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Research article

A new MRI marker of ataxia with oculomotor apraxia

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ABSTRACT

Purpose: Evaluate the specificity and sensitivity of disappearance of susceptibility weighted imaging (SWI) dentate nuclei (DN) hypointensity in oculomotor apraxia patients (AOA).

Method: In this prospective study, 27 patients with autosomal genetic ataxia (AOA (n = 11), Friedreich ataxia and ataxia with vitamin E deficit (n = 4), and dominant genetic ataxia (n = 12)) were included along with fifteen healthy controls. MRIs were qualitatively classified for the presence or absence of DN hypointensity on FLAIR and SWI sequences. The MRIs were then quantitatively studied, with measurement of a ratio of DN over brainstem white matter signal intensity through manual delineation. The institutional review board approved this study, and written informed consent was obtained. In the cross-sectional analysis, the Mann–Whitney test was applied.

Results: Qualitatively, the eleven AOA patients presented absence of both DN SWI and FLAIR hyposignals; three dominant genetic ataxia patients had moderate SWI DN hyposignal and absent FLAIR hyposignal; the thirteen remaining subjects presented normal SWI and FLAIR DN hyposignal. Absence of DN SWI hypointensity was 100% sensitive and specific to AOA. Quantitative signal intensity ratio (mean ± standard deviation) of the AOA group (98·96 ± 5·37%) was significantly higher than in control subjects group (76.40 ± 8.34%; $p < 0.001$), dominant genetic ataxia group (81·15 ± 9·94%; $p < 0·001$), and Friedreich ataxia and ataxia with vitamin E deficit group (87·56 ± 2·78%; $p < 0·02$).

Conclusion: This small study shows that loss of the normal hypointensity in the dentate nucleus on both SWI and FLAIR imaging at 3 T is a highly sensitive and specific biomarker for AOA.

1. Introduction

A growing number of autosomal recessive or dominant hereditary cerebellar ataxia have been genetically identified over the last two decades. Since the family history can be lacking the identification of clinical, biological, and radiological markers suggestive of inherited cerebellar ataxia is crucial. Within autosomal recessive cerebellar ataxia (ARCA), Friedreich Ataxia (FDRA, related to mutation of frataxine gene) remains the most frequent [1]. Distinctive clinical, radiological, and biological markers may help distinct ARCA from FRDA. Among these markers, ocular motor apraxia represents a specific sign of a group of diseases including principally ataxia telangiectasia (AT, related to mutation of the ATM gene), ataxia with oculomotor apraxia type 1 (AOA1, related to mutation of the aprataxine gene), and type 2 (AOA2, related to the mutation of the senataxine gene). Both AOA have a global similar phenotype with progressive cerebellar ataxia,

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peripheral neuropathy and ocular motor apraxia, but AOA type 1 begin usually earlier and clinical signs are more severe. However, although specific, ocular motor apraxia is reported to be inconstant [2–4]. Finding new and more specific markers is therefore a necessary goal to orient diagnosis in difficult these rare cases of progressive cerebellar ataxia.

Among new diagnostic tools, susceptibility weighted imaging (SWI) is particularly sensitive to compounds that distort the local magnetic field such as blood and iron. It has recently been used in cerebellar ataxia, focusing on dentate nuclei (DN) [5,6]. In a preliminary report of five patients with AOA2, we unexpectedly detected the absence of the hypointense DN iron signal on SWI compared to control subjects [7]. This neuro-imaging aspect might first be of great interest for orientation of diagnosis in cerebellar ataxia, and second may help deepen our understanding of the underlying physiopathology in AOA. Therefore, the aim of this study was to confirm the abnormal DN SWI signal in AOA2 and AOA1 patients and evaluate its specificity and sensitivity by comparing it with DN SWI signals of control subjects and patients with other autosomal cerebellar ataxias.

2. Materials and methods

2.1. Subjects

In this monocentric observational study, we prospectively included between January 2012 and April 2016, 27 patients with genetically-determined autosomal cerebellar ataxia, followed in our University Hospital by the different co-authors (CT, ST, PP, AV). Brain MRI was part of the clinical follow-up of patients. Patients were divided and classified in three groups. The first group (AOA group) included nine AOA2 patients (5 males, 4 females) belonging to four families, and two AOA1 patients (2 female sisters) (n = 11; mean ± standard deviation (SD) age: 34.3 ± 9.3 years). The second group (FRDA/AVED group) included autosomal recessive cerebellar ataxias (n = 4; mean ± SD age: 43.3 ± 11.7 years): three FRDA (3 females) and one (male) ataxia with vitamin E deficit (AVED) patients. The third group (DGA group) included autosomal dominant genetic ataxia (n = 12; mean ± SD age: 51.52 ± 16.1 years): one spinocerebellar ataxia 1(SCA1) (male), two SCA2 (1 female, 1 male), three SCA3 (2 females, 1 male), two SCA6 (2 female sisters), and four episodic ataxia 2 (EA2) patients (3 females, 1 male) (Supplementary-Table 1). Fifteen healthy subjects were included in this study to serve as control group (11 females, 4 males; mean ± SD age: 42.8 ± 12.72 years).

For each patient, two neurologists (CT, SR) clinically evaluated cerebellar ataxia, oculomotor and extra-cerebellar neurological signs. Ataxia was quantitatively assessed using the international co-operative ataxia rating scale (ICARS) [8] and the scale for the assessment and rating of ataxia (SARA) [9]. Ages and scores were compared between groups of patients.

Five of the eleven AOA2 patients have been previously studied [7] in order to investigate the regional specificity of cerebellar degeneration using T1-weighted MRI sequences, in comparison to five normal subjects. This study unexpectedly detected the absence of the hypointense DN iron signal on SWI. In this manuscript we report specific analysis of DN SWI signal in a cohort of patients with progressive cerebellar ataxia.

This study was performed in agreement with French law for observational study (March 4, 2002) and the Declaration of Helsinki (2003-036B). All patients were informed and gave written consent for inclusion in this study.

2.2. MRI acquisitions

MR image acquisition was performed in the radiology department of two sites of our University Hospital, on two 3 T MR systems with a 32-channel head coil (Achieva 3 T, and Ingenia 3 T, Philips Medical system, Best, The Netherlands). The MRI protocol included a high-resolution 3D T1, 3D Fluid-attenuated inversion recovery (FLAIR), and a SWI sequence. MRI parameters were:

-Ingenia 3 T: 3D T1: Repetition time/echo time (TR/TE) = 10.9 /5 ms; voxel resolution = 0.53 × 0.833 × 0.833 mm^3; field of view (FOV) = 265 × 480 × 480; 3D FLAIR: TR/TE/inversion time (TI) = 8000/341.9/2400 ms; voxel resolution = 0.68 × 0.5 × 0.5 mm^3; FOV = 330 × 288 × 288; SWI: TR/TE = 62.7/0 ms; voxel resolution = 0.299 × 0.299 × 2mm^3; FOV = 768 × 768 × 65.

-Achieva 3 T: 3D T1: TR/TE = 6.7/3 ms; voxel resolution = 0.9 × 0.469 × 0.469 mm^3; FOV = 200 × 512 × 512; 3D FLAIR: TR/TE/TI = 8000/356.7/2400 ms; voxel resolution = 0.6 × 0.434 × 0.434 mm^3; FOV = 300 × 576 × 576; Ven-BOLD: TR/TE = 21.2/30.1 ms; voxel resolution = 0.344 × 0.344 × 0.7 mm^3; FOV = 640 × 640 × 143.

2.3. Qualitative analysis

Two examiners performed patient classification based on the DN signal on FLAIR and SWI images. The first examiner (SR) classified MRI with knowledge of identity, whereas the second examiner (FC), a neuroradiologist with more than 20 years of experience, was blinded to control or patients' clinical status and identity, and to the first examiner's results. DN signal on MRI was classified into two categories based on FLAIR images: (+) = hypointense and (-) = no hypointense DN; and into three categories based on SWI images: category 1 = high hypointensity, category 2 = mild hypointensity, and category 3 = no hypointensity.

Sensitivity and specificity were calculated on the patients' data only. Sensitivity was calculated as "no DN hyposignal" over the AOA group (true positive). Specificity was calculated as "DN hyposignal" (mild or high on SWI) over the non-AOA groups (true negative).

2.4. Image processing

Both left and right DN were manually delineated by the same operator (SR) on FLAIR images using the MITK-3M3 software (http://docs.mitk.org/3m3-1.1/). Delineation for patients with no FLAIR DN signal was performed on 3D T1 images. As described by Kanda et al. [10], two additional regions of interest (ROI) of similar sizes were delineated in the right middle cerebellar peduncle and the pons as a square of 25 × 25 voxels each, approximately next to the emergence of the acoustic-facial bundle.

FLAIR and T1 images that were used for mask delineation were each registered to the SWI image using the FLIRT toolbox of the fMRIB software Library [11]. To this end, an affine linear registration (12 parameters) was used. This transformation was then applied to the corresponding delineated ROIs while applying a nearest-neighbor interpolation.

SWI image intensity of all subjects were then normalized using the histogram matching function in 3D Slicer (https://www.slicer.org). This step normalizes the grayscale values of patients' images based on the grayscale values of a reference image (a patient picked randomly).

Intensity values of DN, right middle cerebellar peduncle and pons were then extracted from SWI images. Finally, the DN over middle cerebellar peduncle and the DN over pons signal intensity ratios [10] were calculated for each subject. The mean of the two ratio values, called DN/Brainstem white matter (WM) ratio, was calculated for each subject and used for statistical analysis.

2.5. Statistical analysis

The STATISTICA software (v10, Statsoft, Tulsa, OK, USA) was used for the statistical analysis. In the cross-sectional analysis, the Mann–Whitney test was applied to compare age, ataxia scores and SWI DN/Brainstem WM ratio between the different groups (controls, DGA, FRDA/AVED, AOA). The level of significance was set at $p < 0.05$.

Table 1
Ataxia score results.

Groups	ICARS Score (mean ± SD)		SARA Score (mean ± SD)	
AOA (n = 11)	60·64 ± 20·23		22·00 ± 7·90	
FRDA/AVED (n = 4)	32·25 ± 11·15		10·00 ± 7·07	
DGA (n = 9)	38·67 ± 16·96		13·63 ± 5·88	
Comparison between groups	p	Z	p	Z
AOA vs. FRDA/AVED	0·02	−2·28	0·02	−2·28
AOA vs. DGA	0·02	−2·27	0·04	−1·98
FRDA/AVED vs. DGA	0·55	−0·59	0·49	−0·68

AOA: ataxia with oculomotor apraxia; FRDA: Friedreich ataxia; AVED: ataxia with vitamin E deficit; DGA: dominant genetic ataxia; ICARS: International cooperative ataxia rating scale; SARA: Scale for the assessment and rating of ataxia.

3. Results

3.1. Subjects

Patients in the DGA group were significantly older than those in the AOA group (Z = 2·36 p < 0·02). There was no significant difference in age between the other groups. Clinical and genetic data are summarized in Supplementary-Table 1. Ataxia scores, performed in 24 of the 27 patients (missing data: DGA n = 3), were significantly higher in the AOA group as compared to FRDA/AVED and DGA groups (Table 1).

3.2. MRI

3.2.1. Qualitative analysis

Results of qualitative MRI analysis are presented in Table 2. Forty-two MRIs were visually checked and analyzed. Examiners had a 100% concordance in their DN classification. Examples of T1, FLAIR, and SWI sequences in patients of different groups are illustrated in Fig. 1.

On FLAIR images, fourteen patients (33%) had no DN hypointensity (category (-)), corresponding to the eleven AOAs, one SCA3 patient (patient 21) and the two SCA6 patients (patient 22 and 23). The remaining 28 subjects (13 patients and 15 controls) had DN hypointensity (category (+)). The DN FLAIR signal was increased in the AOA patients, and moderately increased in the SCA6 patients (Fig. 1).

Patients exhibiting no DN hypointensity on FLAIR (category (-)) had either a mild DN hypointensity (category 2) or no hypointensity (category 3) on SWI images. Those with category 2 hypointensity (N = 3) corresponded to both SCA6 patients (patient 22 and 23) and one SCA3 (patient 21), while those with category 3 hypointensity (N = 11) corresponded to the AOA patients. The other subjects (N = 28) had a hypointense DN signal on SWI (category 1). DN was visible as a hypointensity on 3DT1 in the eleven AOA patients.

According to patient's data, absence of DN hypointensity on FLAIR for diagnosis of AOA has a specificity of 81, 25% and a sensitivity of 100% while absence of DN SWI hypointensity has a specificity and a sensitivity of 100%.

Table 2
Qualitative classification of dentate nuclei signal.

Subject	Group	FLAIR category: DN hyposignal N (%)		SWI category DN hyposignal N (%)		
		+	–	1	2	3
C1-C15	Control (N = 15)	15 (100%)	0	15 (100%)	0	0
Patients 1–11	AOA (N = 11)	0	11	0	0	11
Patients 12–15	AVED/ FRDA (N = 4)	4	0	4	0	0
Patients 16–27	DGA (N = 12)	9	3*	9	3	0
*Patient (21,22,23)		0	3	0	3	0
Total Patients (N = 27)		13 (48%)	14 (52%)	13 (48%)	3 (11%)	11 (41%)

C: Control; SWI: susceptibility weighted imaging; DN: dentate nucleus; SIR: Signal intensity ratio; WM: white matter; AOA: ataxia with ocular motor apraxia; FRDA: Friedreich ataxia; AVED: ataxia with vitamin E deficit; DGA: dominant genetic ataxia.
On FLAIR images: category (+) = hypointense and (-) = no hypointense DN; on SWI images: category 1= high hypointensity, category 2= mild hypointensity, and category 3= no hypointensity.

3.2.2. Quantitative analysis

Results of quantitative MRI analysis are presented in Fig. 2. 41/42 MRIs were quantitatively analyzed; patient 21 (83 years of age) was excluded from the analysis due to the severity of cerebellar atrophy that made the registration step impossible to perform. DN was delineated on 28 FLAIR images (category (+)) and 13 T1 images (category (-)). The mean signal intensity ratio of DN/Brainstem WM of AOA group was close to 100% (mean ± SD = 98·96 ± 5·37%) and was significantly higher than in control subjects (76.40 ± 8.34%; Z=-4.25, p < 0.001), the DGA group (81.15 ± 9.94%; Z=-3.68; p < 0.001); and FRDA/AVED group (87.56 ± 2.78%; Z=-2.41; p < 0.02) (Fig. 2). The mean signal intensity ratio of DN/Brainstem WM of FRDA/AVED group was higher than the control group (Z=-2.45, p = 0.014). There were no significant differences between the FRDA/AVED group and the DGA group (Z = 1.24; p = 0.21).

4. Discussion

In this study, the absence of DN SWI hypointensity for the diagnosis of AOA has a specificity and a sensitivity of 100%. This distinctive sign appears to be maintained with the evolution of the disease. For example, in the four AOA2 siblings who were of different age (18–32 years) and disease duration (2–17 years) the DN signal remained unchanged. The only exception was a weaker (but not absent) SWI hypointensity in the two SCA6 patients and one of the SCA3 patients, in the context of severe atrophy. The absence of DN hypointensity on FLAIR was also observed with a sensitivity of 100% for the diagnosis of AOA, but a specificity of 81.25%. Interestingly, on FLAIR sequences, hyperintensity of the DN was clearly visible in the eleven AOA patients and to a lesser extent, in the two SCA6 patients. These radiological biomarkers, specific of AOA in the present cohort of autosomal genetic cerebellar ataxias, have to be further tested in ataxia telangiectasia patients.

Magnetic susceptibility imaging has gained a general interest, particularly in cerebellar ataxias in deep cerebellar nuclei imaging. SWI, originally called BOLD venographic imaging or venbold, allows for an appropriate echo time to visualize the susceptibility differences between adjacent tissues. Contrast magnitude image is produced by the combination of magnitude and phase data. SWI and venbold are particularly sensitive to iron, and other metal storage [12]. SWI has recently been used to focus on the anatomy of the DN, which is considered as an iron-rich cerebral structure [13]. Solbach et al. recently used this sequence to demonstrate DN atrophy in FRDA patients in comparison to normal subjects [14]. Atrophy of cerebellar nuclei has also been observed with SWI in SCA3 and SCA6 versus controls. Interestingly, DN volume reduction, present in all of these diseases, was most prominent in SCA6 as compared to FRDA and SCA3 [5]. MRI resolution does not always allow the visualization of DN anatomical circumvolutions, especially in atrophic brains. Also, the DN size can be overestimated in phase images due to the "blooming effect", blurring anatomical borders. Therefore, evaluating the signal intensity rather than anatomical atrophy on SWI sequences may be much more

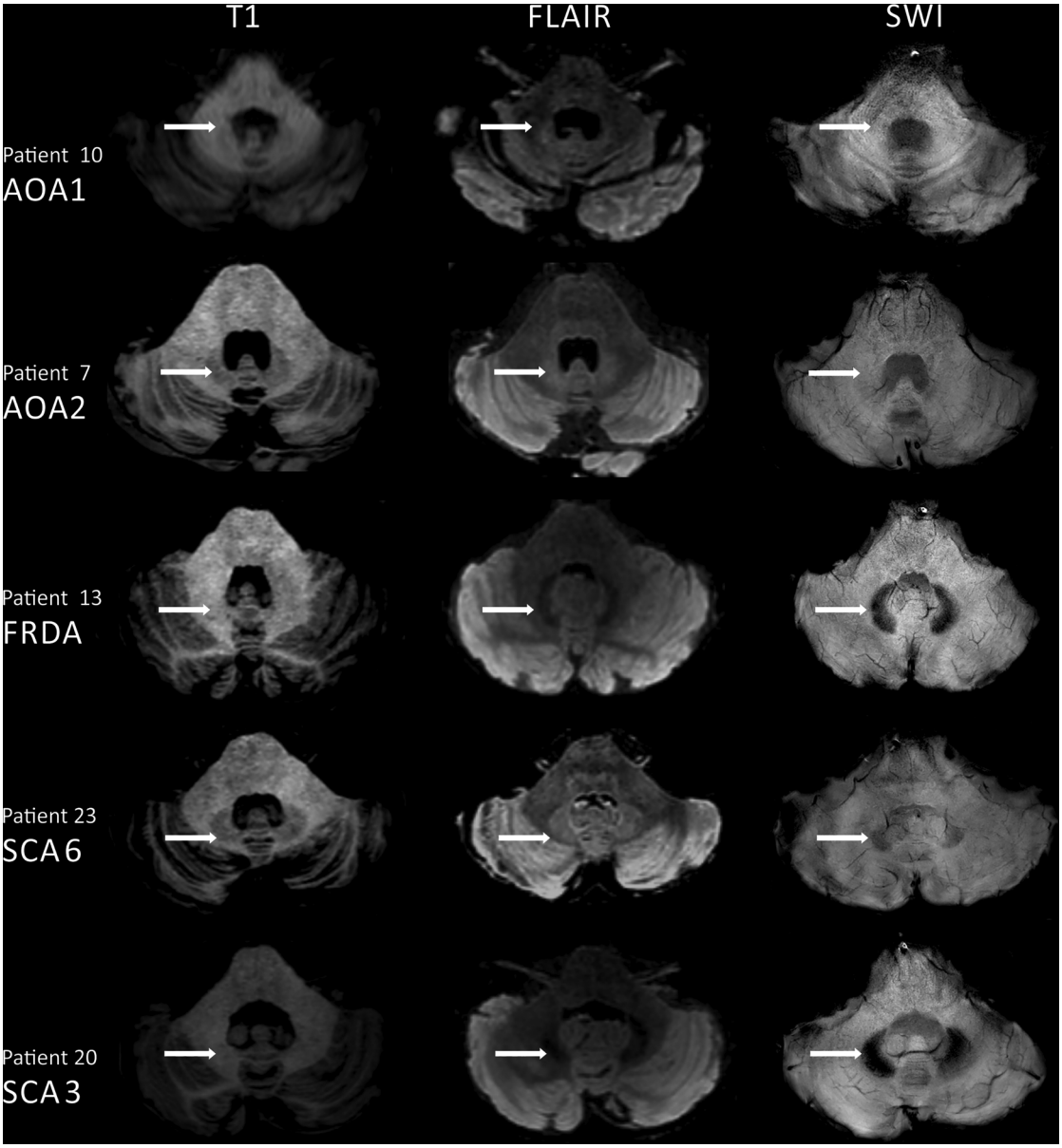

Fig. 1. Examples of T1, FLAIR, and SWI sequences in patients of different groups. AOA: ataxia with oculomotor apraxia; FRDA: Friedreich ataxia; AVED: ataxia with vitamin E deficit; SCA: spinocerebellar ataxia. In the 2 AOA patients, DN hyposignal can be seen on T1, but is absent on FLAIR and SWI. In the FRDA and the SCA3 patient, DN hyposignal is seen on FLAIR and SWI. In the SCA6 patient, DN appears hypointense but not absent on SWI. In the 2 AOA and the SCA6 patients, DN appears hyperintense on FLAIR.

pertinent even when using routine clinical MRI.

In this study, we demonstrated that qualitative analysis of SWI DN signal allows to distinguish AOA patients from other autosomal genetic cerebellar ataxia patients. A weaker DN hyposignal was found in two SCA6 patients and one SCA3 patient, and was associated with more severe cerebellar atrophy. This is consistent with previous observations in the cohort reported by Stefanescu et al. [5], in which the DN was not visible in two SCA6 patients, whom had worse SARA scores and probably the more atrophied cerebelli. The higher ataxia scores in the AOA group of the present study cannot, however, explain the absence of DN hyposignal, given that this signal can be found normal in FRDA with equivalent scores [5]. The quantitative evaluation corroborated the visual results. It suggests the absence of a difference in signals between the DN and the posterior fossa WM. Furthermore, FLAIR DN signal was found hyperintense in all AOA patients and the two SCA6 patients. An explanation is still lacking, but this observation would suggest analyzing DN FLAIR signal in patients with cerebellar ataxia, then adding SWI when FLAIR hypersignal is observed.

The disappearance of the DN signal on SWI versus its persistent presence and visibility on T1, suggest that the underlying mechanism is not atrophy, but a change in the DN content, such as a decrease in iron concentration. More frequently, iron has been found to accumulate in various cerebral nuclei, including DN, in many neurodegenerative disorders [15]. More specifically, in FRDA, the DN seems to present a higher relaxation rate relative to controls, known to appear as increased hypointensities, suggesting for some teams, the physio-pathological hypothesis of iron accumulation. Previous studies suggested that higher relaxometry rate found in the DN of FRDA patients was correlated with increased iron content [6,16–18]. However, neuropathological studies and more recent imaging studies tend to refute this hypothesis. Indeed, iron content is equivalent but its concentration is increased only due to atrophy [14,19,20], as is the case of Copper and Zinc [20].

The present results suggest that, for AOA patients, there is a lack of atrophy and a disappearance of the hyposignal. No neuropathology

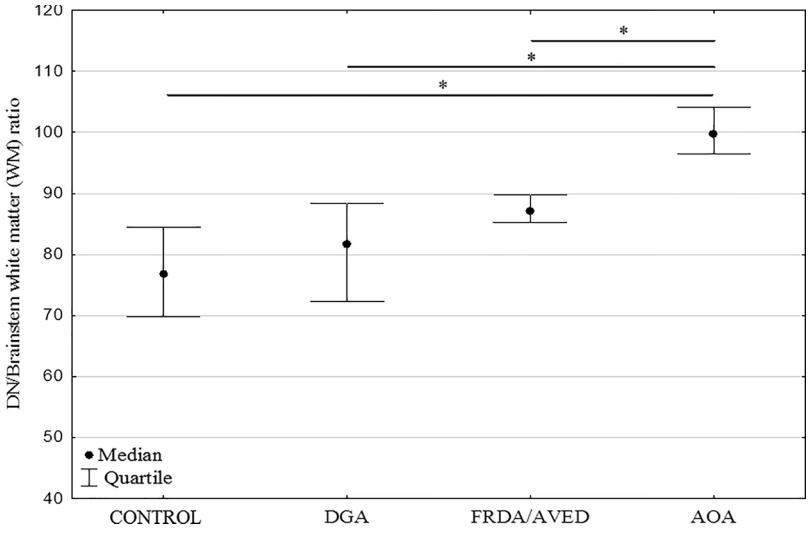

Fig. 2. Median (dot) dentate nucleus/brainstem white matter intensity ratios measured on SWI sequences of each group, with two standard deviations (bars). DGA: dominant genetic ataxia; FRDA: Friedreich ataxia; AVED: ataxia with vitamin E deficit; AOA: ataxia with oculomotor apraxia. *Significant results; AOA group presented significant higher mean intensity ratio as compared to other groups.

data on iron concentration in AOA are available. In the rare autopsied AOA patients, the number of neurons in the DN was preserved or slightly reduced in number [21,22]. Therefore, preservation of deep cerebellar nuclei relative to cortical cerebellar atrophy in AOA versus marked deep cerebellar nuclei atrophy relative to preservation of cerebellar cortex in FRDA could be one explanation of the different SWI DN signals. However, this is not enough to explain the absence of iron signal as compared to other types of inherited cerebellar ataxia or to control subjects.

In the literature, data are available in SWI dentate nuclei signal in Friedreich ataxia, SCA3, SCA6, and AOA2 in our previous article. Our actual cohort contains these four diseases but also AOA1, SCA1, SCA2, AVED and Episodic ataxia. Data about the DN signal in Ataxia Telangiectasia are missing.

5. Conclusion

Hypointensity due to iron deposition normally observed on SWI in the DN is not observed on MRI in AOA patients. Loss of the hyposignal of the DN on FLAIR and SWI is a promising diagnostic criterion for AOA. We suggest neuroradiologists to focus on DN signal on FLAIR sequences, and to add SWI sequences in case of FLAIR DN hyperintensity.

Conflicts of interest

The authors declare that there is no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2018.11.035.

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