Central nervous system involvement in Anderson–Fabry disease: a clinical and MRI retrospective study

S Buechner,1 M Moretti,2 A P Burlina,3 G Cei,4 R Manara,5 R Ricci,6 R Mignani,7 R Parini,8 R Di Vito,9 G P Giordano,2 P Simonelli,2 G Siciliano,4 W Borsini2

ABSTRACT

Background: Anderson–Fabry disease (AFD) is an X-linked lysosomal storage disorder caused by deficiency of alpha-galactosidase A. Central nervous system (CNS) manifestations consist mainly of cerebrovascular events. Brain MRI results are often abnormal.

Purpose: The aim of the study was to describe CNS involvement in a group of Italian patients with AFD.

Methods: Clinical and brain MRI data of 43 patients with AFD (25 men, 41.94 ± 10.83 years old and 18 women, 52.48 ± 17.50 years old) were analysed retrospectively. 17 male patients and 7 female patients were under treatment with enzyme replacement therapy (ERT).

Results: All 43 patients had signs or symptoms of AFD. 16 men (64%) and 13 women (72%) demonstrated CNS involvement, although with varying severity. Overall, 6 men and 5 women had suffered from cerebrovascular accidents with an age at onset of 33.64 ± 13.65 years and 53.68 ± 11.71 years, respectively. Brain MR images were abnormal in 16/25 men and in 13/16 women. During CNS monitoring, some patients receiving ERT (5/17 men and 2/6 women) demonstrated neurological deterioration, especially those who had presented with cerebrovascular disease already before starting ERT.

Conclusions: The study demonstrated a high frequency of CNS involvement in homozygous and heterozygous AFD patients, often characterised by early age at onset and abnormal brain MRIs. At present, ERT is widely used; however, potential beneficent effects may be disguised by the progression of irreversible pathology in short-term follow-up. Therefore, primary and secondary prophylaxes of cerebrovascular disease are extremely important.

PURPOSE

The aim of the present study was to describe clinical and MRI features of CNS involvement in a group of Italian patients with AFD who performed periodical neurological evaluations at the Departments of Neurological Sciences within their multiorgan monitoring.

PATIENTS AND METHODS

Patients

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Florence, and informed consent was obtained from all participating subjects.

A total of 43 patients with AFD (25 men, 41.94 ± 10.83 years old and 18 women, 52.48 ± 17.50 years old) referring to several Italian Hospitals (Florence, Milan/Monza, Rimini, Pisa, Livorno, Ortona, Padova, Chieti and Rome) attended, periodically, neurological visits at the Departments of Neurological Sciences of the Universities of Florence, Pisa and Padova; their multiorgan monitoring was independent of the presence or not of neurological problems. A total of 24/43 patients with AFD (17 men and 7 women) were under treatment with ERT (10 patients with ReplagalTM, 14 patients with Fabrazyme®), with a mean duration of 2.92 ± 1.06 years in the male patients and 2.18 ± 0.65 years in the female patients. The homozygous AFD patients had cerebral vasculopathy, including anatomical abnormalities (eg, small-vessel occlusive disease, and large-vessel ectasia and tortuosity), impairment of endothelial function13–15 and dysregulation of cerebral blood flow.14, 15 Gb3 storages within neurons,5 cerebrovascular risk factors16–18 and genetic factors19 might, additionally, increase the likelihood of developing cerebrovascular disease. Brain MRI results often altered in patients with AFD.7–10 In detail, neuroradiological findings include periventricular white matter signal intensity abnormalities and single or multiple lacunar infarcts (alterations typical of small-vessel disease), large ischaemic cerebral infarctions,7–10 12–20 and posterior thalamus involvement (the so-called pulvinar sign).21 Progress has been made in the treatment of AFD as a result of the introduction of enzyme replacement therapy (ERT) in June 2001 in Europe. ERT has been shown to markedly reduce the cellular storage deposition of Gb3 in vascular endothelial cells.22 However, the long-term clinical effects of ERT, especially on cerebrovascular disease, remain to be fully assessed.
started ERT at the age of 36.56±11.22 years, whereas the heterozygous AFD patients started at an advanced adult age (53.32±8.23 years). Eight men and 11 women were not on ERT: some of them had started treatment shortly after performing the present study (4 men and 5 women). Others (2 men and 2 women) had refused ERT due to personal reasons. In some cases, interruption of treatment was necessary either due to severe disability (1 man and 1 woman) or due to significant allergic reactions related to ERT (1 man). Finally, in 5 female patients, ERT was not indicated because of their very mild clinical AFD presentation.

Methods
Each visit included a short history-taking with registration of cerebrovascular risk factors and current pharmacological treatment, neurological examination and brain MRI. In detail, the cerebrovascular risk factors included smoking of cigarettes, diabetes mellitus, arterial hypertension, atrial fibrillation and hyperlipidaemia. Furthermore, during each visit, the multiorgan character of AFD was evaluated, looking especially for renal and cardiac dysfunction. Cardiac dysfunction was classified in: 1) silent cardiomyopathy associated with abnormal electrocardiograph (EGC) and/or echocardiographic findings; and 2) symptomatic cardiomyopathy. The severity of renal dysfunction was measured by means of the glomerular filtration rate (GFR) (ie, chronic renal disease stage I with GFR = 60–100 ml/min, stage II with GFR = 40–59 ml/min, and stage III with GFR = <30 ml/min), which requires dialysis or renal transplant). Disability and life quality were measured by the Rankin scale and EuroQol questionnaire, respectively. Finally, 20 male patients with AFD and 15 female patients with AFD had received more than one neurological evaluation, with a mean duration of neurological monitoring of 3.58±3.42 years and 3.89±3.12 years, respectively.

From 41/43 patients with AFD, brain MR T1-weighted (repetition time [TR]/echo time [TE] 600/25 milliseconds, matrix 256×256), proton density/T2-weighted (TR/TEI/TE2 4,500/15/100 milliseconds, matrix 256×256) and fluid-attenuated inversion recovery (FLAIR)-weighted (TR/TE 9,000/108 milliseconds, slice thickness 6 mm, matrix 512×448) images were available. Only two female patients had not received brain MRI due to claustrophobia. All MR images were available. Only two female patients had not received ERT due to personal reasons. In some cases, interruption of treatment was necessary either due to severe disability (1 man and 1 woman) or due to significant allergic reactions related to ERT (1 man). Finally, in 5 female patients, ERT was not indicated because of their very mild clinical AFD presentation.

RESULTS
AFD-related clinical manifestations (excluding CNS signs and symptoms)
All 45 patients had signs or symptoms of AFD (data not shown) and even the youngest patients (a 19-year-old female patient and a 21-year-old male patient) had disease manifestations in at least one organ. In 24/25 male patients with AFD and in 11/18 female patients with AFD, multiple organs were involved. Only one male patient demonstrated single organ involvement, namely of the heart. The most frequently observed AFD manifestation by our male patients was angiookeratoma (88%) and cornea verticillata by our female patients (72%). A total of 18/25 men (72%) gave a current or previous history of painful acroparesthesias, whereas only 5/18 women (28%) of our patients reported neuropathic pain. However, in most male patients, the acroparesthesias were mild or moderate and occurred only with fever and physical exercise. Indeed, only a few male patients (17%) needed continuous analgesic medication.

Cardiac involvement, including ECG and echocardiographic abnormalities, as well as symptomatic cardiomyopathy, was observed in 68% of men with AFD and 39% of women with AFD. Renal dysfunction was reported in 76% of men and 28% of women. However, end-stage renal failure (ie, chronic renal insufficiency stage V) occurred only in male patients with AFD (3 on dialysis and 8 with renal transplants). Thus, the number of involved organs, as well as the involvement’s severity, were higher in the male heterozygous patients than in the female heterozygous patients. Reduced life quality (EuroQol >3) was observed in 4/25 men and 4/18 women and moderate-severe disability (Rankin scale >2) in 9/25 men and 4/18 women, both interfering with the patients’ daily activities (table 1).

CNS signs and symptoms
At least one neurological manifestation was reported in 16/25 (64%) male patients with AFD and 15/18 (72%) female patients with AFD (table 1). Overall, 5 men and 3 women had presented with TIA, followed in all cases by stroke. In total, 11 patients (6 men and 5 women) with AFD had suffered from stroke. Age at onset of cerebrovascular events was 53.64±13.65 years in men and 53.68±11.71 years in women. At that time, no patient had been on ERT. Isolated and often not well-defined central neurological manifestations such as diplopia, migraine/recurrent headache, vertigo and hearing loss were common findings in the examined Italian AFD group. Finally, 7 patients (5 men and 4 women) with AFD reported cognitive problems (from very mild amnestic deficits to moderate dementia). However, no patient had performed neuropsychological testing for its evaluation and quantification.

Brain MRI findings
Brain MR images results were abnormal in 16/25 males (64%) and 13/16 females (81%) (table 2). Multifocal leukoencephalopathy, in severe cases extended to the subcortical brain, was visible in all 29 abnormal neuroimages. One case of significant leukoencephalopathy is shown in figure 1. Leukoencephalopathy severity ≥2 of Fazekas’ scale occurred in 13/16 male homozygous patients with abnormal brain MR images (81%) and 10/15 female heterozygous patients with abnormal brain MR images (77%). Other common findings were given by lacunar ischaemic lesions located in the deep arterial territory, the basal ganglia and the brainstem, and cerebral atrophy (fig 2). Watershed infarctions were detected in two male patients (data not shown) and the so-called pulvinar
sign (ie, increased pulvinar signal intensity on T1-weighted MRI) in two other brain MRIs of male patients with AFD. Finally, only one brain MR image of a 74-year-old female showed the outcome of a haemorrhagic stroke in the cerebellum, which had occurred during treatment with oral anticoagulant therapy at the age of 68 years.

### Clinical and neuroimaging features of CNS involvement

Combining clinical and brain MRI findings together, we defined the cerebrovascular disease of AFD as: (1) symptomatic cerebrovascular disease characterised by cerebrovascular events; (2) minor neurological manifestations (eg, diplopia, vertigo, headache, hearing loss) associated with abnormal brain MRI findings; and (3) silent cerebrovascular disease characterised by abnormal brain MRI findings without any neurological clinical manifestation. In total, 16/25 (64%) male patients with AFD and 13/18 (72%) female patients with AFD presented with cerebrovascular involvement (table 3). All patients with TIA and/or stroke demonstrated abnormal brain MR images. In 14 patients (7 men and 7 women), minor neurological signs or symptoms were associated with brain MRI abnormalities. Finally, 4 (3 men and 1 women) patients with AFD presented with asymptomatic cerebrovascular disease.

Clinical and MRI features of the patients’ subgroup presenting with symptomatic cerebrovascular disease implied involvement of the vertebrobasilar and carotid area in the male patients (6/6 patients with clinical and brain MRI features of the vertebrobasilar area, 3/6 with clinical and 6/6 with brain MRI features of the carotid area) and mainly of the carotid area in the female patients (5/5 patients with clinical and brain MRI features of the carotid area, 1/5 with clinical and 2/5 with brain MRI features of the vertebrobasilar area) (data not shown).

### Cerebrovascular risk factors

The evaluation of common cerebrovascular risk factors in our AFD group (data not shown) detected smoking of cigarettes in only two male patients, and mild hyperlipidaemia in 7 patients (5 men and 2 women), whereas no patient suffered from diabetes mellitus. With increasing age, the frequency of arterial hypertension, cardiomyopathy and nephropathy tended to increase, especially in patients with cerebrovascular disease.

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#### Table 1 CNS involvement: clinical features of the 43 patients with Anderson–Fabry disease

<table>
<thead>
<tr>
<th></th>
<th>Male patients (n = 25)</th>
<th>Female patients (n = 18)</th>
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<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
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<tr>
<td>Age (mean ± SD)</td>
<td>41.94 ± 10.83 years</td>
<td>52.48 ± 17.50 years</td>
</tr>
<tr>
<td>Range of age</td>
<td>21–62 years</td>
<td>19–74 years</td>
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<tr>
<td>Most common CNS manifesta</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A) Total no. of patients with cerebrovascular events</td>
<td>6 (20%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>TIA</td>
<td>5 (20%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (24%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Age at onset (mean ± SD)</td>
<td>33.64 ± 13.65 yrs</td>
<td>53.68 ± 11.71 yrs</td>
</tr>
<tr>
<td>Recurrence</td>
<td>6 (24%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>First episode during ERT</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>B) Total number of patients with minor neurological manifestations</td>
<td>15 (60%)</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>5 (20%)</td>
<td>3 (17%)</td>
</tr>
<tr>
<td>Migraine/recurrent headache</td>
<td>5 (20%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>8 (32%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>9 (36%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Reported cognitive problems</td>
<td>3 (12%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Total percentage of patients with any kind of clinical CNS manifestation</td>
<td>16 (64%)</td>
<td>13 (72%)</td>
</tr>
<tr>
<td>Total percentage of patients without any kind of clinical CNS manifestation</td>
<td>9 (36%)</td>
<td>5 (28%)</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rankin scale ≥2</td>
<td>9 (36%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>EuroQol ≥3</td>
<td>4 (16%)</td>
<td>4 (22%)</td>
</tr>
</tbody>
</table>

CNS, central nervous system; ERT, enzyme replacement therapy; manifest., manifestations; No., number; SD, standard deviation; TIA, transitory ischaemic attack.

#### Figure 1

Brain MRI (Flair) of a 54-year-old female patient with AFD: Multifocal silent leukoencephalopathy.
However, no statistically significant relationship between these risk factors and CNS involvement was measured. Furthermore, all patients presenting with hyperlipidaemia and/or arterial hypertension obtained specific treatment with satisfactory results. Finally, all patients who had suffered from cerebrovascular events received acetylsalicylic acid or other antithrombotic agents.

Interestingly, some male patients demonstrated severe cerebrovascular disease (representing also their the clinical prominent manifestation of AFD) in the absence of any common cerebrovascular risk factor or significant alterations of the cerebral circulation, as demonstrated by Doppler ultrasound or angiography, and without meaningful cardiac or renal involvement. One example is given by a 56-year-old male patient who presented with TIA at the age of 27 years. By then, he had suffered only from very mild acroparesthesias and few angiokeratomas during adolescence. Subsequently, he developed a highly aggressive form of cerebrovascular disease presenting with a “multiple-sclerosis like” course due to recurrent strokes that progressively led to severe disability (pseudobulbar signs, tetraplegia, autonomic and cognitive deficits) and finally to death. Instead, other patients of our AFD group suffered from one or two ischaemic strokes followed by good clinical recovery. In a few cases, cerebrovascular events were clearly related to vascular risk factors and/or the late complications of AFD such as cardiomyopathy (eg, stroke secondary to atrial fibrillation on account of cardioembolic pathogenesis).

Clinical and neuroimaging course of CNS involvement

Finally, we analysed the clinical and neuroimaging behaviour during neurological monitoring in those patients presenting with two or more neurological visits and/or brain MR images (data not shown). New cerebrovascular events occurred in 1/3 male patients not receiving ERT (42.67 ± 15.78 years old) and 4/9 female patients not receiving ERT (42.95 ± 20.87 years old). Follow-up duration was 3.62 ± 2.33 years and 3.49 ± 2.53 years, respectively. Neurological deterioration occurred also in 5/17 men receiving ERT (57.27 ± 11.45 years old) and 2/6 women receiving ERT (55.26 ± 8.99 years old). Follow-up-duration was 2.25 ± 1.43 years and 1.41 ± 0.96 years, respectively. All latter patients with AFD on ERT had presented with symptomatic cerebrovascular disease already before starting treatment.

Brain MR images presented with new lesions in 1/3 male patients not receiving ERT (38.68 ± 7.30 years old) and 3/6 female patients not receiving ERT (44.49 ± 15.86 years old). Follow-up duration was 1.52 ± 1.91 years and 5.44 ± 4.36 years, respectively. Neuroradiological deterioration also occurred in 5/10 men receiving ERT (36.74 ± 9.11 years old) and 2/5 women receiving ERT (50.18 ± 5.06 years old). Follow-up duration was 1.41 ± 0.96 years and 1.62 ± 0.82 years, respectively. Again, nearly all those patients with AFD who were on ERT had presented with abnormal neuroimaging already before starting treatment (in 2/3 men and in both women).

DISCUSSION

One of the most important results of the present study is the high frequency of CNS involvement in the examined AFD population. Considering the presence of at least one CNS sign or symptom and/or abnormal brain MR image, the frequency was 64% in male patients and 72% in female patients. The high percentage in our heterozygous female patients is particularly interesting as it confirms the fact that AFD occurs in both genders.23–27 Certainly, our observed frequency of the cerebrovascular disease of AFD is higher than reported in the literature because our data derive from the inclusion of any kind of CNS involvement (ie, cerebrovascular events, minor neurological}

<table>
<thead>
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<th>Male patients</th>
<th>Female patients</th>
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<tr>
<td>Number of patients (%)</td>
<td>Number of patients (%)</td>
</tr>
<tr>
<td>Symptomatic cerebrovascular disease (ie, TIAs and strokes)</td>
<td>6 (24%)</td>
</tr>
<tr>
<td>Minor neurological manifestations with brain MRI abnormalities</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Silent cerebrovascular disease (ie, only abnormal brain MRI)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Total</td>
<td>16 (64%)</td>
</tr>
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TIA, transitory ischaemic attack.
manifestations and/or brain MRI abnormalities) and from a group of patients with AFD who had periodically undergone neurological visits at the Departments of Neurological Sciences. Studying the frequency of CNS involvement in such a “selected” group of patients with AFD might pose a risk for over-estimation; however, our patients underwent neurological visits within their routine multiorgan evaluation and not primarily because of having neurological problems. We are also aware of the fact that the observed higher frequency of CNS involvement in our women than in our men is not related only to AFD itself, but probably also to the higher age of the women. Indeed, it is well known that the frequency and severity of cerebral vasculopathy increases with age. Nonetheless, our study provides a detailed description of the clinical and MRI features of cerebrovascular disease in AFD and several of our findings are similar to those of other studies reported in the literature—for example, our calculated frequency of cerebrovascular accidents (about 24% in male and female patients) corresponds to the data of the cross-sectional studies of MacDermot and colleagues, which included 158 patients with AFD. The Fabry Outcome Survey (FOS) registry, including 366 patients, showed nearly the same frequency of cerebrovascular events in female patients as our data (27% vs. 28%). In addition, our finding regarding the young age at onset of cerebrovascular disease, especially in hemizygous AFD patients, is confirmed by numerous studies—for example, a cohort study of 43 men demonstrated a mean age at onset of 55.8 years; in the abovementioned FOS registry, mean age at onset was 28.8 years in male and 45.4 years in female patients, and in a prospective study about cryptogenic stroke it was 40 years in both genders. Finally, a high frequency of brain MRI abnormalities in patients with AFD is also reported in the FOS registry. In contrast, our findings regarding the affected vascular area in the cerebrovascular complications of AFD are different: although several studies in the literature documented a predominant involvement of the vertebrobasilar area, our clinical and neuroimaging findings were common in both vascular areas, carotid and vertebrobasilar. Interestingly, our female patients demonstrated even a predominant involvement of the carotid territory.

Our extended definition of the cerebrovascular disease of AFD includes silent CNS involvement because it is well known that leukoencephalopathy seems to be predictive for cerebrovascular events. The brain MR image in figure 1 confirms this statement: the MR image shows severe leukoencephalopathy in a 54-year-old woman with AFD who was asymptomatic at the time of neuroimaging acquisition and who had developed a minor stroke with left hemiparesis only 2 years later (fig 1).

Another finding of our study is the progression of CNS involvement in some of our patients while receiving ERT. In addition, studies reported in the literature evaluating the effect of ERT on clinical outcomes observed TIA's and strokes during the first years of ERT. Agalsidase alpha and beta, which are biweekly administrated by endovenous infusion, enter in the circulation but they do not cross the blood–brain barrier. Indeed, it is well known that the frequency and severity of cerebral vasculopathy increases with age. Nonetheless, our study provides a detailed description of the clinical and MRI features of cerebrovascular disease in AFD and several of our findings are similar to those of other studies reported in the literature—for example, our calculated frequency of cerebrovascular accidents (about 24% in male and female patients) corresponds to the data of the cross-sectional studies of MacDermot and colleagues, which included 158 patients with AFD. The Fabry Outcome Survey (FOS) registry, including 366 patients, showed nearly the same frequency of cerebrovascular events in female patients as our data (27% vs. 28%). In addition, our finding regarding the young age at onset of cerebrovascular disease, especially in hemizygous AFD patients, is confirmed by numerous studies—for example, a cohort study of 43 men demonstrated a mean age at onset of 55.8 years; in the abovementioned FOS registry, mean age at onset was 28.8 years in male and 45.4 years in female patients, and in a prospective study about cryptogenic stroke it was 40 years in both genders. Finally, a high frequency of brain MRI abnormalities in patients with AFD is also reported in the FOS registry. In contrast, our findings regarding the affected vascular area in the cerebrovascular complications of AFD are different: although several studies in the literature documented a predominant involvement of the vertebrobasilar area, our clinical and neuroimaging findings were common in both vascular areas, carotid and vertebrobasilar. Interestingly, our female patients demonstrated even a predominant involvement of the carotid territory.

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CONCLUSION

Cerebrovascular disease is common in patients with AFD, often characterised by early age at onset and abnormal brain MR images. CNS involvement affects both male and female patients, and sometimes it represents the most relevant and disabling clinical feature of AFD. Brain MRI is a sensitive tool that can detect asymptomatic cerebrovascular disease and it should therefore be included in monitoring in young adult patients with AFD. At present, ERT is widely used to prevent the pathological progression of AFD; however, potential beneficial effects on cerebral vasculopathy still remain to be assessed. In these patients, it is mandatory associating ERT with primary and secondary prophylaxes of cerebrovascular disease.

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