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*Review*

# MRI CNS atrophy pattern and the etiologies of progressive ataxias

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**Abstract:** MRI shows in-vivo the three archetypal patterns of CNS volume loss underlying progressive ataxias, namely spinal atrophy (SA), cortical cerebellar atrophy (CCA) and olivopontocerebellar atrophy (OPCA). The MRI-based CNS atrophy pattern was reviewed in 128 progressive ataxias. A CNS atrophy pattern was identified in 91 conditions: SA in Freidreich’s ataxia, CCA in 5 acquired and 72 (24 dominant, 47 recessive, 1 X-linked) inherited ataxias, OPCA in Multi-System Atrophy and 12 (9 dominant, 2 recessive, 1 X-linked) inherited ataxias. The MRI-based CNS atrophy pattern may be useful for genetic assessment, identification of shared cellular targets, and repurposing therapies or enlargement of drugs indications in progressive ataxias.

**Keywords:** Ataxia; MRI; CNS

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## 1. Introduction

Progressive ataxias are a group of many uncommon yet often very disabling diseases, which can be inherited or acquired. The average prevalence of recessive hereditary ataxias is 3.3/105 and of dominant hereditary ataxias is 2.7/105 [1]. Although the world frequency of each type of progressive ataxia is ethnically and regionally inhomogeneous reflecting the clustering effect of inherited conditions, overall Friedreich ataxia (FRDA) and spinocerebellar ataxia type 3 (SCA3) are the most common types of recessive and dominant ataxia, respectively [1]. Multi-System Atrophy cerebellar type is the most common type of acquired ataxia [2].

Neuropathological studies between 1877 and 1922 [3-5] recognized three archetypes of progressive ataxias based on the predominant distribution of severity of the neuronal systems damage among the spinal cord, brainstem and cerebellum, namely spinal atrophy (SA), cortical cerebellar atrophy (CCA), and olivopontocerebellar atrophy (OPCA).

Since last decade of the twentieth century, genetic and molecular genetic studies have revealed that an increasing number of mutations of different protein coding genes can underlie dominant, recessive and X-linked progressive ataxias and this allows to classify inherited ataxias according to presumed molecular pathogenesis [6-8]. Moreover, screening has revealed that genetic causes are also involved in up to 22% of patients presenting with sporadic progressive ataxia [2, 9-14]. This justifies systematic search of possible gene mutations also in such patients. As a matter of fact, the number of “idiopathic” cases of progressive ataxia is decreasing, but a high number of potential candidate genes needs ultimately to be assessed in the diagnostic work of the single patient [8, 15-19].

In particular, introduction of modern instruments for gene sequencing [Next Generation Sequencing (NGS)] has made it easier to reach a genetic diagnosis in cases with typical phenotypes using targeted multigene panels or whole-exome sequencing. Moreover, whole genome sequencing has further expanded the genetic causes of ataxia in patients with atypical phenotypes [15, 18, 20, 21]. Not unexpectedly, once sporadic causes have been excluded, it is tempting to use NGS techniques as first diagnostic step in patients with progressive ataxia, according to a “reverse phenotyping” approach in which phenotype characterization follows genetic results [15, 20]. However, the large number of repeat-expansion disorders underlying progressive ataxias is not well covered by NGS techniques [8, 22, 23], and it has been emphasized that proper classification and phenotype characterization according to a “phenotyping first” approach is still fundamental to offer the patient a custom gene testing [8, 24].

Magnetic Resonance Imaging (MRI) is a safe technique and constitutes a fundamental tool for both differential diagnosis of the causes of acute and subacute ataxia [25] and characterization of patients with progressive chronic ataxia with in-vivo demonstration of three archetypal CNS atrophy patterns demonstrated by pathology [26-29]. The contribute of conventional MRI to the diagnosis in patients presenting with the most frequent acquired or inherited progressive ataxias has recently been re-assessed [30-33] and a variable combination of distributed atrophy pattern and signal changes in the brain and spinal cord has been recognized as a valuable support for diagnosis and inserted in the diagnostic workflow and algorithms [24, 30, 32]. However, progressive ataxias show often non-specific and sometimes overlapping MRI findings which seldom allow per se a definite diagnosis.

Since the pattern of CNS atrophy on MRI correlates with a definite list of diagnostic possibilities in inherited and acquired progressive ataxias, it is possible to group these diseases just according to the three archetypes [28, 29]. This clumping approach might primarily help to define the patient’s phenotype and contain the need of costly genetic panels by narrowing the etiological hypotheses to those belonging to each category [34]. The purpose of this review is to update the correlation between the MRI CNS atrophy pattern and etiologies of progressive ataxias that was originally proposed for 28 conditions [28] and here is extended to 128 progressive ataxias.

## 2. Materials and Methods

### 1. Classification and nomenclature of progressive ataxias.

Classification of ataxias is complex and in the case of inherited ataxias, following NGS introduction, subject to continuous additions. To establish an updated correlation between the MRI CNS atrophy pattern and etiology in progressive ataxias, the following mixed procedure to select the diseases to be evaluated was set to be inclusive while defining some borders.

We focused our attention on progressive subacute and chronic ataxias, namely those with onset in months or years, and excluded both acute and episodic ataxias [35]. Four main types of progressive ataxias were identified: acquired, dominantly inherited, recessively inherited, and X-linked. The constant updates of the list of inherited ataxias and the variable names attributed to each entity suggest for classification of inherited ataxias to adopt the Online Mendelian Inheritance in Man (OMIM) nomenclature and number. However, a survey at OMIM in October 2021 using “ataxia” as “key-word” yielded 1440 entities, whereas 67 entities were obtained using “SCA” (Spinocerebellar Ataxia, dominant), 307 using “SCAR” (Spinocerebellar Ataxia Recessive), and 5 using “X-linked ataxias” [<https://www.omim.org> Accessed on, October 26, 2021]. The huge number of recessive ataxias labelled as “SCAR” in the OMIM system overwhelms any reasonable and useful analysis. As a matter of fact, in the last years two proposals for classification of

recessive ataxias based on the frequency and predominance of the cerebellar ataxia symptoms and signs in recessive diseases were proposed. They collect 58 [8], and 92 [6] entities, respectively.

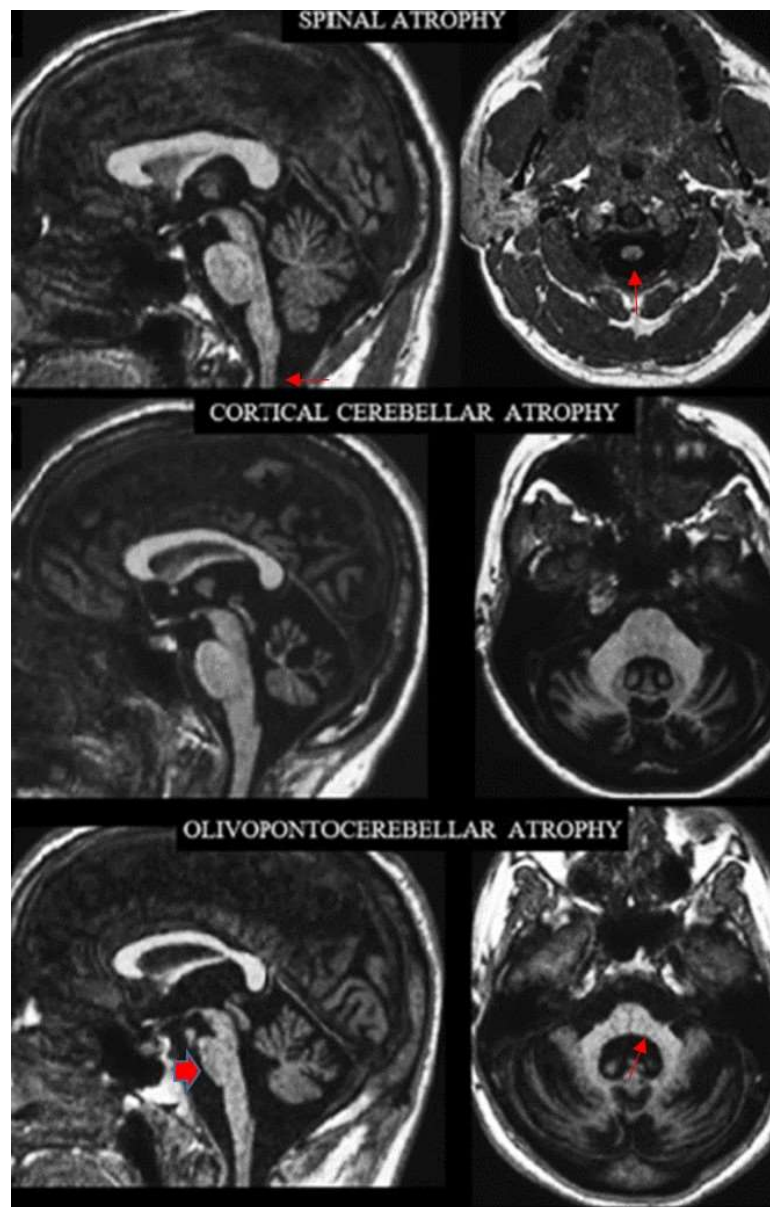
We decided to assume as a reference base for our purpose the 58 recessive ataxias recognized as primary autosomal recessive cerebellar ataxias by the Ataxia Task Force report in 2019 [8]. This was preferred to the list of 92 entities listed by the International Parkinson and Movement Disorder Society Task Force on Classification and Nomenclature of Genetic Movement Disorders [6], because the latter excluded a priori entities in which purely sensory ataxia is prominent and cerebellar symptoms and signs are lacking. Moreover, the many multisystem recessive disorders which can present ataxia as clinical feature [8] or entities in which ataxia is combined with other often prominent movement disorders [6] were beyond the scope of the present review and were excluded. However, differently from the Ataxia Task Force [8], we included entities labeled as SCAR or X-linked Ataxia in OMIM that although described in a single family are well characterized for the causative genetic abnormality (as recognized in OMIM with the # suffix), whereas excluded entities with a not fully defined genetic abnormality (as indicated in OMIM with the % suffix) as SCA4, SCA9, SCA18, SCA25, SCA30, SCA32, SCAR3, SCAR6, and SCAX5. As well, we excluded purely malformative conditions, as the Joubert syndrome or Dandy Walker malformation, and considered only the mitochondrial diseases contained in the Ataxia Task Force 2019 list or in OMIM under the “SCAR” label.

Finally, the list of inherited ataxias was integrated with the Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome (CANVAS) (OMIM 614575), the fragile X tremor ataxia syndrome (FXTAS) (OMIM 300623), and the PRPS1 Gene Mutation [21] found in a PubMed survey by October 2021.

Overall, the list of progressive ataxias covered in this review is not exhaustive, but representative of most of the less rare and better genetically characterized entities, yielding a total of 128 diseases: 11 acquired and 117 inherited (42 dominant, 72 recessive and 3 X-linked).

## 2. Definition of the archetypes on MRI.

The names of the three archetypes of atrophy convey the distribution of the predominant loss of bulk in the CNS underlying progressive ataxias. It affects the spinal cord in SA, the cortical cerebellum in CCA and the brainstem and cerebellum in OPCA. Visual assessment of conventional MRI allows recognition of these patterns (Fig.1). The three atrophy patterns can also more objectively defined according to the distribution of abnormally decreased bidimensional (linear or area) measurements in sagittal and axial MR images [26] which were not used in this review. Patients with SA have abnormal values for the cervical spinal cord, but had no additional abnormal values, except for the fourth ventricle and the medulla. Patients with CCA have abnormal values for the cerebellar vermis or hemispheres but had no additional abnormal values except for the fourth ventricle and the middle cerebellar peduncle. Patients with OPCA have abnormal values for the cerebellar vermis or hemispheres and at least two abnormal values within the basis pontis, middle cerebellar peduncles, and medulla oblongata.



**Fig. 1.** Sagittal (left column) and axial (right column) T1 weighted MR images in three exemplificative patients show the three CNS atrophy patterns underlying progressive ataxias (modified by ref. 29). The typical features of spinal atrophy (SA), namely thinned medulla and cervical spinal cord (arrows) with normal volume of the pons and cerebellar vermis, are observed in a patient with Friedreich ataxia (top). Loss of bulk of the vermis and cerebellar hemispheres with enlarged interfolia spaces but normal volume of the pons, middle cerebellar peduncles and of the cervical spinal cord are the hallmark of cortical cerebellar atrophy (CCA) in a patient with sporadic adult onset ataxia (SAOA) (mid). Atrophy of the brainstem, more pronounced in the inferior portion of the basis pontis (arrowhead), of the vermis, of the middle cerebellar peduncles (arrow) and of the cerebellar hemispheres characterizes olivopontocerebellar atrophy (OPCA) in a patient with SCA2 (bottom). Note the thinning of the superior cervical medulla that can be observed as result of secondary axonal and transynaptic degeneration.

In reviewing the MR images of each disease, I tried to apply the distinction indicated by Poretti and Boltshauser [36] between cerebellar “hypoplasia” and “atrophy” that unfortunately are sometimes used interchangeably leading to confusion and possible misdiagnosis. Cerebellar hypoplasia refers to a cerebellum with a reduced volume but normal shape which are stable over time. Cerebellar atrophy is defined as a cerebellum in a posterior fossa with normal size, which displays enlarged fissures and interfolial spaces secondary to irreversible loss of tissue due to a progressive disease or a single injury. Admittedly, the distinction between cerebellar atrophy and cerebellar hypoplasia based on a single examination can be problematic. However, to differentiate the OPCA pattern from “pontocerebellar hypoplasia” we also considered, on the one hand, the typically flattened shape of the basis pontis in sagittal images and the “pointed” shape in the coronal images of the middle cerebellar peduncles which are observed in OPCA [37], and, on the other hand, the “dragonfly” or “butterfly” appearance of the cerebellum on coronal MR images that is peculiar of pontocerebellar hypoplasia [38], with the flattened cerebellar hemispheres represent “the wings”, associated to a less pronounced (dragonfly) or proportional (butterfly) vermis size decrease. Since computed tomography (CT) does not allow assessment of the brainstem and spinal cord, it was not considered to attribute a CNS atrophy pattern underlying progressive ataxias.

### 3. Review of the MRI features

The reviewer has a 35-year experience in neuro-MRI with a specific interest in ataxias [28, 29, 39, 40].

To update the correlation between the CNS atrophy pattern and aetiologies of acquired progressive ataxias he consulted three review articles [30-32] and source papers cited in the reviews themselves [41]. For the inherited progressive ataxias, he reviewed the MRI images or the descriptions of the MRI features contained in Ataxia Task Force paper on recessive ataxias [8] and in the papers on inherited ataxias accessible through OMIM using the links provided under each disease category. Additionally, using access through PubMed, he scrutinized further MRI images or descriptions in recent papers dealing with progressive ataxias [42-46] and originally reporting cases with new mutations not yet included in OMIM [21].

The review yielded 7 possible outcomes: 1) Typical CNS atrophy pattern among SA, CCA and OPCA; 2) Ponto-cerebellar hypoplasia; 3) Generalized CNS atrophy; 4) Absence of CNS atrophy; 5) Impossible evaluation (when neither MR images nor description of the MRI features were available); 6) Uncertain CNS atrophy pattern; 7) Progressive ataxias in which characteristic MRI signal abnormalities are prominent as compared to mild or absent atrophy and presumably explained the progressive ataxia.

### 3. Results

A disease-associated MRI CNS atrophy pattern was identified in the majority, 71%(91/128), of the diseases.

Table 1 shows the distribution of MRI based atrophy pattern among the acquired and inherited and progressive ataxias.

**Table 1 MRI CNS atrophy pattern and etiologies in progressive ataxias**

<b>MRI CNS atrophy pattern</b>			<b>Etiology</b>
Spinal atrophy	Cerebellar Cortical Atrophy	Olivopontocerebellar atrophy	
	Alcoholic cerebellar degeneration Gluten ataxia Anti-GAD ataxia Paraneoplastic cerebellar degeneration SAOA/ILOCA	MSA-C	Acquired
-	SCA5(600224), SCA6(183086) SCA8(608768), SCA10(603516) SCA11(604432), SCA12(604326) SCA13(605259), SCA14(605361) SCA15/16(606658) SCA19/22(607346), SCA20(608687) SCA21(607454), SCA26(609306), SCA27(609307) SCA28(610246), SCA31(117210) SCA35(613908), SCA37(615945) SCA38(615957), SCA42(616795) SCA43(617018) SCA44(617691), SCA47(617931) SCA48(618093)	DRPLA(125370) SCA1(164400), SCA2(183090) SCA3(109150), SCA7(164500) SCA23(610245), SCA29(117360), SCA34(133190), SCA36(614153)	Inherited Dominant
FRDA (229300)	AOA1 (208920) AOA2/SCAN2/SCAR1 (606002) AOA4(616267) ARCA1/SCAR8 (610743) ARCA2(612016) ARSACS (270550) AT (208900) Cayman ataxia(601238) CLN11(614706) GHS(212840) Gillespie syndrome(206700) HLD7(607694), HLD8(614381) Mithochondrial complex IV deficiency(220110) MTDP7 syndrome(271245) MGCA5(610198) MMS(248800) PBD6B(614871) PHARC(612674)	BNS (215470/2754) SCAR7(609270)	Inherited Recessive



	Progressive myoclonic epilepsy 6(614018) SCAN1(607250), SCAN3(618387) SCAR2(213200) SCAR5(25130) SCAR9(612016), SCAR10(613728) SCAR11(614229) SCAR13(614831), SCAR14(615386) SCAR16(615768), SCAR17(616127) SCAR18(616204), SCAR19(616291) SCAR20(616354), SCAR21(616719) SCAR22(616948), SCAR24(617133) SCAR25(617584), SCAR26(617633) SCAR28 (618800), SCAR29(619389) SCAR30(619405), SCAR31(619422) SPAX5(614487) SPG7 (607259), SPG46(614409) SPG76(616907), SPG79(615491)		
-	SCAX1(302500)	PRPS1 Gene Mutation	Inherited X-linked

#### Number in parenthesis corresponds to OMIM code

**Abbreviations:** Anti-GAD ataxia = Anti-Glutamic Acid Decarboxylase; AOA = Ataxia with Oculomotor Apraxia; ARCA = Autosomal Recessive Cerebellar Ataxia; ARSACS = Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; AT = Ataxia Telangiectasia; BNS = Boucher Neuhauser syndrome; CLN = Ceroid Lipofuscinosis Neuronal; DRPLA = DentatoRubral-PallidoLuisian Atrophy; EOCA = Early Onset Cerebellar Ataxia with retained tendon reflexes; FRDA= Friedreich's Ataxia; GAD = Glutamic acid decarboxylase; ILOCA= Idiopathic Late Onset Cerebellar Ataxia; GHS= Gordon Holmes Syndrome; HLD=Hypomyelinating LeukoDystrophy; MGCA5 =3 MethyGlutaConic Aciduria 5; MMS= Marinesco-Sjogren Syndrome; MSA-C = Multi System Atrophy Cerebellar type; MTDP7 = Mitochondrial DNA Depletion syndrome 7; PHARC = Polyneuropathy Hearing loss Ataxia Retinitis pigmentosa and Cataract; PBD = Peroxisome Biogenesis Disorder; PRPS1 = phosphoribosyl pyrophosphate synthetase 1; SAOA=Sporadic Adult Onset Ataxia; SCA = Spinocerebellar Ataxia; SCAN= Spinocerebellar Ataxia with axonal Neuropathy; SCAR = Spinocerebellar Ataxia Recessive; SPG = Spastic Paraplegia; SPAX =Spastic Ataxia; XSCA = X-linked recessive spinocerebellar ataxia

The SA pattern was identified only in Freidreich's ataxia. The CCA pattern was observed in 77 conditions: five acquired (Alcoholic cerebellar degeneration, Gluten ataxia, Anti-Glutamic Acid Decarboxylase ataxia, Paraneoplastic Cerebellar degeneration and Sporadic Adult Onset Ataxia/ Idiopathic Late Onset Cerebellar Ataxia) and seventy-two (24 dominant, 47 recessive, 1 X-linked) inherited ataxias. The OPCA pattern was recognized in Multi-System Atrophy Cerebellar type and 12 (9 dominant, 2 recessive, 1 X-linked) inherited ataxias.

MRI showed pontocerebellar hypoplasia in three recessive progressive ataxias, namely Cerebellar Ataxia Mental Retardation with/out Quadrupedal locomotion type 1 (CAMRQ1, OMIM 224050), type 2 (CAMRQ2, OMIM 610185) and type 3 (CAMRQ3, OMIM 613227).

A Generalized CNS atrophy was observed in two dominantly inherited diseases, i.e. SCA17 (OMIM 607136) and Autosomal Dominant Cerebellar Ataxia, Deafness and Narcolepsy (OMIM 604121).

No evidence of CNS atrophy was reported in four inherited ataxias; three dominant including SCA41 (OMIM 616410), SCA46 (OMIM 617770) and Spastic Ataxia type 1 (SPAX1, OMIM 108600), and one recessive, namely SCAR23 (OMIM 616939).

To define presence and type of CNS atrophy was impossible in two recessive conditions, namely Ataxia Telangiectasia Like Disease (OMIM 604391) and Spastic Ataxia type 4 (SPAX4, OMIM 613672).

The CNS atrophy pattern was uncertain in 11 progressive ataxias. This reflected the small number of patients examined with MRI in two dominant ataxias, i.e. SCA40 (OMIM 616053) and SCA45 (617769), and two recessive ataxias, i.e. SCAR12 (614322) and SCAR15 (615705). Also uncertain was judged the pattern in three recessive ataxias in which the MRI findings were heterogeneous or non-specific findings as cerebral periventricular T2 hyperintensities. These included SeSAME syndrome (OMIM 612780), Spastic Ataxia type 2 (OMIM 611302) and Spastic Paraplegia 5A (OMIM 270800). In four further instances CNS atrophy pattern was uncertain because different patterns among SA, CCA and OPCA were reported comprising Early Onset Cerebellar Ataxia (EOCA) with retained tendon reflexes, Ataxia with Vitamin E Deficiency (AVED) (OMIM 277460), SCAR27 (OMIM 618369/618128) and Cerebellar Ataxia, Neuropathy and Vestibular Areflexia Syndrome (CANVAS) (OMIM 614575).

Finally, fifteen progressive ataxias were characterized by MRI signal abnormalities that were predominant over the absent or mild atrophy of the CNS structures. They are detailed in table 2. Acquired causes and included tumors, Creutzfeldt-Jakob disease, siderosis and Vit B12 deficiency. Inherited causes included two dominant ataxias, Ataxia-Pancytopenia syndrome (OMIM 159550) and SCA20 (OMIM 608687), eight recessive ataxias as CerebroTendinous Xanthomatosis (OMIM 213700), 2-Hydroxy Glutaric Aciduria (OMIM 236792), Hypomyelinating Leukodystrophy type 2 (OMIM 608804), Hypomyelinating Leukodystrophy type 4 (OMIM 612233), Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (OMIM 611105), Leukoencephalopathy with ataxia (OMIM 615651), Sensory ataxic neuropathy, dysarthria and ophthalmoparesis (OMIM 607459) and SCAR4/SCA24 (OMIM 607317), and one X-linked ataxia, namely Fragile-X tremor ataxia syndrome (OMIM 300623).



**Table 2. Progressive ataxias characterized by predominant MRI signal changes**

Etiology		Signal changes	References number
Acquired	Tumors	Variable	47
	Kreutzfeld-Jakob disease	Basal ganglia and cortex T2 hyperintensity and decreased diffusion	48
	Siderosis	T2-T2* low signal rim of CNS surfaces	31
	Vit B12 deficiency	T2 hyperintense posterior columns of the spinal cord	31
Dominantly inherited	ATXPC(159550)	T2 hyperintense cerebral WM	49
	SCA20 (608687)	T2-T2* low signal of the dentate due to calcifications	50
Recessively inherited	CTX(213700)	T2 hyperintense peridentate and cerebral WM	51
	2-Hydroxic Glutaric Aciduria (236792)	T2 hyperintense cerebral WM	52
	HLD2(608804)	T2 hyperintense cerebral, cerebellar, brainstem and spinal cord WM	53
	HLD4(612233)	Lack of normal WM myelination	54
	LBSL(611105)	T2 hyperintense cerebral WM and WM tracts in cerebral and cerebellar peduncles, brainstem and spinal cord	55
	Leukoencephalopathy with ataxia (615651)	T2 hyperintense internal capsule, cerebral peduncles and middle cerebellar peduncles with restricted diffusion	56
	SANDO(607459)	T2 hyperintense thalami, middle cerebellar peduncle and cerebellar WM	57
	SCAR4/SCA24(607317)	T2 hyperintense basal ganglia and cerebral WM	58

X-linked inherited	FXTAS (300623)	T2 hyperintensity of the middle cerebellar peduncles, splenium corpus callosum and of the cerebral WM	59
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Number in parenthesis corresponds to OMIM code

**Abbreviations:** ATXPC = ATaXia PanCytopenia syndrome; CTX = CerebroTendinous Xanthomatosis; FXTAS = Fragile-X Tremor Ataxia Syndrome; HLD = Hypomyelinating Leukodystrophy; LBSL= Leukoencephalopathy with Brainstem and Spinal cord involvement and Lactate elevation; SANDO = Sensory Ataxic Neuropathy, Dysarthria and Ophthalmoparesis; SCA = Spino-Cerebellar Ataxia (dominant); SCAR = SpinoCerebellar Ataxia Recessive; SPG5A = Spastic Paraplegia 5A; SPAX2 = Spastic Ataxia 2; WM = White Matter

#### 4. Discussion

Review of images and descriptions in the published cases allowed to recognize a typical MRI-based CNS atrophy pattern in the majority (71%; 91/128) of progressive ataxias.

The SA pattern was exclusively observed in FRDA. The CCA pattern was observed in several acquired ataxias (Alcoholic cerebellar degeneration, Gluten ataxia, Anti-Glutamic acid decarboxylase ataxia, Paraneoplastic cerebellar degeneration and Sporadic Adult Onset Ataxia/Idiopathic Late Onset Cerebellar Ataxia), in many dominant ataxias (SCA5, SCA6, SCA8, SCA10, SCA11, SCA12, SCA13, SCA14, SCA15/16, SCA19/22, SCA20, SCA21, SCA26, SCA27, SCA28, SCA31, SCA35, SCA37, SCA38, SCA42, SCA43, SCA44, SCA47 and SCA48), all recessive ataxias with the exception of the Boucher Neuhauser Syndrome (BNS) and SCAR7, and in one X-linked ataxia (SCAX1).

The OPCA pattern was identified MSA-C, in few dominant (SCA1-3, SCA7, SCA34, SCA36, DRPLA), two recessive ataxias (BNS and SCAR7) and the X-linked ataxia associated with the PRPS1 gene mutation.

The CNS atrophy pattern was uncertain in 11 progressive ataxias. Small number of patients were examined with MRI in SCA40, SCA45, SCAR12 and SCAR15, and heterogeneous and non-specific MRI findings were observed or reported in SeSAME syndrome, Spastic Ataxia type 2 and Spastic Paraplegia 5A.

More complex are the reasons for inclusion in the category of uncertain CNS atrophy pattern in 4 further progressive ataxias, namely EOCA, AVED, SCAR27 and CANVAS. EOCA is recognized as a heterogeneous sporadic condition which was initially considered separated from FRDA. However, FRDA patients can present with an EOCA phenotype [60]. Initially a CCA pattern was described in patients with EOCA possibly contributing to the differentiation with FRDA [61]. However subsequent reports described accompanying atrophy of the brainstem and spinal cord [27, 62]. AVED is a recessive condition for which relatively few data on CNS morphology are available. In some patients no abnormality was observed on CT or MRI, whereas cerebellar atrophy was observed in others [63]. Although in the only patient examined with spinal MRI no abnormality was found [64], decreased size of the upper cervical cord was apparent in a case shown by Heidelberg et al.[30]. Hence, despite the reasonable assumption of a SA pattern in AVED reflecting the sensory ataxia and the clinical similarity with FRDA [8, 29], no definitive evidence of it has been provided so far. In the original description of SCAR27 in two unrelated patients a CCA pattern was recognized [65]. However, in a further patient it was accompanied by

atrophy of the pons and midbrain [42]. CANVAS is recessive condition with marked clinical heterogeneity that has recently been recognized responsible of apparently sporadic progressive ataxia [14, 45, 46, 66]. CANVAS showed the more pronounced heterogeneity concerning the distribution of the CNS atrophy in an inherited progressive ataxia. In fact, the CCA pattern was observed in some families [43], but this was combined with atrophy in the spinal cord in others [44] and also OPCA pattern was reported [45, 46].

Interestingly, MRI showed pontocerebellar hypoplasia in all three recessive diseases characterized by progressive ataxias, mental retardation with/out quadrupedal locomotion type 1 (CAMRQ1, CAMRQ2 and CAMRQ3). On the other hand, unfortunately, in some instances the term “hypoplasia” was used to describe MRI findings of probable CAA as in SCAR25, SCAR28, SCAR31, and in SCAX1.

Finally, some progressive ataxias are characterized by signal changes in conventional MRI which irrespective of the CNS atrophy severity and distribution patterns can considerably help in identifying them.

As expected, the distribution of the loss of bulk matched a CNS atrophy pattern and well correlates with the constellation of clinical symptoms and signs [6, 7]. For instance, most of the so called pure cerebellar dominant ataxias (ADCA type III) show a CCA pattern, whereas dominant ataxias with additional extra-cerebellar symptoms and signs (ADCA type I) show a OPCA pattern. As well FRDA in which there is prominent sensory involvement shows a SA pattern and spinal cord atrophy.

This review substantially confirms the correlation between the MRI CNS atrophy pattern and etiologies in progressive ataxias [28]. Changes with respect to the 2008 classification include: displacement of SCA13 from OPCA to CCA pattern, following the report by Subramony et al. [67] in a large family and three index cases, and displacement of SCA17 from CCA to a generalized CNS atrophy pattern.

Obviously for diagnostic purposes the correlation between the MRI CNS atrophy pattern and etiologies in progressive ataxias must be integrated with other clinical and laboratory data and, in case of inherited progressive ataxias, with ethnicity and geographical distribution [8, 68]. However, before this use two notes of caution are worthy.

First, it is conceivable that in advanced stages of different ataxias a general atrophy of the CNS including cerebellum, brainstem, spinal cord and cerebrum takes places as result of secondary axonal and transynaptic degeneration with waning of differences between SA, CCA and OPCA patterns. This possibility is confirmed by occurrence of cerebellar cortex atrophy in advanced cases of FRDA, the prototype of SA [69], atrophy of the spinal cord in SCA1 and SCA3 that are typical examples of OPCA [70, 71], and of pontine atrophy in SCA13 and SCA36, two conditions characterized by CCA in the early phases [67, 72, 73]. However, the proposed correlation is generally valid for the early and full clinical manifestation of diseases, and data in pre-symptomatic patients with dominantly transmitted ataxia show that early loss of bulk involves the cerebellum and pons in SCA1 and SCA2, two examples of OPCA pattern [74], but the cerebellum alone in SCA48 [75] that is an example of CCA.

Second, theoretically, in line with the known phenotype and genotype heterogeneity of inherited ataxias [8], it cannot be excluded that different CNS atrophy patterns can correspond to the same disease entity.

Beyond the diagnostic purpose, two additional potential consequences of awareness of the correlation between the three MRI-based CNS atrophy patterns and the etiologies of progressive ataxias can be envisioned. First, it may contribute to identify shared cellular targets or metabolic pathways for diseases exhibiting the same archetypal CNS atrophy pattern thus improving our understanding of physiopathological mechanisms of progressive ataxias [8]. Second, in a therapeutic perspective, it may bring to repurpose of drugs or enlarge indications for inherited or acquired ataxia diseases sharing the same MRI atrophy distribution pattern (and similar distribution of neuronal systems damage) and corresponding patients [8], as it was attempted in cases of CCA [76].

The updated classification according to the MRI-based CNS atrophy pattern is not definitive and further amplifications and modulations are awaited. Moreover, this review has certainly some limitations. First, some progressive disorders which may present with ataxia as relevant clinical feature were arbitrarily excluded. For them reference is made to other reviews [6, 8]. Second, the visual assessment of the published MR images I have pursued is subjective. This can be overcome by expert panel blinded reviews. However possible discrepancies between the MRI CNS atrophy pattern reported by the Authors and the one I attributed by evaluating the MR images was restricted to the above few instances concerning the difficult distinction between “hypoplasia” and “atrophy” [36]. Third, symmetric signal hyperintensities in T2 or T2\* weighted MR images changes reflecting wallerian degeneration of white matter (WM) tracts can accompany the SA and OPCA pattern and contribute to their full respective picture [37, 39]. However, these signal changes usually are observed in advanced phases of the diseases when loss of bulk is already appreciable and are more sensitive to the operator variability and to the technical details of the sequence and magnetic field strength. For these reasons they were not considered to define the SA or OPCA patterns. Also hyperintensity of the dentate signal in T2 weighted images which have been reported in some inherited ataxias as SCA48 [77] and SPG7 [32] were not accounted for. Fourth, MRI quantitative techniques to evaluate the microstructure of the WM, as diffusion weighted or diffusion tensor imaging [78-80], or of the dentate and other gray matter nuclei, as T2 relaxometry [81] or susceptibility weighted imaging [82] were not taken into account. should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

## 5. Conclusions

In line with the neuropathological discoveries of the XIX and XX centuries, MRI confirms in vivo today that three are the fundamental distributions of damage underlying progressive ataxias. They are SA, CCA and OPCA and can be inherited or acquired. Although the present trend driven by the molecular genetics advances is to split progressive ataxias into hundreds of sometimes very rare conditions, a simple clumping of them according to the MRI-based CNS atrophy pattern is possible and might help diagnosis, possibly improve physiopathology understanding, and even rethinking therapies for these uncommon but disabling diseases.

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