate nuclei;

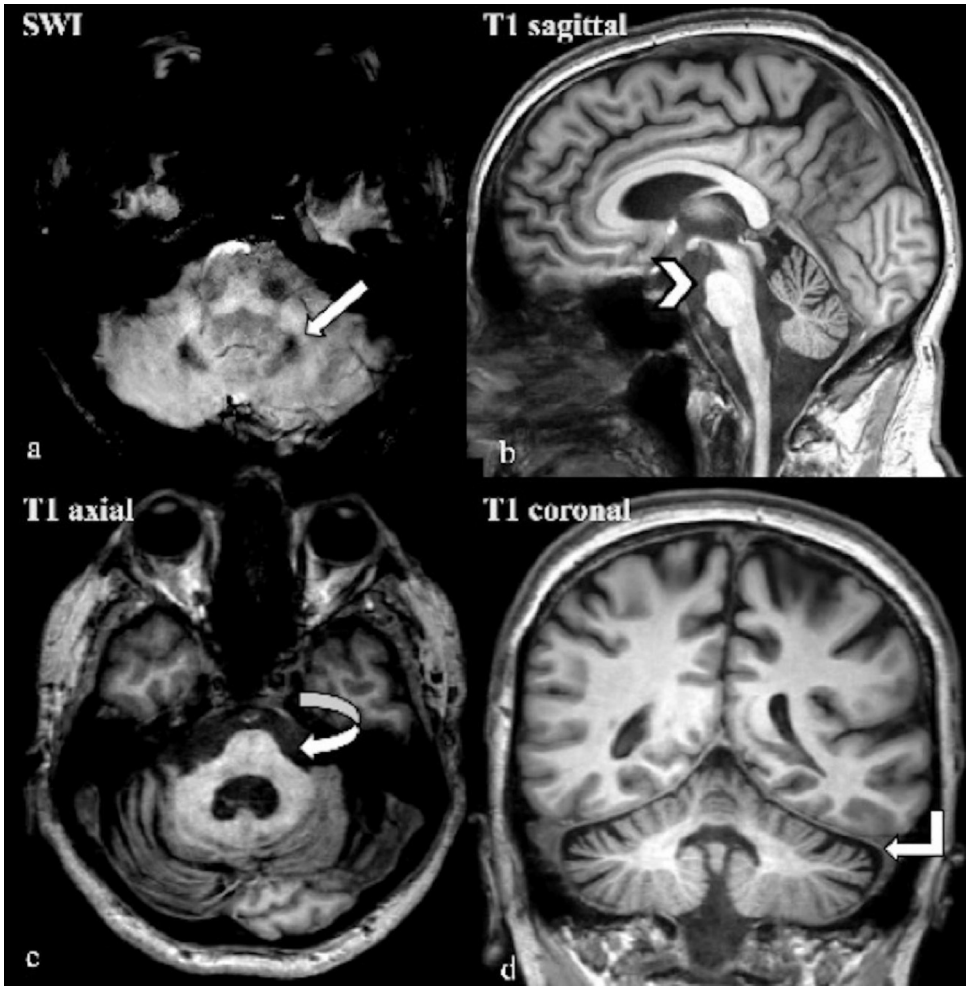

Figure 7. Spinocerebellar ataxia type 3 in an 83-year-old female: a) Normal iron-induced SWI hyposignal of dentate nuclei, accompanied by a volume reduction (straight arrow); b) Brainstem atrophy associated with mild anterior vermis atrophy (chevron); c) Middle cerebellar peduncles atrophy (curved arrow); d) Diffuse mild cerebellar atrophy (long evolution of the disease) (angled arrow).

- atrophy of the middle cerebellar peduncles;
- in later stages, linear hyperintense lesions in the midline of the pons coursing an anteroposterior direction can often be observed.

SCA3 is best diagnosed when associating a disease onset after 30 with brainstem atrophy and fourth ventricle enlargement.

Spinocerebellar ataxia type 6 (SCA6)

SCA6 is an autosomal dominant disease caused by mutation of the *CACNA1A* gene. Clinically, SCA6 has been regarded largely as a pure cerebellar syndrome with dysarthria, intention tremor, gaze-evoked as well as downbeat nystagmus. These signs of cerebellar origin are often accompanied by dysphagia, sensory, pyramidal and extrapyramidal motor deficits. SCA6 symptoms commonly begin at the sixth decade of the patient's life (almost always after fifty) [9,38–40].

Typical MRI pattern of SCA6 includes [9,39,40] (Fig. 8):

- marked atrophy of the vermis and the cerebellum;
- almost no atrophy of the brainstem and absence of enlargement of the fourth ventricle;
- discrete volume reduction of dentate nuclei;
- no atrophy of middle cerebellar peduncles.

SCA6 is best diagnosed when associating its late onset with marked cerebellar and vermis atrophy and no brainstem atrophy.

Fragile X-associated tremor/ataxia syndrome (FXTAS)

FXTAS is caused by a premutation CGG-repeat expansion in the 5'UTR of the fragile X mental retardation 1 (*FMR1*) gene. The classical clinical manifestations include tremor, cerebellar ataxia, cognitive decline and psychiatric disorders. Other less frequent features are peripheral neuropathy and autonomic dysfunction. Cognitive decline, a form of frontal subcortical dementia, memory loss and executive function deficits are also characteristics of this disorder. Clinical onset is typically around 60 [41–46].

Additionally, diffusion tensor imaging in patients with FXTAS showed significant fractional anisotropy reduction in multiple white matter tracts, including the middle cerebellar peduncle (MCP), the superior cerebellar peduncle, the cerebral peduncle, and the fornix and stria terminalis. Axial and radial diffusivities in the middle cerebellar peduncle and the cerebral peduncle have been shown to be increased in asymptomatic premutation carriers, without alteration in fractional anisotropy [47]. This could

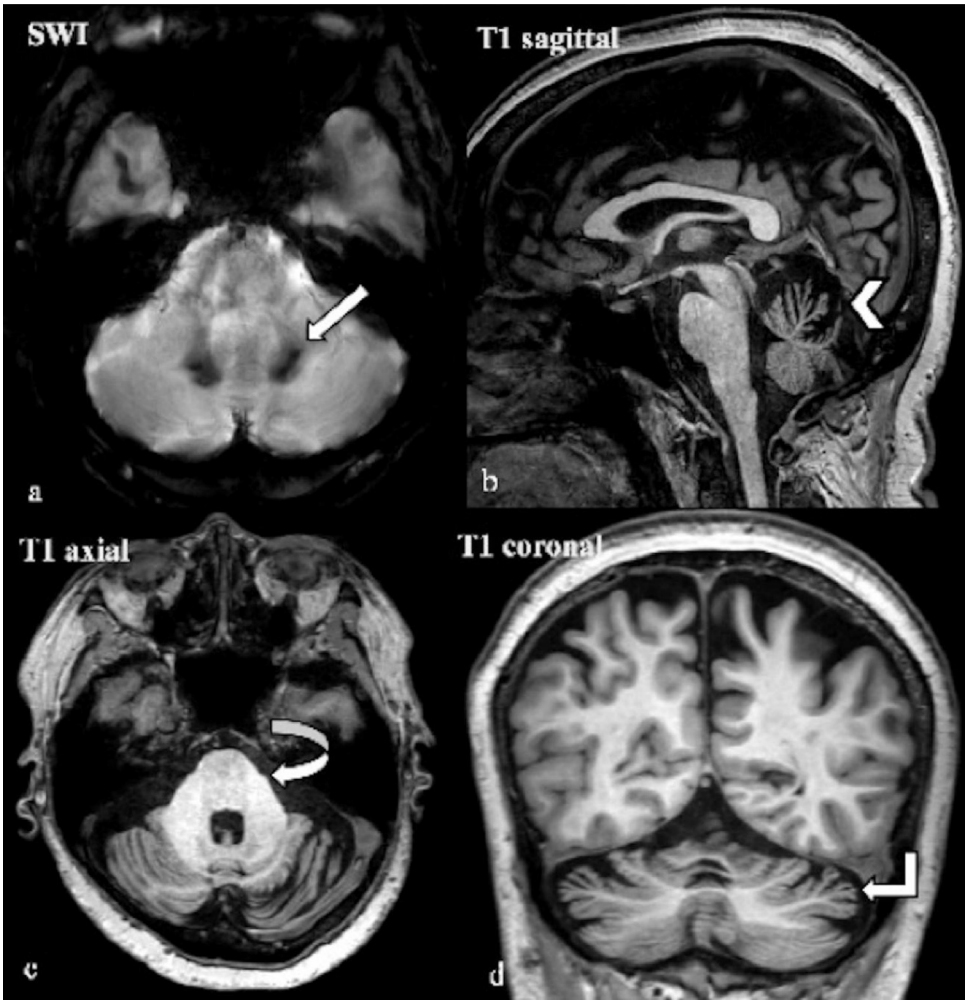

Fig. 8. Spinocerebellar ataxia type 6 in a 58-year-old female: a) Normal iron-induced SWI hyposignal of dentate nuclei, alongside a discrete volume reduction (straight arrow); b) Marked vermis atrophy with normal brainstem volume (chevron); c) No middle cerebellar peduncles atrophy (curved arrow); d) Diffuse cerebellar atrophy (angled arrow).

allow the identification of patients for early targeted treatments for FXTAS.

Typical MRI pattern of FXTAS includes [41–46] (Fig. 9):

- bilateral T2/FLAIR hyperintensities of middle cerebellar peduncles;
- white matter T2/FLAIR hyperintensities: white matter, splenium of the corpus callosum, pons, insula;
- moderate to severe generalized atrophy;
- atrophy of the cerebrum, cerebellar cortex, corpus callosum and pons.

Theses abnormalities are classically less severe in women. FXTAS is diagnosed based on a symmetric and bilateral hypersignal of the middle cerebellar peduncles with a cerebellar atrophy.

Discussion

Radiologists could be confronted to cerebellar diseases when exploring a neurological symptom: progressive ataxia or more frequently an unusual symptomatology, and/or fortuitously discovering a cerebellar atrophy. When facing a cerebellar atrophy, several diagnoses should be evoked: atrophy due to toxic consumptions (i.e. alcohol, . . .); autoimmune cerebellar encephalitis, either paraneoplastic or not (anti-Yo, Anti-Hu, anti-Tr, Anti-VGCC, anti-CV2, anti-Zic4, anti-Ma. . .), usually rare but underestimated; and genetic etiologies. In this review, we mainly focused on the genetic etiologies, more precisely on inherited neurodegenerative cerebellar ataxias.

Hereditary ataxias classification has represented a challenge for decades because of their wide and heterogeneous phenotypic presentations. In addition to the various clinical manifestations of cerebellar ataxias (sensitomotor involvement, cognitive impairment, epilepsy, spasticity, oculomotor apraxia, . . .) and the age at disease onset, MRI could potentially play a crucial role to depict and differentiate between the countless different types of ataxias. Indeed, by associating the patients' clinical assessment with atrophy measures in the cerebellum and the cerebellar peduncles, as well as signal alterations in the dentate nucleus evaluated on FLAIR and/or SWI sequences, a differential diagnosis could be achieved. For example, the absence of the dentate nuclei hyposignal on

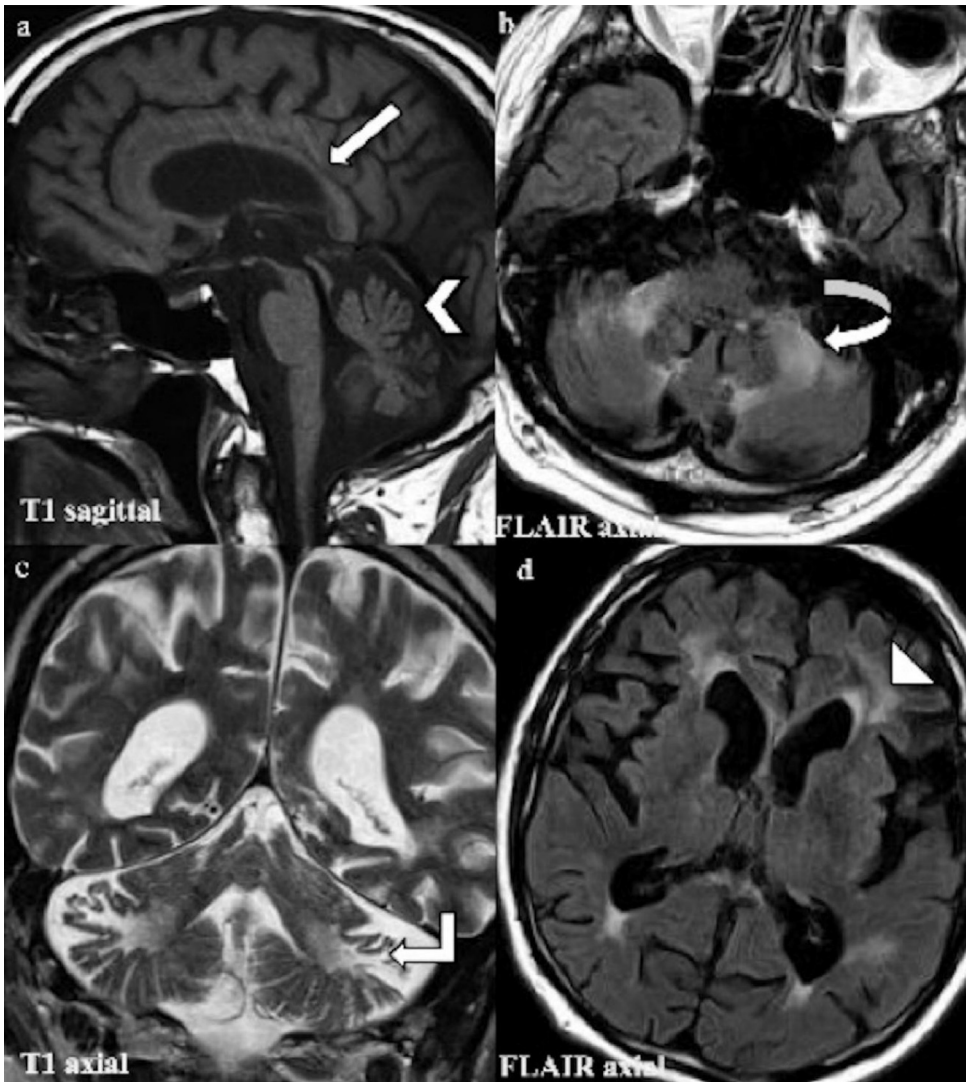

Fig. 9. Fragile X-associated tremor/ataxia syndrome in an 80-year-old female: a) Corpus callosum atrophy (straight arrow) associated with brainstem and cerebellar atrophy (chevron); b) Middle cerebellar peduncles FLAIR hyperintensities (curved arrow); c) Cerebellar white matter hyperintensities and cerebellar atrophy (angled arrow); d) Diffuse cerebral atrophy and white matter hyperintensities (arrow head).

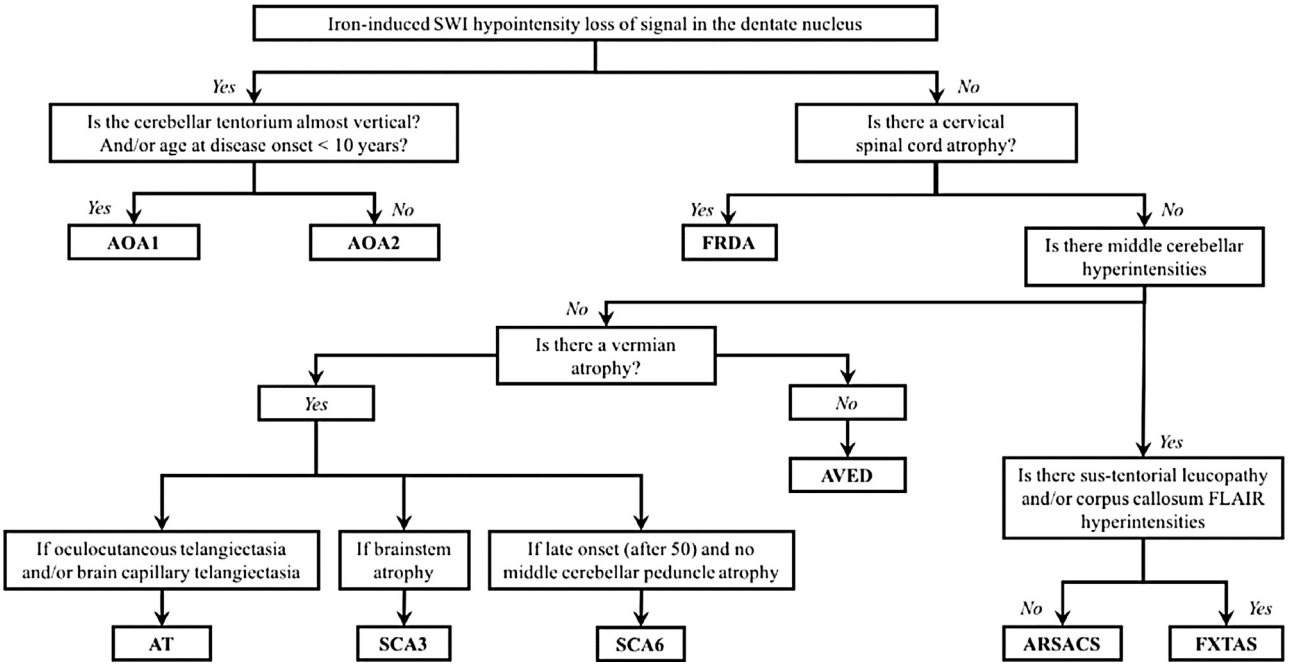

Fig. 10. Recognition of the most frequent inherited cerebellar ataxia based on brain MRI outcomes and age at disease onset. This is far from an exhaustive algorithm; however, it may help direct physicians to a differential diagnosis. (*AOA1: Ataxia with Oculomotor Apraxia Type 1; AOA2: Ataxia with Oculomotor 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*).

SWI suggests only AOA1 and AOA2 as possible etiologies. We therefore believe that MRI can help narrow-down the differential diagnosis of inherited neurodegenerative cerebellar ataxias.

Numerous inherited cerebellar ataxias (more than 100 genes mutations) have been previously reported [48]. To this end, this review focused on helping radiologists and neurologists differentiate between the most frequent types of ataxias by providing a decisional diagram, based on age at disease onset, clinical symptoms and specific MRI patterns. Three MRI sequences are of great interest for the diagnosis of such pathologies: 3D T1 for atrophy evaluation, 3D FLAIR for the evaluation of signal changes, and SWI for the evaluation of iron composition in the dentate nuclei [29]. Based on the results obtained from the three sequences, a decisional diagram was developed to facilitate the MRI recognition approach (Fig. 10).

First, iron-induced SWI hypointensity normal signal or loss of signal in the dentate nucleus (a key element of the cortico-cerebellar loop) is evaluated. Because of its small size and high iron content, SWI is optimal for its identification. The loss of this physiologic hypointensity is pathognomonic of AOA1 and AOA2, and is associated with a decrease of the number of dentate nuclei neurons [28]. In addition to the dentate nucleus hypointensity loss, age at disease onset inferior to ten years and/or an almost vertical cerebellar tentorium are specific criteria to an AOA1 diagnosis.

Secondly, if an iron-induced SWI hypointensity normal signal was observed in the dentate nucleus, spinal cord atrophy is evaluated. If results are positive for spinal atrophy, diagnosis is thereby highly suggestive of FRDA [17,28]. This finding is linked to myelinated fibers loss, gliosis in the posterior and lateral columns, and upper portion atrophy of the spinal cord, which are histopathological hallmarks of FRDA [12].

Thirdly, if cervical spinal cord volume was normal, middle cerebellar peduncles intensity is checked. The middle cerebellar peduncles are arranged in three fasciculi composed entirely of centripetal fibers that connect the cerebellum to the pons. Middle cerebellar peduncles T2/FLAIR hyperintensities are suggestive of FXTAS or ARSACS. However, bilateral and symmetric hypersignals are not. FLAIR hyperintensities could be observed in adult with leucodystrophy like adrenoleucodystrophy, hypoglycemia, extrapontine myelinolysis, wallerian degeneration due to paramedian pontine infarction [49], and other rare diseases such as Hereditary Motor and Sensory Neuropathy Type VI, 4H syndrome, Creutzfeld Jacob disease. In multiple sclerosis, vascular lesions and progressive multifocal leukoencephalopathy hyperintensities remain asymmetric [50]. Also, there is an involvement of the U-fibers and a linear “edge” on DWI consistent with advancing demyelinating edge, DWI restriction in acute ischemia... If strongly suspecting an inherited cerebellar ataxia, the association of supra tentorial leucopathy with FLAIR middle cerebellar peduncles and/or corpus callosum hyperintensities are in favor of FXTAS.

Finally, if there were no middle cerebellar peduncle hyperintensities, vermian atrophy was evaluated. The absence of vermian abnormalities (along with a normal encephalic MRI) orients the diagnosis towards AVED. The presence of vermian atrophy coupled with oculocutaneous and/brain capillary telangiectasia is pathognomonic of AT. If none were detected, brainstem atrophy was checked and its occurrence associate with SCA3. When age at disease onset is superior to 50, SCA6 was diagnosed.

In conclusion, when suspecting an inherited ataxia, our described approach, illustrated and summarized in Fig. 10, could be used for the establishment of a differential diagnosis, keeping in mind that various inherited cerebellar ataxias can be differentiated from each other based on their age of onset and clinical symptoms. In case of progressive or subacute cerebellar atrophy, others diseases such as chronic alcoholism and paraneoplastic cerebellar degeneration, should be kept in mind. Unfortunately, a large part of inherited neurodegenerative ataxias (especially SCAs) has nonspecific MRI patterns: SCA20 demonstrate a more frequently increased

bulbar olivary T2 signal (as a correlate of palatal tremor) while SCA7 is more characterized by a linear hyperintensity in the pons, also called "hot cross bun sign", which is due to transverse pontine fibers degeneration [51]. This "hot cross bun sign" is indeed nonspecific since it occurs in several others SCAs and in Multi-Systematized Atrophy Type C [51]. In the numerous cases of patients' non-specific MRIs, neuroradiologists have to perfectly describe MRI findings for an optimal orientation towards a neurodegenerative disease. During the specialized consultation, neurologists will have to use clinical algorithms such as the one proposed in this neuroradiological review to find the etiology of the patient's ataxia [51].

Disclosure of interest

The authors declare that they have no competing interest.

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