Magnetic resonance imaging in "typical" and "late onset" Friedreich's disease and early onset cerebellar ataxia with retained tendon reflexes

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MRI makes it possible to study the in vivo brain and spinal cord morphology of patients with hereditary ataxia. We performed T1- and T2-weighted studies in eleven patients with Friedreich's disease (FD), five with "late onset" FD and ten with early onset cerebellar ataxia with retained tendon reflexes (EOCA). Cervical cord atrophy was constant in FD and "late onset" FD and often associated with atrophy of the cerebellum and of the brainstem; T2-weighted studies showed posterior column degeneration in the cervical cord. The most frequent finding in EOCA was cerebellar atrophy, pure or associated with cervical cord or brainstem atrophy; the cerebellar atrophy was marked in a few cases and was related to disease duration.

Key Words: magnetic resonance imaging — Friedreich's disease — early onset cerebellar ataxia with retained tendon reflexes.

Introduction

Harding proposed a classification of hereditary ataxias mainly based on clinical and genetic features [9]; pathological findings were not considered useful for clinical diagnosis, because they are rarely available and various diseases may have a similar pathological pattern. Among the autosomal recessive ataxias of unknown etiology, she described Friedreich's disease (FD) and early onset cerebellar ataxia with retained tendon reflexes (EOCA) as being the most frequent. The onset of both diseases occurs before the age of 20 years, with the presence of knee jerks and a more benign course differentiating EOCA from FD. The gene responsible for FD (FRDA) has been mapped to the long arm of chromosome 9 with no evidence of genetic heterogeneity [2]; no molecular genetic analysis has yet been performed in EOCA, which appears to be clinically and genetically heterogeneous [6]. A "late onset" form of FD (LOFD), with onset from 21 to 36 years, has also been recognized and linkage studies have shown its genetic homogeneity with FD [3].

MRI makes it possible to study the in vivo brain and spinal cord morphology of these forms of hereditary ataxia [1, 14]: Wüllner et al. have recently reported constant spinal atrophy in FD and LOFD, and heterogeneous findings in EOCA with frequent cerebellar atrophy [15].

The aim of the present study was to verify whether the MRI findings in FD, LOFD and EOCA were sufficiently homogeneous and disease-specific to be helpful in classifying doubtful cases.

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In addition, we correlated the MRI findings with disease duration and severity.

Patients and Methods

A diagnosis of FD was made in eleven patients from ten families on the basis of the following criteria: disease onset before the age of 20 years, autosomal recessive inheritance, progressive ataxia, the absence of lower limb jerks and the presence of at least one of the following signs in the index case: dysarthria, an extensor plantar response or echocardiographic signs of hypertrophic cardiomyopathy [5]. Eight of the patients were female and three male; their mean age ±SD was 27.1±8.9 years, and the duration of the disease 16.0±8.2 years. Disease severity was evaluated according to the Inherited Ataxia Progression Scale (IAPS): Stage 1, affected asymptomatic case; Stage 2, symptoms present but mild; Stage 3, fully developed disease, patient unable to walk without support; Stage 4, patient confined to wheelchair. Eight of the patients were in IAPS Stage 4, two in Stage 3 and one in Stage 2.
LOFD was diagnosed in five patients from four different families. Except for the age of onset, the diagnostic criteria were the same as for FD. Three patients were female and two male; their mean age was 38.0±5.2 years, and the duration of the disease 8.8±6.3 years. Three patients were in IAPS Stage 2, and two in Stage 3.
Linkage analysis, performed in nine FD and three LOFD patients, showed the cosegregation of the disease with the polymorphic markers of the FRDA region.
EOCA was diagnosed in ten patients from ten different families on the basis of the following criteria: disease onset before the age of 20 years, the exclusion of dominant inheritance, the presence of progressive ataxia and retained knee jerks, the absence of any known etiology or of any associated features, such as hypogonadism or myoclonus. Six patients were male and four female; their mean age was 27.0±9.0 years, and the duration of disease 18.5±10.6 years. Seven patients were in IAPS Stage 2 and three in IAPS Stage 3; six showed signs of corticospinal involvement (patients 17, 19, 21, 24, 25 and 26), and four dysphagia (patients 20, 21, 24 and 26).
Ten healthy subjects (2 males, 8 females; mean age 24.0±5.4 years), were evaluated as controls.
MRI was performed using either a 1 T superconductive (Magnetom, Siemens AG) or a 0.5 T system (Toshiba or Vectra, General Electric). T1-weighted sagittal, axial and coronal images were obtained in order to study the supratentorial and infratentorial structures (cerebellar hemispheres and vermis, middle cerebellar peduncles, midbrain, pons, fourth ventricle and medulla oblongata). On the middle sagittal plane, the cerebellar vermis was divided into superior, middle and inferior vermis using the primary and prepyramidal fissures. T1-weighted sagittal and axial images were acquired in order to examine the cervical cord. T2-weighted studies were performed in most brain and in somes spinal cord studies. Conventional spin-echo and sometimes gradient-echo sequences were used.
The severity of any changes was rated using a score ranging from − (normal) to + + + (maximum severity); the reported values are the median scores of three blind examiners.
Correlations were studied using Spearman's correlation coefficient.

Results

The MRI findings were negative in all of the controls, except in the case of one 29 year old female who was scored + for cerebral cortex atrophy.
The MRI findings of the T1-weighted studies are shown in Table I. Atrophy of the cervical cord was present in all eleven FD patients: severe in one case, moderate in three and slight in the others. The reduced anteroposterior diameter of the spinal cord was evident in the axial images. Nine patients showed slight cerebellar atrophy, with the superior vermis always involved and the hemispheres in six cases. Brainstem atrophy was present in six patients with the medulla ablongata being the most frequently involved (five cases). The fourth ventricle was enlarged in five patients and the middle cerebellar peduncles were atrophic in four (Fig. 1) Three patients had supratentorial atrophy, consisting of cortical atrophy in two cases and lateral ventricle enlargement in one. All LOFD patients showed slight cervical cord atrophy, which was associated with cerebellar atrophy in two cases (Fig. 2). Eight of the EOCA patients showed cerebellar vermis atrophy, associated with hemisphere atrophy in six cases. In two patients cerebellar involvement was marked. The middle cerebellar peduncles were atrophic in three patients, the brainstem in two and the cervical cord in three (Fig. 3).
The T2-weighted images showed increased signal intensity of the posterior columns in all four of the FD or LOFD examined (Nos. 7, 10, 11, 13; Fig. 4), and a small frontal vascular lesion in one LOFD patient (No. 12).
Finally, we investigated the relationship of disease duration and severity (IAPS Stage) with the global atrophy scores of the cerebellum (hemis-

TABLE I. *MRI findings.*

Patient	Sex	Age	Disease duration	IAPS Stage	Degree of atrophy										
					Supra tentorial	Infratentorial									Cervical Cord
						CH	SV	MV	IV	MCP	MB	PO	FV	MO	
Friedreich's disease															
1	M	34	28	4	–	+	+	–	–	+	–	–	–	–	+
2	F	19	15	4	–	–	–	–	–	–	–	–	+	–	+ +
3	F	34	26	4	+	+	+	–	+	+ +	+	+	+ +	+ +	+ + +
4	F	42	24	4	–	–	+	+	–	–	–	–	–	–	+
5	F	28	15	4	–	–	+	–	+	–	–	–	+	+	+
6	F	23	10	3	+	+	+	+	+	–	+	–	+	+	+
7	M	24	11	3	–	–	+	+	–	–	–	+	–	+	+ +
8	M	36	22	4	–	+	+	+	+	–	–	+	–	–	+
9	F	21	11	4	–	+	+	–	–	+	–	+	+	+	+ +
10	F	26	13	4	+	+	+	+	+	+ +	–	–	–	–	+
11	F	11	1	2	–	–	–	–	–	–	–	–	–	–	+
Late onset Friedreich's disease															
12	F	45	19	3	–	–	–	–	–	–	–	–	–	–	+
13	M	35	5	2	–	–	–	–	–	–	–	–	–	–	+
14	F	33	3	2	–	–	–	–	–	–	–	–	–	–	+
15	F	35	7	3	–	+ +	+ +	+ +	+	+	–	–	+	–	+
16	M	42	10	2	–	–	+	+	–	–	–	–	–	–	+
Early onset cerebellar ataxia with retained tendon reflexes															
17	M	27	19	2	–	+	+ +	+	–	–	–	–	–	–	–
18	M	24	12	2	–	–	+	+	+ +	+ +	+	+ +	+ +	+ + +	+ + +
19	F	24	6	3	–	–	–	–	–	–	–	–	–	–	+
20	F	49	46	3	+	+ +	+ + +	+ + +	+ + +	+	–	–	+ +	–	–
21	F	16	13	2	–	–	+	+	+	–	–	–	+	–	–
22	F	21	18	2	–	+	+	+	+	–	–	–	–	–	–
23	M	31	21	2	–	+	+	+	+	–	–	–	–	–	–
24	M	32	20	3	–	+ +	+ +	+ +	+ + +	+	–	–	+ +	–	–
25	M	22	16	2	–	–	–	–	–	–	–	+	–	–	–
26	M	24	14	2	–	+	+	+	+ +	–	–	–	+ +	–	+

IAPS = Inherited Ataxia Progression Scale, see Methods.
CH = cerebellar hemispheres; SV = superior vermis; MV = middle vermis; IV = inferior vermis; MCP = middle cerebellar peduncles; MB = midbrain; PO = pons; FV = fourth ventricle; MO = medulla oblongata.
+, + +, + + +: presence and relative severity of atrophy; –: absence of atrophy. Patients 5 - 6 and 13 - 14 are siblings.

pheres + vermis) and brainstem (midbrain + pons + medulla oblongata). The cerebellar global atrophy score was directly related to disease duration in EOCA ($r_s = 0.77$; $p < 0.05$), but not in FD + LOFD ($r_s = 0.20$). There was a trend towards a positive correlation between cerebellar atrophy and IAPS in both FD + LOFD ($r_s = 0.49$) and EOCA ($r_s = 0.42$). No significant correlation was found for brainstem atrophy. The clinical features, such as corticospinal involvement and dysphagia, were not related to any particular MRI pattern in EOCA.

Discussion

The most relevant central nervous system pathological finding in FD is atrophy of the long ascending and descending spinal tracts (the dorsal columns, the direct and indirect spinocerebellar tracts and the pyramidal tracts). Despite compensatory gliosis there is always shrinkage in the cross-section of the cord. Atrophy or degeneration of gracile and cuneate nuclei, as well as of other lower brainstem nuclei have been frequently reported and a loss of Purkinje cells in the superior folia of the cerebellum, atrophy of the nucleus dentatus and the superior and middle cerebellar peduncles, together with atrophy and degeneration of other fiber systems and nuclei have sometimes been described. A loss of Betz cells has also been reported [8, 12]. To our knowledge, there are no post mortem studies of LOFD.

There are four pathological reports of patients with a possible diagnosis of EOCA [4, 7, 11]: all of the patients showed cerebellar atrophy, and two had additional degeneration of the brainstem and a small spinal cord suggesting olivopontocerebellar atrophy. However, some of the studies are incomplete and the two cases described by Nonne had optic atrophy and mental impairment, which

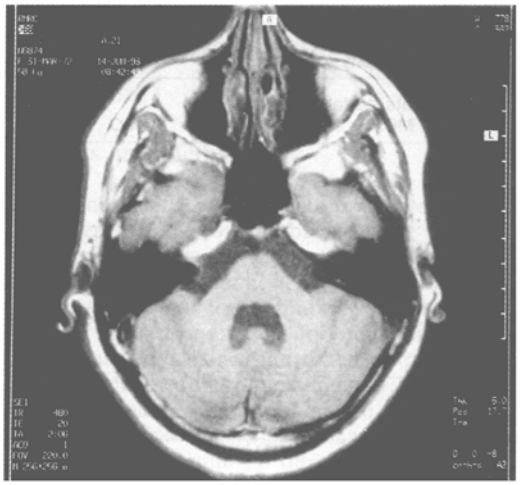

Fig. 1. *Axial T1-weighted spin-echo sequence (1 T) at the level of the middle cerebellar peduncles in an FD patient (No. 9) showing a slight enlargement of the fourth ventricle and atrophy of the pons and the middle cerebellar peduncles.*

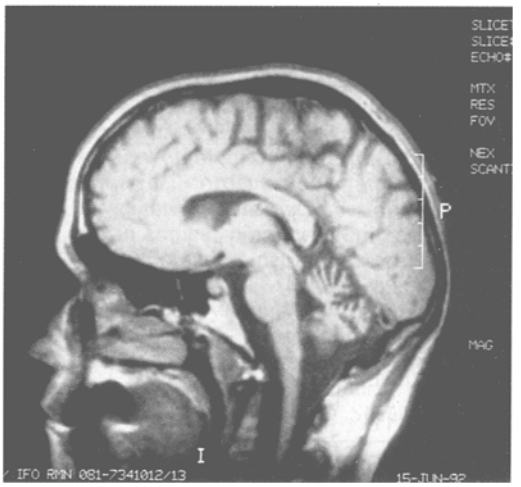

Fig. 2. *T1-weighted spin-echo sequence (0.5 T) in the middle sagittal plane in an LOFD patient (No. 15) showing moderate vermian atrophy and slight fourth ventricle enlargement.*

are unusual clinical features [11].

Our MRI study revealed constant atrophy of the cervical spinal cord in FD. We often found atrophy of the cerebellum, and sometimes of the brainstem and the middle cerebellar peduncles. In a recent study of seven FD patients, Wüllner et al. [15] reported constant cervical cord atrophy, rarely associated with an enlargement of the fourth ventricle and atrophy of the medulla oblongata, middle cerebellar peduncles and pons; cerebellar measurements were always in the normal range. Our different methodological approach accounts for the higher occurrence of cerebellum and brainstem atrophy in the present study: Wüllner et al. adopted a statistical approach using computerized measurements of the regions of interest,

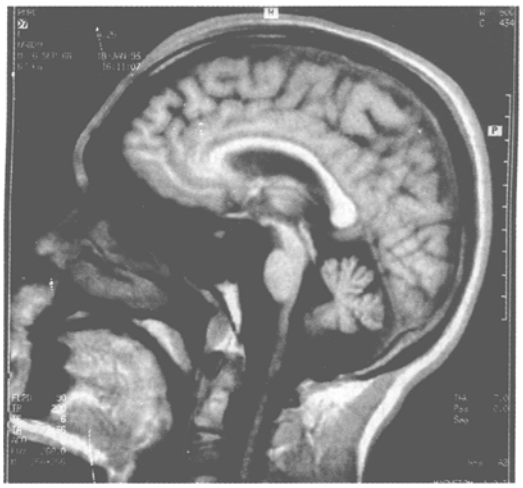

Fig. 3. *T1-weighted gradient-echo sequence (1 T) in the middle sagittal plane in an EOCA patient (No. 18) showing vermis, brainstem and spinal cord atrophy.*

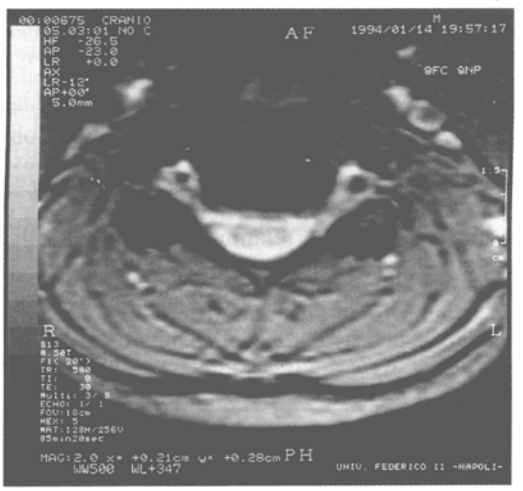

Fig. 4. *Axial T2-weighted gradient-echo sequence (0.5 T) at the level of the middle cervical cord in an FD patient (No. 11) showing the reduced antero-posterior diameter of the cord and the increased signal of the posterior columns.*

considering values that were 2 SD away from normal control values as abnormal; our method was based on subjective evaluation and may detect even slight atrophic changes. Our results showing atrophy of the cerebellum, brainstem and middle cerebellar peduncles are consistent with the pathological findings in FD [8, 12].

The MRI pattern in LOFD patients is similar to that of FD patients but, although the number of our patients was small, cerebellum and brainstem atrophy appeared to be rarer in LOFD.

Recently, Mascalchi et al. [10] used MRI to study the cervical cord and found cord atrophy and abnormal signals in the posterior or lateral columns of nine out ten patients; we found increased intensity in the T2-weighted images of the posterior columns in both FD and LOFD patients.

The frequency of spinal and bulbar atrophy is lower in EOCA than in FD; that of cerebellar atrophy is similar, but its severity is more marked in EOCA. Pure cerebellar atrophy was found in four cases; in a further four patients, cerebellar atrophy was associated with atrophy of the middle cerebellar peduncles and/or the brainstem and/or the spinal cord. This suggests olivopontocerebellar atrophy, a pattern often found in autosomal dominant and sporadic cerebellar ataxias of adult onset. However, in these forms, brainstem atrophy is usually more marked and the pontine transverse fibers show abnormal signal intensity [13]. The frequency of the findings in our EOCA patients is the same as that found by Wüllner et al. [15], except for the higher frequency of cerebellar hemisphere atrophy in our study (60% vs 18%).

The clinical features of the EOCA patients were not related to the pattern of atrophy, but the degree of cerebellar atrophy was directly related to disease duration.

Differential diagnosis between FD and EOCA is mainly based upon clinical features, although neurophysiological and molecular genetic studies may be useful in doubtful cases. In our experience, the absence of cervical cord atrophy and the presence of marked cerebellar atrophy may help to exclude a diagnosis of FD.

However, MRI findings in EOCA are heterogeneous and sometimes no different from those found in FD.

Sommario

La Risonanza Magnetica permette lo studio morfologico "in vivo" dell'encefalo e del midollo spinale nei pazienti con atassia ereditaria. Noi abbiamo eseguito uno studio con immagini T1- e T2-pesate in 11 pazienti con Malattia di Freidreich (MF), 5 con MF ad esordio tardivo e 10 con atassia cerebellare ad esordio precoce con conservazione dei riflessi osteotendinei (Early Onset Cerebellar Ataxia with retained tendon reflexes, EOCA).

L'atrofia del midollo cervicale era costante in MF ed MF ad esordio tardivo, spesso in associazione con atrofia cerebellare e del tronco. Le immagini T2-pesate mostravano degenerazione dei cordoni posteriori nel midollo cervicale.

In EOCA il reperto più frequente era l'atrofia cerebellare, pura od in associazione con atrofia del midollo cervicale o del tronco. L'atrofia cerebellare in EOCA era marcata in pochi casi ed era correlata con la durata di malattia.

References

[1] Bradac G.B., Riva A., Mortara P., Orsi L., Riccio A.: *Primary progressive cerebellar ataxia.* Neuroradiology, 31: 16-18, 1989.

[2] Chamberlain S., Shaw J., Rowland A. et al.: *Mapping of mutation causing Friedreich's ataxia to human chromosome 9.* Nature, 334: 248-250, 1988.

[3] De Michele G., Filla A., Cavalcanti F. et al.: *Late onset Friedreich's disease: clinical features and mapping of mutation to FRDA locus.* J. Neurol. Neurosurg. Psychiatry, 57: 977-979, 1994.

[4] Fickler A.: *Klinische und pathologisch-anatomische Beiträge zu den Erkrankungen des Kleinhirns.* Deut. Zeit. Nervenheikunde, 41: 306-375, 1911.

[5] Filla A., De Michele G., Caruso G., Marconi R., Campanella G.: *Genetic data and natural history of Friedreich's disease: a study of 80 Italian patients.* J. Neurol., 237: 345-351, 1990.

[6] Filla A., De Michele G., Cavalcanti F. et al.: *Clinical and genetic heterogeneity in early onset cerebellar ataxia with retained tendon reflexes.* J. Neurol. Neurosurg. Psychiatry, 53: 667-670, 1990.

[7] Fraser D.: *Defect of the cerebellum occurring in a brother and sister.* Glasgow Med. J., 13: 199-210, 1880.

[8] Greenfield J.G.: *The spinocerebellar degenerations.* Oxford: Blackwell Scientific Publications, 21-31, 1954.

[9] Harding A.E.: *Classification of the hereditary ataxias and paraplegias.* Lancet, i: 1151-1155, 1983.

[10] Mascalchi M., Salvi F., Piacentini S., Bartolozzi C.: *Friedreich ataxia. MR findings involv-*

ing the cervical portion of the spinal cord. Am. J. Roentgenol., 163: 187-191, 1994.
[11] NONNE M.: *Über eine eigenthümliche familiäre Erkrankungsform des Zentralnervensystem.* Arch. Psychiatr. Nervenkr., 22: 283-316, 1891.
[12] OPPENHEIMER D.R.: *Brain lesions in Friedreich's ataxia.* Can. J. Neurol., Sci., 6: 173-176, 1979.
[13] SAVOIARDO M., STRADA L., GIROTTI F. et al.: *Olivopontocerebellar atrophy: MR diagnosis and relationship to multisystem atrophy.* Radiology, 174: 693-696, 1990.
[14] WESSEL K., SCHROTH G., WIENER H.C., MÜLLER-FORELL W., DICHGANS J.: *Significance of MRI-confirmed atrophy of the cranial spinal cord in Friedreich's ataxia.* Eur. Arch. Psychiatry Neurol. Sci., 238: 225-230, 1988.
[15] WÜLLNER U., KLOCKGETHER T., PETERSEN D., NAEGELE T., DICHGANS J.: *Magnetic resonance imaging in hereditary and idiopathic ataxia.* Neurology, 43: 318-325, 1993.

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