

# WHITE MATTER LESIONS IN FABRY DISEASE BEFORE AND AFTER ENZYME REPLACEMENT THERAPY

## A 2-year follow-up

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**ABSTRACT - Purpose:** To report the clinical and neuroimaging, central nervous system (CNS) findings of patients with Fabry disease (FD) during 24 months of enzyme replacement therapy (ERT) with agalsidase-alpha. **Method:** Eight patients were included. Six completed 24 months of ERT. Clinical and magnetic resonance imaging (MRI) data were obtained at 0, 12 and 24 months of ERT. White matter lesions (WML) were evaluated as well as their relation to age, symptoms and neurological examination (CNS score). **Results:** MRI was stable in 3 patients. WML and CNS score worsened in one patient, fluctuated in another, and improved in the sixth patient. In the whole series, there were 15 WML at baseline, and 19 at the 24<sup>th</sup> month. In two years, 4 lesions disappeared, whereas 8 appeared. **Conclusion:** A widespread pattern of silent WML in FD was seen. In two years, some WML appeared, and some disappeared. If these phenomena were related to the natural history, remains to be demonstrated.

**KEY WORDS:** Fabry disease, enzyme-replacement therapy, magnetic resonance imaging, alpha-galactosidase A, white matter lesion.

### Lesões da substância branca na doença de Fabry antes e depois da terapia de reposição enzimática : um seguimento de 2 anos

**RESUMO - Objetivo:** Relatar os achados neurológicos e de imagem do sistema nervoso central (SNC), observados durante 24 meses de tratamento de reposição enzimática (ERT) com agalsidase-alfa, em pacientes com a doença de Fabry (FD). **Método:** 8 pacientes foram incluídos; 6 completaram 24 meses de ERT. Os dados foram obtidos aos 0, 12 e 24 meses de ERT. Lesões de substância branca (WML) foram avaliadas assim como sua relação com a idade e o exame neurológico (escore SNC). **Resultados:** Os achados de ressonância nuclear magnética foram estáveis em 3 pacientes. As WML e o escore SNC pioraram em um caso; fluctuaram em um outro caso; e melhoraram no sexto paciente. No todo, havia 15 WML antes da ERT e 19 WML depois de 24 meses de ERT. Em dois anos, 4 lesões desapareceram e 8 novas surgiram. **Conclusões:** Viu-se um padrão difuso de WML assintomáticas, na FD. Em dois anos, algumas WML surgiram, enquanto outras desapareceram. Resta demonstrar se esses fenômenos fazem parte da história natural da doença.

**PALAVRAS-CHAVE:** doença de Fabry, terapia de reposição enzimática, ressonância nuclear magnética, alfa-galactosidase A, lesões de substância branca.

Fabry disease (FD) is an X-linked disorder resulting from a mutation of the  $\alpha$ -galactosidase A gene at Xq22. The gene defect causes a very low specific activity of the enzyme  $\alpha$ -galactosidase ( $\alpha$ -Gal A

(NM\_000169), which leads to a progressive lysosomal deposition of globotriaosylceramide (GL-3) in vascular endothelium and smooth muscle cells, myocardium, renal epithelium, and the central nervous sys-

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tem (CNS). In middle age, most males develop cardio or cerebrovascular disease, or both, mainly due to multifocal small vessel involvement<sup>1</sup>. Cranial T2 and fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) may show cerebral vasculopathy in the form of multiple hyperintense lesions, typically present in deep gray matter, brainstem, and deep white matter of the hemispheres supplied by the perforating arteries<sup>2-4</sup>.

Many studies show that enzyme replacement therapy (ERT) with human  $\alpha$ -Gal A safely reverses the pathogenesis of several major clinical manifestations, specially those due to renal, cardiovascular, peripheral nerve and hearing involvement<sup>5-8</sup>. The effect of ERT on CNS involvement is still not clear. We have previously reported the clinical and radiological CNS findings of 8 FD patients during their first 12 months of ERT with agalsidase-alpha<sup>9</sup>. MRI results in that study were either neutral or even negative. The most consistent finding of that study was an asymmetric, widespread pattern of deep white matter lesions (WML), hyperintense on T2 and FLAIR-weighted images, observed at baseline in 4 patients, and preceding consistent neurological findings. Those lesions showed a trend towards worsening in 12 months of follow-up, in spite of ERT. New WML had appeared in the left frontal lobes of two of eight patients. Although we did not know why ERT could not prevent the aggravating picture of WM, we speculated that without ERT the clinical picture of those two patients could have been worse.

These previous findings pointed to the need to follow the evolution of WML in FD in order to understand their clinical significance and their possible relation to ERT. The objectives of the present study were to extend the observation of CNS manifestations dur-

ing more time of ERT, and, more specifically, to give account of the disappearance of some WML in this time.

## METHOD

Eight FD patients (7 males, 1 female) from 4 families were included in an open-label protocol using agalsidase-alpha. Six patients completed 24 months of ERT; two patients voluntarily left the trial due to noncompliance. Diagnosis of FD was confirmed by demonstration of reduced activity of  $\alpha$ -galactosidase A in plasma or leukocytes. Mean age of the group at the beginning of the investigation was 32 years (range: 24-46 years). Clinical, biochemical and molecular characteristics of these patients have already been published<sup>9</sup>, and some data were shown in Table 1. The following investigations (described below) started immediately before inclusion of these individuals in the protocol with agalsidase-alpha, 0.2 mg/kg qo week, and continued at regular intervals during a period of 24 months. The only concomitant medication was carbamazepine, used to control acroparesthesias. There were no cases of hypertensive disorder, smoking, hyperlipidemia, or other chronic diseases. Throughout the 2 years of the study, patients did not present with any other neurological picture but a transient ischemic attack (TIA). No cases of multiple sclerosis or meningoencephalitis occurred. This study was approved by the Ethics Committee of the institution where it was conducted and informed consents were obtained from all patients.

A standard neurological examination (NE) was performed at regular intervals. NE, as previously reported<sup>9</sup>, generated a score which varied from zero (normal examination) to 100 (NE completely abnormal). For the purposes of the present analysis, we have only analyzed NE scores resulting from CNS involvement (NE CNS score; range: 0 to 85).

All MRI data were obtained with a 1.5 T system (Signa, GE Medical Systems, Milwaukee, Wis) equipped with a standard circularly polarized head coil. Axial FLAIR (TR/TE=9000/100), axial and coronal T2-weighted images (TR/TE=4000/99) were obtained. The MRI was performed at the beginning, after 12 months, and after 24 months of ERT. The

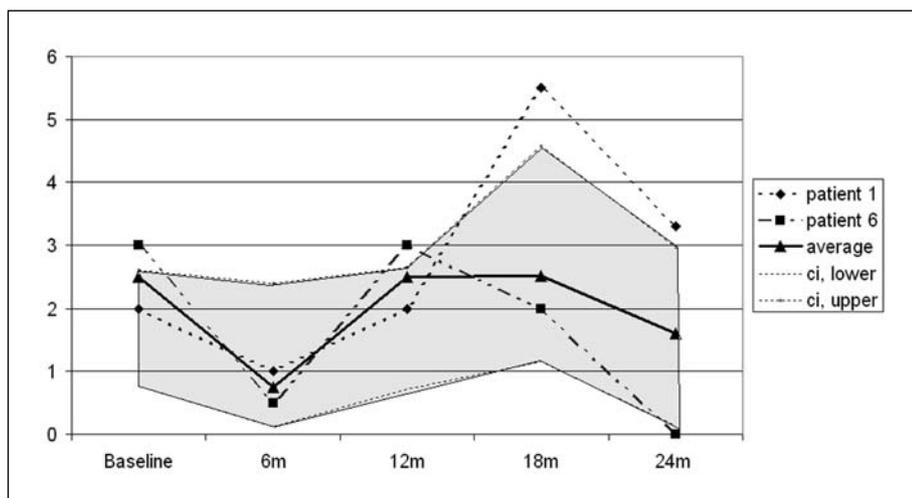


Fig 1. Mean scores of neurological examination, with standard deviations shown in grey. Patients 1 and 6, who crossed the confidence interval of 95%, were highlighted.

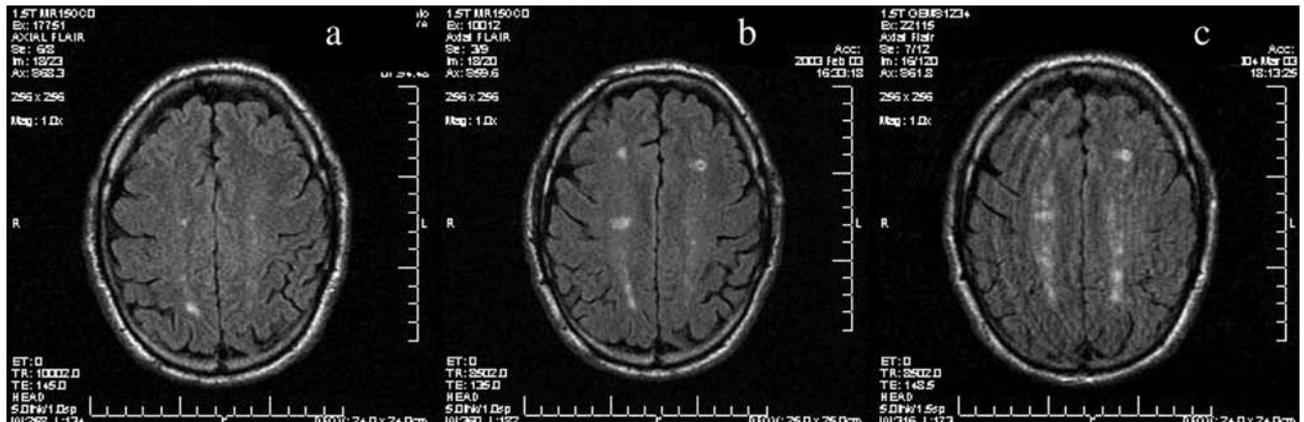


Fig 2. Magnetic resonance images, axial FLAIR-weighted images at baseline (a), the 12<sup>th</sup> (b) and the 24<sup>th</sup> months (c) of enzyme replacement therapy of patient 1. Note the increasing number of white matter lesions.

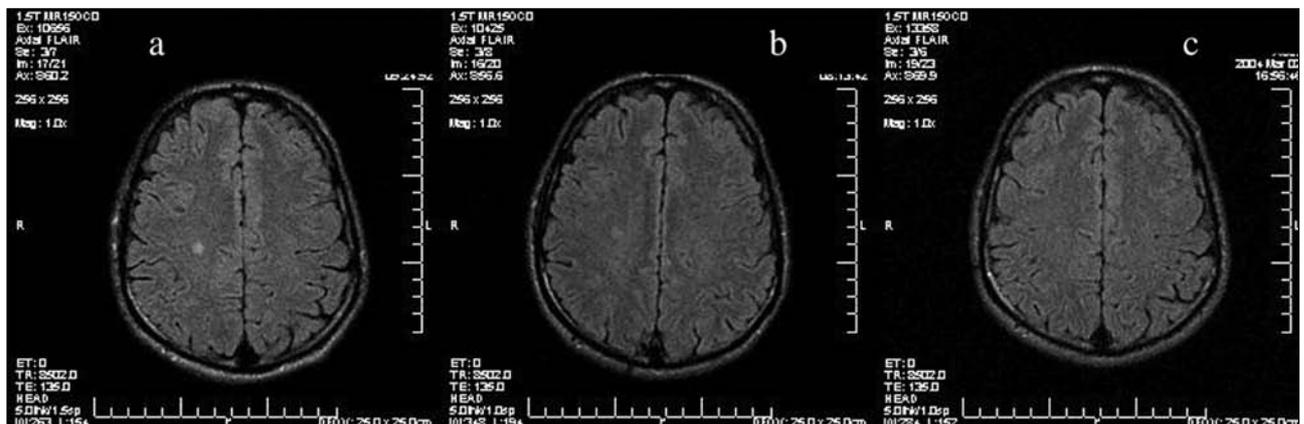


Fig 3. Magnetic resonance images, axial FLAIR-weighted images at baseline (a), the 12<sup>th</sup> (b) and the 24<sup>th</sup> months (c) of enzyme replacement therapy of patient 6. Note the progressive disappearance of the white matter lesion in the right parietal lobe.

presence, location, distribution and number patterns of WML were evaluated as well as their relation to age, symptoms and neurological examination.

Two neuroradiologists (F.A., L.M.V.) experienced in the interpretation of FD evaluated WML. Both were blinded to clinical findings. Comparisons between groups were performed using Student's t test for means. CNS scores at baseline (before ERT) and after 3, 6, 12 and 24 months of ERT were compared using ANOVA linearity test.

## RESULTS

**Baseline** – As already reported, there were few previous CNS signs and symptoms. NE CNS scores varied from zero to 3 (average: 1.7). Four patients showed a widespread pattern of deep WML, absent on T1 and hyperintense on T2 and FLAIR-weighted images, mainly in frontal and parietal lobes. Patient 1 (46 y-o) had a previous history of TIA two years before the start of ERT. WML of this group showed a trend related to age and to the presence of hypoacusia.

### *Evolution of NE CNS scores in 24 months of ERT –*

The average of NE CNS scores obtained was 1.7 at baseline, 1.2 at the 6<sup>th</sup> month of ERT, 1.7 at the 12<sup>th</sup> month, 2.9 at the 18<sup>th</sup> month, and 1.6 at the 24<sup>th</sup> month. The whole group showed no significant differences in mean neurological examinations at each time point in the 24-month period of ERT ( $p > 0.05$ ). Table 1 shows the progression of NE CNS scores during this timeline. However, at the end of the observation, two patients differed statistically from the others: one got worse (patient 1) and the other had a total normalization of NE (patient 6). Figure 1 shows the averages and the 95% confidence intervals of these observations, emphasizing the evolution of patients 1 and 6, the two patients who crossed these limits at the end of the 24 months of ERT.

Variations in NE CNS scores did not correlate with residual enzymatic activity in these patients.

**Evolution of MRI during 24 months of ERT** – MRI at the 12<sup>th</sup> month remained normal in 4 out of 8 patients, showed the same WML in other 2 cases, and

Table 1. General findings of CNS scores, obtained from neurological examination (NE CNS scores) and from magnetic resonance images (MRI), according to patient's age and family.

Family (mutation, when known)	Patient number	Age at baseline	Time (months) of observation on enzyme replacement therapy (0 means baseline)	Glomerular filtration rates (ml/min) (normal: 100 or more)	Proteinuria (mg/day) (normal: up to 150)	Progression of NE CNS scores, on neurological examination, at baseline, 12 and 24 months, respectively (range: 0 to 85)	Number of WML, in each time interval - baseline, 12 and 24 months - during ERT
A (Exon 1 mutation - 30delG)	1	46	0 → 24	90 → 58	1300 → 930	2 → 2 → 3	6 → 9 → 10
	2	36	0 → 24	100 → 90	180 → 140	4 → 3 → 2	6 → 8 → 8
B (Exon 1 - L36F)	3	31	0 → 24	140 → 160	170 → 200	1.5 → zero → 2	1 → 1 → 1
C (Exon 7 mutation - W349X; TGG to TAG nucleotide 1046 G to A) <sup>a</sup>	4	27	0 → 24	27 → 28*	13000 → 1500*	2 → 1 → 1	zero → zero → zero
D (Exon 1 mutation - 30delG) <sup>b</sup>	5	27	0 → 12**	90 → 110	210 → 130	0 → 1	zero → zero
	6	24	0 → 24	150 → 140	130 → 50	0 → 1 → 0	2 → 2 → zero
	7	24	0 → 12**	105 → 107	210 → 410	5 → 2.5	zero → zero
	8		0 → 24	140 → 110	100 → 90	0 → 0 → 0	zero → zero → zero

\*patient went to end-stage renal disease and kidney transplantation, in the 12<sup>th</sup> month of ERT; \*\*patients who voluntarily left the trial; <sup>a</sup>G. Pastores, personal communication; <sup>b</sup>Ashton-Prolla et al.<sup>10</sup>.

the worsening of WML in another 2 related patients (patients 1 and 2), who were also the oldest. In the 6<sup>th</sup> month of ERT, one of the two patients (patient 1) had a second TIA very similar to a former one he had 2 years before the study began; all his symptoms (sudden dizziness, vertigo, and hearing loss) resolved in 12 hours. The new MRI of these two patients showed WM lesion progression mainly in the left frontal lobe, as shown in Figure 2.

Six patients completed the 24 months of ERT. MRI was stable in 3 (normal in 2 and showing the same lesions in the other). WML worsened in patient 1, fluctuated in patient 2 and, surprisingly, disappeared in patient 6 (Figures 2 and 3). Due to these fluctuations, appearances and disappearances, these hyperintense WML at T2 were analyzed individually.

Adding lesions seen in these patients, there were 15 WML at baseline, 20 at the 12<sup>th</sup> month, and 19 at the 24<sup>th</sup> month of ERT. In two years, 4 lesions disappeared, whereas 8 new appeared. Lesions grew in number in patients 1 and 2, i.e., the oldest patients. Other lesions disappeared in patient 6, i.e., the youngest of the series, and also in patient 2. The topography of these vanishing lesions was mainly subcortical, but also in the deep white mater of the hemispheres. Table 1 and Fig 4 summarize these events.

These variations in WML numbers did not correlate with residual enzymatic activity presented by the present patients.

## DISCUSSION

Cerebrovascular manifestations are a well-known complication of FD. They result mainly from multifocal small vessel involvement and may include thrombosis, transient ischemic attacks, basilar artery ischemia and aneurysm, seizures, hemiplegia, hemianesthesia, aphasia, labyrinthine disorders, or frank cerebral hemorrhage. Vascular involvement usually appears in middle age<sup>1,2,4,10,11</sup>. Thus, following cerebrovascular manifestations in cohorts of FD patients (and especially in clinical trials) is an obligatory task of clinical research. Clinical and neurological examinations as well as image studies are among the methods used to assess CNS compromise, and were the methods we chose in this study.

Previous studies showed that WML are a common effect of FD on CNS<sup>12</sup>. Reviewed FLAIR images acquired from 1997 to 2001 in the NIH Fabry cohort (n=79) and were able to show that WML are an age-related phenomena, in this disease. Our first follow-up report, during ERT, showed that WML continued to increase in number, in each patient individually, after

Topography of lesions	Lesion number	Time interval during ERT			Patient (age at baseline)
		Baseline	12 months	24 months	
Periventricular	1				(46 y-o) 1
	2				
	3				
	4				
	5				
	6				
	7				(36 y-o) 2
	8				
	9				(30 y-o) 3
	10				
	11		//		
	12		//		
	13		//		1
	14			//	
subtotals		10	13	14	
Deep White Matter	15				2
	16				
	17				
	18			//	(24 y-o) 6
	19			//	
	20			//	2
subtotals		5	5	4	
Subcortical	21		// //		2
	22		// //		
	23			//	
subtotals			2	1	
<b>Total</b>		15	20	19	

//: means that the onset and the disappearance of a given lesion were known (registered in MRIs).

Fig 4. Evolution of each white matter lesion, according to topography and time of observation.

one year of ERT<sup>9</sup>. The present study had a prospective design that followed annually each FD patient, and aimed to report if individual lesions were maintained or not, and if new lesions have appeared.

Although autopsy studies of FD patients demonstrated a widespread glycosphingolipid neuronal storage<sup>13</sup>, to date no reports on the possible correlations between radiological findings and histopathological analysis have been presented. The etiology of WML in FD therefore remains unknown.

Other sophisticated studies evaluated the effect

of ERT on CNS through the study of regional cerebral blood flow, measured by [<sup>15</sup>O] H<sub>2</sub>O, positron emission tomography and transcranial Doppler studies<sup>3,14,15</sup>. These studies showed significant improvement in abnormal vascular responses after 18 to 24 months of treatment. Although the relation between increased risk of stroke in FD and increased regional cerebral blood flow remains unclear, evidences point to an increased production of reactive oxygen species in FD<sup>16</sup>.

In the present cohort, NE was either normal or

only slightly abnormal during all the time of observation. On the other hand, we saw a widespread pattern of WML which seemed either to precede possible neurological events, or to be actually silent. Indeed, 4 out of 8 patients already showed WML at baseline, although only one (patient 1) had a previous history of TIA. In previous reports, it was already seen that these pre-clinical WML were associated with age, although some discrepancies on the predominant distribution, if in areas supplied by the vertebro-basilar or in the areas supplied by the anterior circulation, remained<sup>9,12</sup>.

When we analyzed WML per patient, the lesions seemed to continuously worsen in the older patients (patients 1 and 2) and, at the same time, to improve in the youngest individual (patient 6). Actually, the MRI showed an increase in number of WML in 2/8 patients (1 and 2) at the 12<sup>th</sup> month, and at 24<sup>th</sup> month (patient 1 only). Patient 1 was also the patient who suffered two similar TIAs: the first TIA two years before and the second TIA six months after starting ERT. However, at first glance, the most intriguing MRI finding was the disappearance of WML in patient 6, after 24 months of ERT. Therefore, we decided to analyze WML as individual events in order to quantify them and to look for any correlation with age, topography, or ERT.

The first question raised was: what is the natural history of these anatomical findings? We obviously do not have the answer to this question. At the beginning of the observations, several WML already existed, and most of them persisted after 24 months of ERT. Some subcortical lesions appeared and disappeared during this time interval, especially in patient 2, suggesting that the lesions occurred perhaps independently from the effects of ERT. The "behavior" of these lesions was perhaps the same of those 2 deep WML which completely disappeared from patient 6. As a matter of fact, we cannot be sure if any of these disappearances were natural or due to ERT. Finally, some new lesions, periventricular and in deep WM, appeared and were present at the end of follow-up (in patients 1 and 2). Patient 2 (36 y-o at baseline) was particularly informative, since his lesions appeared, were maintained, or vanished. The observation of two apparently opposite evolutions in the same patient strongly suggests that the disappearance of WML was independent from the FD mutation, from age, and from age at the start of therapy, and perhaps from ERT itself. Disappearance of WML seemed to be a specific phenomenon, for which no

explanation can be hypothesized by now. The data presented in Tables 1 and Fig 4 suggest that the older a Fabry patient is, the more stable will be his WML.

Fig 4 relates the evolution of these WML to their topography. Although six patients was, in fact, a very small series, patients presented the following as to the total number of WML: 15 lesions at the start of the observation, and 19 at the end; most lesions located in periventricular regions, where no lesion resolved in this interval; whereas lesions that disappeared located either in subcortical or in deep white matter.

Counting lesions is a problem since deciding on what is one large lesion versus two smaller ones close to each other is very difficult in this type of imaging abnormality. A lesion in Fabry disease can remain single but enlarge in size over time. In such a case it would be counted as "stable" disease in the face of progression in fact. We took this in consideration, when we decided to evaluate the evolution of WML by counting them: we understood that we would always undervalue any change (either in the direction of increase or in the decrease). Changes in counting can fail to detect subtle alterations. However, changes in counting were not supposed to run into a beta error - a situation where an observational study decides that some event happened when in fact it did not. Although counting WML is a rough method, observation of lesions that appear or disappear creates absolute numbers, and although their aspect depends on the resolution of the scan, they were hardly subject to errors in the instrument of detection.

Coming back to the analysis per patient, we point out two cases because they deviated from other participants. Patient 1 and patient 6 had opposite evolutions both in NE and in their MRI. Both cases, although unrelated, had the same mutation. Of many possible explanations, we speculated if this would be the effect of their ages. Patient 1 received ERT from age 46 to 48, and patient 6, from age 24 to 26. NE scores worsened in patient 1, but normalized in patient 6 (Fig 1). The total number of FLAIR WML in patient 1 increased (from 6 to 10), whereas it diminished (from 2 to zero) in patient 6. It is possible to interpret these findings as a suggestion that ERT would be effective in the resolution of pre-clinical, CNS lesions of FD, if the treatment is started at an early age, or at least in the beginning of the thirties. However, we should keep in mind, first, that the present study is an open label-protocol, so we cannot compare the present findings with what happens in untreated patients. FLAIR MRI were already followed

in historical series of untreated FD patients<sup>12</sup>. These authors reported a clear association between age, or disease duration, and WML prevalence. However, the design of this previous study did not follow each lesion individually, and for this reason it would not be able to detect a disappearance of any lesion at all. As a matter of fact, few other studies on the natural history of CNS impact of FD have been published to date<sup>2,17-19</sup>, and we have already discussed this topic<sup>9</sup>.

The second objection is that any positive effect of ERT on cerebral parenchyma would only be expected if one assumes that these lesions were secondary to a vascular event. As far as we know, ERT does not cross blood-brain barrier. However, we are not sure that these WML were due to ischemic insults: and this is particularly troublesome, because the major trend in literature is to interpret WML as secondary to an occlusive cerebrovascular small vessel disease. The answer is that ischemic lesions do not disappear on image studies, as it happened with some of WML in the present study. The lack of rational, as, an ischemic insult, as well as the observation of two apparently opposite evolutions in the same patient (case 2), strongly suggest that the disappearance of WM lesions, in general, can be independent from ERT.

In previous studies of WML in the elderly with histopathological correlation, a number of etiologies were found following postmortem T2-weighted MRI<sup>20,21</sup>. In histological areas corresponding to T2-weighted high signal intensities more vascular ectasia and arteriosclerosis was found compared to control regions, followed by patchy zones of gliosis, myelin pallor and demyelination. Only one area of true infarction was noted. As already discussed by Moore et al.<sup>12</sup>, the high signal WML probably represents a combination of gliosis, demyelination and increased interstitial water, in FD. The present data, showing that T2-weighted high signal intensities can vanish, support the hypothesis that, at least in the case of these unstable WML, they should be due to reversible, altered white matter metabolism, perhaps secondary to a blood flow and interstitial fluid dysregulations.

In conclusion, the main importance of the present series is the serial follow-up of WML in FD patients. MRI revealed that, during ERT, although still silent, WML can progress in some patients, at least in those who already are in their forties. More surprisingly, MRI showed that these lesions can disappear. No explanation can be drawn to this observation, mainly because the nature of the WML is un-

known. Whether this finding can happen during the natural history of FD or is related to ERT remains to be demonstrated.

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