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Brain MRI findings in children and adolescents with Fabry disease

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ABSTRACT

Objective: To evaluate the presence of white matter and hemorrhagic lesions in brain MRI of children and adolescents with Fabry disease (FD).

Methods: Brain MRI studies in 44 consecutive children and teenagers (20 boys, mean age 14.6 years, range 7–21 years) were evaluated using classic sequences as well as, GRE-weighted images, for white matter lesions (WML) and chronic microbleed detection. All patients lacked history of stroke or TIA. Brain MRI findings in 46 consecutive children and adolescents without FD, referred for the evaluation of headaches (36 females, mean age 14.1 years, range 7–21 years) were evaluated as a control group. Additionally, we assessed the clinical manifestations of FD.

Results: Seven children (15.9%) with FD had brain MRI evidence of asymptomatic WML (5 girls, mean age 14.8 years, range: 13–20 years) compared with 3 children (6.5%) in the control group ($p = 0.01$). Brain abnormalities in patients with FD revealed WML, deep gray matter and infratentorial involvement. Three patients presented two lesions each. None of the children showed microbleeds. Regarding clinical manifestations, 90.9% of the patients had signs or symptoms of FD.

Conclusion: We identified asymptomatic white matter brain lesions in 15.9% of children with FD without clinical history of stroke. FD is a treatable disorder that should be routinely included in the differential diagnosis of both symptomatic and asymptomatic brain lesions in children and adolescents. The detection of brain lesions may foster earlier treatment.

1. Introduction

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by inherited deficiency of the lysosomal enzyme alpha galactosidase A due to mutation of the alpha galactosidase A gene at Xq22.1. This abnormality affects the conversion of globotriaosylceramide (Gb3) to lactosylceramide, with subsequent progressive multisystem intracellular accumulation of glycosphingolipids, particularly Gb3 [1]. Symptoms typically begin in childhood and adolescence with pain and gastrointestinal complaints, followed by renal as well as cardiac involvement and stroke in adulthood [2,3].

Strokes have been identified in 6.9%–11.1% of males and 4.3%–15.7% of females in the two largest Fabry registries. In the Fabry Outcome Survey the observed frequency of stroke among males aged 25–44 years was approximately 12 times that expected in the general population [4,5].

Additionally, FD has been detected in 1%–4.9% of young patients with cryptogenic stroke [6–8]. It was estimated that 1 to 2% of all strokes in the general population within age 18 to 55 may be due to FD [7,9].

Sims et al., reported that among adult patients with FD, 16.9% of males and 6.8% of females presented brain hemorrhages [4]. Chronic brain microbleeds are readily detected by Echo gradient (GRE)-weighted images, and their presence is associated with risk of brain hemorrhage [10]. We have reported the presence of asymptomatic ischemic (44.4%) and microbleeds (11%) lesions in a group of FD adult patients without the history of stroke [11].

The evaluation of brain MRI in FD patients of all ages, without prior history of stroke, allows a better understanding of the natural history of white matter lesions (WML) and microhemorrhagic lesions. Moreover, the occurrence of MRI lesions in children and adolescents with FD without a history of stroke has been scarcely reported [12]. The detection of early brain vascular lesions may foster the start of treatment. The objective of our study was to investigate the presence of WML or

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microhemorrhages in brain MRI of children and adolescents with FD in both genders lacking a history of cerebrovascular accident.

2. Materials and methods

We reviewed the brain MRI of 44 consecutive children and teenagers (20 boys, mean age 14.6 years, range 7–21 years) from 13 different families with FD, with no prior history of cerebrovascular disease, referred from AADELFA [13] to our Department for neurological evaluation between 2006 and 2017. The study was approved by the Institutional Review Board of the Hospital Británico, Buenos Aires, Argentina.

The MRI findings of our patients were compared with those of 46 consecutive children and adolescents without FD referred for the evaluation of headaches (36 females, mean age 14.1 years, range 7–21 years).

Fabry disease was confirmed by enzymatic testing in males and by galactosidase gene mutation analysis in females.

Brain MRI included: T1-weighted (repetition time [TR]/echo time [TE] 600/25 ms, matrix 256–256) images, proton density/T2-weighted (TR/TE1/TE2 4500/15/100 ms, matrix 256–256) and fluid attenuated inversion recovery (FLAIR)-weighted (IR/TR/TE 9000/108 ms, slice thickness 6 mm, matrix 512–448) images were obtained. All transverse slices were arranged parallel to the anterior–posterior commissure line. GRE sequence, 5 mm axial sections, were performed according to the following parameters: TR 700-TE 25-FOV: 24 × 18 MTX 256 × 192-NEX1 in 20 patients. All the MRI performed in both groups were centrally reviewed by the same investigators: CR and PF. Microbleeds were defined as a rounded or ovoid area showing marked and homogeneous signal loss on GRE, not located in sulcal areas, with diameters < 10 mm and devoid of T1-weighted or T2-weighted hyperintensity (such as cavernous malformation, hemorrhagic infarct or melanotic melanoma). Symmetric subcortical and hypointense lesions likely to represent focal calcification were excluded [10]. WML severity were categorized using a simplified visual rating instrument. White matter changes were defined as bright lesions of > 5 mm on FLAIR images. Focal WML or basal ganglia lesions were classified as mild. Confluent WML/deep gray matter lesions or multiple lesions were classified as significant [14,15]. Moreover, we classified the lesions regarding their predominant distribution in the anterior or posterior circulation.

Additionally, we investigated the FD clinical manifestations of these young patients and compared the frequency of clinical findings between the groups with normal and abnormal brain MRI using a chi square test.

Frequency of MRI lesions between both groups were compared using chi square test.

3. Results

Clinical manifestations: 90.9% of the patients had signs or symptoms of FD. Neuropathic pain was the most frequent, followed by cornea verticillata and abdominal pain. Analyzing the other late complications of FD, only 3 patients presented proteinuria.

None of the patients presented hypertension, diabetes, dyslipidemia and 3 were smokers. The frequency of symptoms and signs were similar between both groups (Table 1).

Brain MRI findings: Seven of 44 FD patients (15.9%) showed evidence of asymptomatic WML (5 girls, mean age 14.8 years, range: 13–20 years). All the children and adolescents with abnormal MRI presented the classical phenotype of the disease, and 3 of them (42.8%) were under enzyme replacement treatment for a mean of 11 months.

All brain lesions detected were mild. Three patients presented 2 lesions each: the first patient showed a left putaminal and a right parietal subcortical lesion (Fig. 1, Patient 2); the second presented a frontal subcortical and a left cerebellar lesion (Fig. 1, Patient 5); and the third patient, had very small bilateral lesions in the centrum semiovale (Fig. 1, Patient 7). In the FD group, 7/10 lesions involved the anterior circulation.

Table 1
Symptoms and signs of children and adolescents with Fabry disease.

	Normal brain MRI N = 37	Abnormal brain MRI N = 7
Mean age (range) years	14.6 (13 – 20)	14.8 (7–21)
Females	19	5*
Symptoms or signs %	89.1	100
Neuropathic pain %	75.6	100
Cornea verticillata %	65.4	100
Hearing loss %	24.3	28.5
Abdominal pain %	54	14.2*
Angiokeratomas %	31.4	28.5
Hypohidrosis %	30.5	28.5
Proteinuria %	8.8	0
Cardiac involvement %	0	0

* $p < 0.05$.

Four patients presented hyperintensities in FLAIR with hypointense lesions in T1. Fig. 1 (patients 1–4). The remaining patients presented hyperintensity in FLAIR with normal T1 sequences. Fig. 1 (patients 5 to 7).

None of our patients presented microbleeds or the pulvinar sign [16].

Frequency of WML were significantly higher in patients with FD (15.9%) compared with our control group (3/46, 6.5%, p = 0.01). In the control group, none of the WML were hypointense in T1-weighted images.

Mutations identified in the 7 patients with brain lesions included c.1122_1125delAGGA deletion (1), c.463G > C missense (3) and c.581C > T missense (3). The remaining patients presented the following mutations: c.281G > A missense (2), c.463G > C (16) missense, c.728 T > G missense (1), c.1122_1125delAGGA deletion (1), c.100A > G missense (1), c.658C > T nonsense (1), c.164A > G missense (1), c.581C > T missense (3), c.772 G > T nonsense (1), c.718_719delAA deletion (1), c.888G > A missense (3), c.1244 T > C missense (4), and c.520 T > G missense (2).

4. Discussion

This is the first brain MRI study in a large cohort of FD children and adolescents lacking a history of TIA or stroke.

In our group, 15.9% had subclinical evidence of asymptomatic WML on MRI. Brain abnormalities were more frequent in heterozygous females, underlying that in this disorder both females and males could be affected similarly [17,18].

Moreover, 70% of the lesions were in the anterior circulation, and were detected in patients as early as 13 years of age.

The high proportion of symptoms and signs of FD in this group of young patients referred to us (90.9%) is probably due to the fact that the primary physicians referred the most symptomatic children and adolescents for neurological evaluation. Nevertheless, none of our patients suffered a stroke or transient ischemic attack.

There are only isolated reports of stroke in children and adolescents with FD [4,19–22]. Moreover, asymptomatic lesions in young patients with FD have been only rarely explored. The youngest FD patient reported in the literature with white matter lesions was an 8-year-old boy who presented bilateral silent multiple punctate areas in the subcortical white matter [12].

In our previous study of asymptomatic brain MRI lesions in patients with FD, we identified that 1/10 patients with FD younger than 21 years presented brain lesions at the age of 13 years [11]. In the present study, with a much larger number of subjects, MRI lesions were identified in almost 16% of young patients with FD.

Pathophysiology of WML detected on T2 FLAIR MRI remains poorly understood but they may not only reflect the biology of the