

# Late-Onset Friedreich Ataxia

## Phenotypic Analysis, Magnetic Resonance Imaging Findings, and Review of the Literature

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**Background:** Friedreich ataxia (FA), the most common hereditary ataxia, is caused by pathological expansion of GAA repeats in the first intron of the X25 gene on chromosome 9. Since the discovery of the gene, atypical features are increasingly recognized in individuals with FA, and up to 25% of patients with recessive or sporadic ataxia do not fulfill the Harding or Quebec Cooperative Study on Friedreich's Ataxia criteria for FA. Late-onset FA (LOFA) is defined as onset after age 25 years.

**Objectives:** To describe and further delineate the clinical and magnetic resonance imaging findings in patients with LOFA and to review the literature.

**Design:** Clinical evaluation and comparison of clinical data and investigations.

**Setting:** Ataxia clinics at UCLA and Cedars-Sinai Medical Center.

**Patients:** Thirteen patients with LOFA with 13 sex-matched and Inherited Ataxia Progression Scale–matched patients with typical FA.

**Results:** Gait and limb ataxias were seen in all the participants. Dysarthria, loss of vibration sense, and abnormal eye movements were also common in both groups. Patients with LOFA more often had lower limb spasticity (40% vs 0%;  $\chi^2=4.0$ ;  $P=.04$ ) and retained reflexes (46.1% vs 7.7%;  $\chi^2=3.46$ ;  $P=.05$ ). They had no complaint of sphincter disturbances, and there was no evidence of cardiomyopathy on echocardiograms ( $\chi^2=4.0$ ;  $P=.04$ ). Five of 9 patients with LOFA had cerebellar atrophy on neuroimaging.

**Conclusions:** Patients with gait and limb ataxias, dysarthria, loss of vibration sense, and fixational instability after age 25 years should be considered for molecular testing for GAA expansion in the FA gene. In contrast to previous studies, cerebellar vermian atrophy is not an uncommon finding.

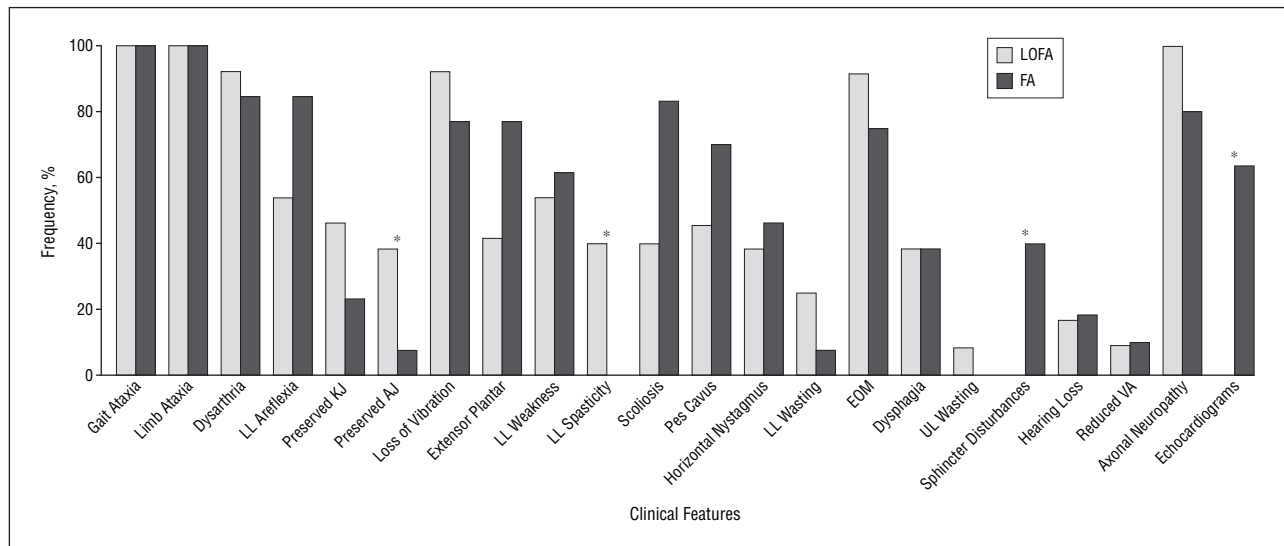
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**F**RIEDREICH ATAXIA (FA) IS THE most common hereditary ataxia, with an estimated prevalence of 1 in 50 000 population in central Europe.<sup>1</sup> Strict diagnostic criteria have been proposed by the Quebec Cooperative Study on Friedreich's Ataxia<sup>2</sup> and by Harding<sup>3</sup> to define a homogeneous group of patients. The Quebec Cooperative Study criteria established that true Friedreich disease must always begin before the end of puberty and at the latest before age 20 years.<sup>2</sup> Harding<sup>3</sup> considered onset before 25 years of age as an essential diagnostic criterion. However, since the discovery of the FA gene,<sup>4</sup> the phenotypic spectrum of FA seems to be wider than defined by both criteria, and up to 25% of patients do not fulfill the Harding or Quebec Cooperative Study criteria for FA.<sup>2,3,5,6</sup> These atypical features include late-onset forms,<sup>7</sup> forms with retained tendon reflexes,<sup>8</sup> and Acadian FA,<sup>9</sup>

which are all caused by mutations in the X25 gene. Late-onset FA (LOFA) is defined as onset after age 25 years. These patients tend to have an overall milder, slowly evolving disease associated with smaller GAA expansion.<sup>10</sup> The time from disease onset to wheelchair confinement was also slower in patients with LOFA.<sup>7</sup> Compared with patients with typical FA, those with LOFA also have fewer skeletal abnormalities.<sup>11</sup> The frequency of cardiomyopathy in LOFA was found to be similar to that in typical FA in some studies<sup>7,12</sup> but significantly lower in others.<sup>13</sup> We investigated the genetic, clinical, and laboratory findings in 13 patients with LOFA and in 13 sex-matched and Inherited Ataxia Progression Scale (IAPS)–matched patients with typical FA to identify common clinical features shared between patients with typical FA and LOFA that would suggest the presence of a frataxin mutation in patients with late-onset ataxia.



**Figure 1.** Frequency of various clinical features in patients with typical Friedreich ataxia (FA) vs those with late-onset FA (LOFA). Asterisk indicates  $P < .05$ ; LL, lower limb; KJ, knee jerk; AJ, ankle jerk; EOM, extraocular movement; UL, upper limb; and VA, visual acuity.

## METHODS

Clinical data from 13 patients with LOFA (6 men and 7 women) from 13 families were compared with those from 13 patients with typical FA matched for sex and IAPS stage. All the patients were retrospectively identified. Patients with typical FA (age at onset  $< 25$  years) were selected from our database of 155 patients with typical FA. Only patients who had undergone neuroimaging were selected for matching. All the patients were homozygous for GAA expansion in the first intron of the X25 gene, and age at onset was known for all. Age at onset was defined as the date that the patient or relatives noticed the first appearance of symptoms such as gait or limb ataxia. Skeletal deformities were not considered in onset of symptoms because it is difficult to establish the exact time of presentation. The smaller and larger in each pair of alleles were identified as GAA1 and GAA2, respectively.

Severity of disease was rated according to the IAPS<sup>7</sup>: stage 1, asymptomatic affected sibling; stage 2, symptoms present but mild; stage 3, patient needs constant care and cannot work; and stage 4, patient confined to a wheelchair. Patients in the control group were selected from individuals who were homozygous for the expanded GAA sequence, but age at onset was younger than 25 years. In addition, each control subject was matched to a patient with LOFA by sex and IAPS stage in pairs. Magnetic resonance imaging was performed using a 1.5-T system (Magnetom; Siemens, Erlangen, Germany). In addition to detailed clinical evaluations, nerve conduction studies, echocardiography, and fasting blood glucose measurements were performed using standard laboratory procedures. Sural nerve biopsy was performed in 1 patient with LOFA. The shareware program Stata (www.stata.com; StataCorp LP, College Station, Tex) was used to perform statistical tests using the paired  $t$  test. The occurrence of features was analyzed using the  $\chi^2$  test. All  $P \leq .05$ , adjusted for multiple comparisons, are reported.

## RESULTS

The 6 men and 7 women with LOFA (from 13 families) had a mean  $\pm$  SD age at onset of  $28.8 \pm 6.4$  years (range, 25.5-48.0 years) and a mean  $\pm$  SD current age of  $50.3 \pm 10.1$  years (range, 32-65 years). One patient developed the disease at

age 48 years, consistent with very LOFA. Six patients were in IAPS stage 2, 3 were in IAPS stage 3, and 4 were in IAPS stage 4. Patients with LOFA had significantly smaller GAA1 alleles compared with patients with typical FA (mean  $\pm$  SD,  $176 \pm 135$  vs  $490 \pm 52$ ;  $P = .03$ ). However, the mean  $\pm$  SD size of the GAA2 allele was not different between patients with LOFA ( $685 \pm 179$ ) and those with typical FA ( $755 \pm 315$ ). Mean  $\pm$  SD disease durations in patients with LOFA ( $18.5 \pm 9.7$  years; range, 2-36 years) and typical FA ( $16.0 \pm 9.1$  years; range, 3-30 years) are also similar. **Figure 1** shows the frequency of various clinical and laboratory findings in patients with LOFA compared with those with typical FA matched for sex and IAPS stage.

The most frequent presenting symptoms in both groups were gait and limb ataxias (100% in both groups), followed by dysarthria (85% in the FA group and 92% in the LOFA group). Patients in both groups also had frequent loss of vibration sense (77% and 92%) and abnormal extraocular movements, particularly fixational instability (75% and 92%). Patients with LOFA more often had lower limb spasticity ( $\chi^2 = 4.0$ ;  $P = .04$ ) and retained reflexes ( $\chi^2 = 3.46$ ;  $P = .06$ ) and less often had sphincter disturbances ( $\chi^2 = 4.0$ ;  $P = .04$ ) and abnormal echocardiographic findings.

Peripheral nerve sensory conduction velocities were abnormal in all 8 investigated patients with LOFA and in 4 of 5 tested patients with typical FA. The results indicate axonal sensory neuropathy in 7 of 8 patients with LOFA and in all tested patients with typical FA. One patient with LOFA underwent a sural nerve biopsy showing the absence of large myelinated fibers, prominent Schwann cell nuclear hyperplasia, numerous hypertrophic onion bulb formations, and increased internodal length variability consistent with demyelinating neuropathy. Fiber teasing revealed approximately 70 thinly myelinated fibers. There was no evidence of axonal or wallerian degeneration in this patient. One patient with typical FA had normal nerve conduction study findings 7 years after the onset of symptoms and was in IAPS stage 2.

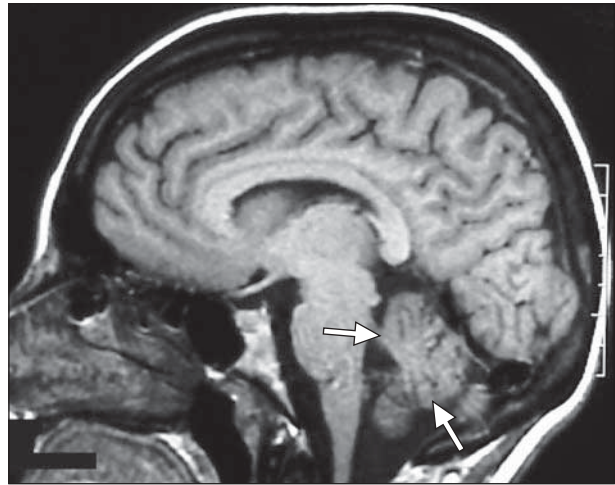
Four patients with LOFA had lower limb spasticity, whereas no spasticity was observed in patients with typical FA. Of these 4 patients with LOFA and lower limb spasticity, 3 had retained ankle reflexes. No patients with LOFA complained of urinary incontinence, even in the group with IAPS stage 4 (maximum disease duration of 27 years), whereas this symptom was observed in 4 patients with typical FA (maximum disease duration of 30 years). The echocardiographic examination of 11 of 13 patients with typical FA demonstrated abnormal concentric left ventricular hypertrophy in 7 patients. This was in contrast to the 5 tested patients with LOFA, in whom no abnormalities or cardiac symptoms were reported. Four patients with LOFA had scoliosis, in contrast to 10 patients with typical FA. Pes cavus was observed in 5 patients with LOFA and in 7 with typical FA. Magnetic resonance imaging showed atrophy of the cervical cord in all the patients with FA and LOFA. Furthermore, 5 of 9 investigated patients with LOFA demonstrated superior cerebellar vermian atrophy, and this was associated with hemispheric atrophy in 3 patients (**Figure 2**); conversely, this finding was reported in only 1 patient with FA.

#### COMMENT

Age at disease onset has traditionally been regarded as an essential criterion for the diagnosis of FA.<sup>2,3,14</sup> For the autosomal recessive–inherited ataxias, an age at onset older than 25 years would conventionally exclude the diagnosis of FA.<sup>3</sup> Since the discovery of the FA gene,<sup>15</sup> the FA phenotypes have expanded to include patients with late-onset disease (after age 25 years), retained reflexes, and Acadian phenotypes.<sup>10,12,16–20</sup> Furthermore, the size of the expanded repeat on GAA1 is inversely related to age at onset and disease severity in FA, whereas GAA2 size is a poor predictor of clinical variation.<sup>5,12,21–23</sup> Earlier age at onset, earlier age when confined to a wheelchair, a more rapid rate of disease progression, and the presence of nonneurologic manifestations, such as scoliosis,<sup>5</sup> cardiomyopathy,<sup>5</sup> and diabetes mellitus,<sup>24</sup> all showed the best correlation with the size of the smaller repeat (GAA1). Sequence variation in GAA repeat expansions may cause different phenotypes in FA, especially in late-onset cases.<sup>25</sup>

#### LOWER LIMB SPASTICITY AND RETAINED REFLEXES

A comparison of clinical and laboratory findings between patients with LOFA and typical FA showed an increased occurrence of lower limb spasticity and retained reflexes and a lower occurrence of abnormal echocardiographic findings and sphincter disturbances. Although the present study findings support previous findings<sup>13,18</sup> of a lower incidence of cardiomyopathy in patients with LOFA, other studies<sup>7,12</sup> reported a similar frequency of cardiomyopathy in both patient groups. In addition, the higher occurrence of spasticity and retained reflexes may suggest an overlap between LOFA and FA with retained reflexes. Coppola et al<sup>19</sup> reported



**Figure 2.** T1-weighted sagittal magnetic resonance image of a patient with late-onset Friedreich ataxia demonstrating atrophy of the cerebellum (arrows) in addition to cervical cord atrophy.

a similar finding of 11 patients with FA with retained reflexes with a mean age at onset of 26 years. Indeed, the presence of spasticity and the Babinski sign were observed in the same patients with LOFA, suggesting involvement of the pyramidal tract in these patients. One of our patients with LOFA still had preserved ankle reflexes after 22 years' disease duration. Advanced pyramidal involvement, supported by a loss of large pyramidal cells in the primary motor areas, is usually a late manifestation in FA, and spastic paraparesis has been reported in 1 patient at the onset age of 24 years and in 2 other patients at the very late onset ages of 49 and 53 years.<sup>26–28</sup> One of our patients with LOFA, who had a very late age at onset at 48 years, demonstrated preserved ankle jerks but had no spasticity. Spastic ataxia has been reported to be a presenting symptom of late-onset cases.<sup>29</sup> In our study, patients with LOFA had fewer skeletal deformities, although the difference did not achieve statistical significance. However, the severity of scoliosis was milder in patients with LOFA compared with those with typical FA with a matched IAPS stage. The neurophysiologic study did not help differentiate patients with LOFA from those with typical FA.

#### CEREBELLAR ATROPHY

Cerebellar atrophy is not a characteristic finding of FA.<sup>30</sup> Pathologically, the cerebellar cortex shows only mild loss of Purkinje cells and occasional axonal torpedoes, in contrast to the deep cerebellar nuclei, where cerebellar efferents originate, which are severely affected.<sup>30</sup> Radiologically, the magnetic resonance imaging pattern in patients with LOFA is similar to that in patients with FA showing significant cervical cord atrophy.<sup>17,31–33</sup> The size of the brainstem and cerebellum was reported to be in the lower reference range, and mild atrophy of the vermis and medulla was observed only in advanced cases in both patient groups.<sup>31,34</sup> Junck et al<sup>35</sup> reported mild generalized cerebral atrophy in patients with FA who met the diagnostic criteria of Harding that correlated with the clinical severity. In the present study, however, 5 of 9

**Table. Summary of Reported Studies of Late-Onset and Very Late-Onset Friedreich Ataxia**

Feature	Present Study (n = 13)	De Michele et al <sup>7</sup> (n = 22)	Montermini et al <sup>12</sup> (n = 8)	Gellera et al <sup>18</sup> (n = 6)	Coppola et al <sup>19</sup> (n = 6)	Klockgether et al <sup>17</sup> (n = 3)	Ragno et al <sup>10</sup> (n = 3)
Age at onset, range, y	25.5-48	21-36*	29-44	34-48	26-45	28-31	38-45
Disease duration, range, y	12-36	1-26	10-27	8-27	8-19	0.6-30	NA
Gait ataxia, %	100	100	NA	100	100	100	100
Limb ataxia, %	100	91	NA	100	100	100	100
Dysarthria, %	92	82	NA	100	100	100	100
Lower limb areflexia, %	54	100	NA	100	0	100	0
Preserved KJ, %	46	0	NA	0	100	0	100
Preserved AJ, %	38	0	NA	0	100	0	100
Loss of vibration sense, %	92	91	NA	100	50	100	67
Extensor plantar response, %	42	55	NA	100	50	67	100
Lower limb weakness, %	54	50	NA	NA	33	33	67
Lower limb spasticity, %	40	NA	NA	NA	NA	33	33
Scoliosis, %	40	55	NA	67	83	NA	100
Pes cavus, %	45	45	NA	NA	33	0	NA
Horizontal nystagmus, %	38	32	NA	NA	NA	33	NA
Abnormal EOM, %	92	NA	NA	NA	NA	100	NA
Lower limb wasting, %	25	23	NA	NA	0	0	NA
Upper limb wasting, %	8	NA	NA	NA	NA	0	NA
Sphincter disturbances, %	0	NA	NA	NA	NA	NA	NA
Hearing loss, %	17	NA	0	0	NA	NA	NA
Reduced visual acuity, %	9	NA	0 (OA)	0 (OA)	NA	NA	NA
Neuropathy, %	100	NA	NA	100	NA	NA	NA
Abnormal echocardiogram findings, %	0	14	57 (CM)	0 (CM)	0	NA	NA
Abnormal neuroimaging findings, %	62	10	NA	NA	NA	NA	NA

Abbreviations: AJ, ankle jerk; CM, reported as the presence of cardiomyopathy; EOM, extraocular movement; KJ, knee jerk; NA, not available; OA, reported as the presence of optic atrophy.

\*De Michele et al<sup>7</sup> defined late-onset Friedreich ataxia as onset after age 20 years.

investigated patients with LOFA had cerebellar atrophy on neuroimaging, in contrast to only 1 patient with typical FA. Of these 5 patients with LOFA, 2 each were in IAPS stages 3 and 4 and 1 was in IAPS stage 2, with a disease duration of more than 10 years in all affected patients. Of the patients with LOFA, the superior vermis rather than the cerebellar hemispheres were particularly affected. De Michele et al<sup>32</sup> reported a similar finding in 1 of 5 patients with LOFA demonstrating moderate atrophy in the superior middle vermis and in both cerebellar hemispheres in addition to cervical cord atrophy. In summary, cerebellar atrophy was not an uncommon finding in our series, in contrast to previously described patients with LOFA.

### COMMON CLINICAL FEATURES

The clinical presentations of patients with FA and LOFA were similar regarding gait and limb ataxias. In addition, dysarthria, loss of vibration sense, and abnormal extraocular movements (particularly fixational instability) were common in both patient groups. Our typical patients with FA closely matched the characteristics of previously reported series.<sup>2,3,12</sup> The frequency of other clinical manifestations, including the presence of knee jerk, extensor plantar response, lower limb weakness, wasting of upper and lower limb muscles, dysphagia, hearing loss, and reduced visual acuity, did not significantly differ. Our patients with LOFA had an overall milder disease, although we cannot compare the severity of dis-

ease between patient groups because we selected matched IAPS patients with FA as controls. However, none of our patients with LOFA had abnormal echocardiographic findings. Previous studies<sup>12</sup> suggested that the presence of cardiomyopathy correlated with disease severity, judged by earlier age at onset and age when confined to a wheelchair in patients with cardiomyopathy. The incidence of reduced visual acuity and hearing loss was small in both our patient groups and probably reflected disease progression. Similar to all previous observations,<sup>1,5,12,24</sup> our patients with LOFA had significantly smaller GAA1 length than patients with typical FA (mean, 176 vs 490). However, the length of the GAA1 repeats in our patients with LOFA ranged from 69 to 410. The smallest symptomatic expansion described in the literature to date involved 66 repeats.<sup>1</sup> Normal chromosomes bear fewer than 40 to 42 triplets, whereas FA chromosomes usually contain approximately 70 to more than 1000 triplets, most commonly 600 to 900.<sup>36</sup> We observe that the minimal length of GAA1 repeats in our patients with LOFA is much lower than those in previous studies, which were reported to be 120 to 500 repeats.<sup>10,16</sup> The **Table** summarizes the frequency of clinical manifestations in our study compared with previously published studies.

Identification of the FA gene has expanded the Friedreich disease phenotype and has proved that atypical cases, including LOFA and FA with retained reflexes, are also caused by the same mutation. Although patients with LOFA have more frequent spasticity and retained reflexes, common features, including gait and limb ataxias, dysarthria,

loss of vibration sense, and fixational instability, are the same in both patient groups. Furthermore, cerebellar atrophy, particularly of the superior vermician structures, was observed in patients with LOFA more frequently than previously reported. Owing to advances in molecular genetics and expanded phenotypes in FA, we suggest that patients with the common features of gait and limb ataxias, dysarthria, loss of vibration sense, and fixational instability should be considered for FA testing.

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