Journal of Statistics on Health Decision

EXTENDED ABSTRACT

A5 The association between potential risk factors and cerebral white matter lesions in Fabry Disease patients

Ana R. Moura[1], Flora Ferreira[2], Estela Bicho[3], José Braga[1], Wolfram Erlhagen[2], Olga Azevedo[4], Miguel F. Gago[4]

[1]Department of Industrial Electronics, University of Minho (UM), 4710-057 Braga, Portugal
[2]Centre of Mathematics, University of Minho (UM), 4800-058 Guimarães, Portugal
[3]Algoritmi Center, Department of Industrial Electronics, University of Minho (UM), 4800-058 Guimarães, Portugal
[4]Cardiology Department, Reference Center on Lysosomal Storage Disorders, Hospital Senhora da Oliveira, 4835-044 Guimarães, Portugal; and Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho (UM), 4710-057 Braga, Portugal; and ICVS/3Bs PT Government Associate Laboratory, Braga/Guimarães, Portuga

Introduction

Fabry disease (FD) is an X-chromosome-linked lysosomal storage disease characterized by deficient or even absent activity of enzyme alpha-galactosidase A originated by mutations in the galactosidase alpha gene (GLA) leading to cellular globotriaosylceramide deposits (Gb3) [1]. FD is classified as a rare disease (affects fewer than 1 in 2000 people in Europe [2]) and often leads to progressive organ failure and premature death [1]. This disease affects several parts of the body, including progressive brain white matter lesions (WMLs) due to GB3 endothelial vasculopathy [1]. White matter is the brain region responsible for the transmission of nerve signals between different regions of the brain. WMLs have been associated with stroke, cognitive decline, and dementia [3, 4], which have a prominent impact on global public health [5]. Growing evidence suggests a relationship between the presence of WMLs and lifestyle-related risk factors including obesity [6] as well as other modifiable risk factors such as depression, anxiety, diabetes, and hypertension [7, 8]. It is of great public interest to increase the knowledge of risk factors associated with WMLs in order to promote health prevention activities. However, the risk factors associated with WMLs in FD patients are unclear, and the etiology of vasculopathy may be confounded by other cerebrovascular risk factors. In this study, we aimed to evaluate the association of potential risk factors, including age, sex, obesity, diabetes, hypertension, depression, and anxiety, with the presence of WMLs in FD patients.

Methods

We retrospectively enrolled 94 Fabry (GLA gene mutation c.337T>C (p.F113L)) disease patients (40.4% male) aged 18-89 years from the Reference Center on Lysosomal Storage Disorders, Hospital Senhora da Oliveira, Guimarães. Except for age, all variables included in this study are dichotomous variables, indicating the sex or the presence of a clinical condition (1 = presence and 0 = absence).

First, univariate analysis, including the Student's t-test and Fisher exact test, was conducted to evaluate the association between the presence of WMLs and each single potential risk factor. Cohen's d value for continuous variables and Phi coefficient for categorical variables were calculated to evaluate the effect size [9]. Significant variables in univariate analysis were then tested in univariate and multivariate (adjusted for age) logistic regression analysis. Point-biserial correlation coefficients were used to measure the association between age and the other variables. All statistical analyses were performed using IBM SPSS Statistics 26 software and the significance level was set as 0.05. Due to the low number of younger patients with WMLs, all the analysis was also performed for a subgroup of patients aged 40 years and older.

Results

Patients with WMLs were significantly older than the group of patients without WMLs (Table 1). The presence of WMLs was significantly associated with anxiety and hypertension in both samples (Table 1). It is noticeable that in FD patients older than 17 years old, age presents significant positive correlations with WMLs, hypertension, depression, anxiety, and diabetes. In FD patients older than 39 years old, the coefficient values were lower, but significant correlations were also observed between age and WMLs, and between age and hypertension (Table 2).

Keywords:
Aging; Fabry disease; Risk factors; White matter lesions

Corresponding author:
Flora Ferreira
flora.ferreira@gmail.com

Conflict of interest:
The authors declare no conflict of interests.

First published: 22JUN2021

Table 1 - Univariate analysis of risk factors of WMLs

Variables	FD patients over 17 years old (n=94)				FD patients over 39 years old (n=68)			
	With WMLs (n=50)	Without WMLs (n=44)	*p**	Effect size+	With WMLs (n=44)	Without WMLs (n=24)	*p**	Effect size+
Age	56.7±14.9	40.2±14.1	**<0.001**	1.133	60.5±11.1	50.8±8.4	**<0.001**	0.953
Male	19 (38.0)	19 (43.2)	0.676	-0.053	18 (40.9)	10 (41.7)	1.000	-0.07
Depression	16 (32.0)	7 (15.9)	0.093	0.187	15 (34.1)	4 (16.7)	0.163	0.186
Anxiety	20 (40.0)	8 (18.2)	**0.025**	0.238	19 (43.2)	4 (16.7)	**0.034**	0.268
Hypertension	24 (48.0)	7 (15.9)	**0.001**	0.341	24 (54.5)	6 (25.0)	**0.023**	0.284
Diabetes	7 (14.0)	3 (6.8)	0.327	0.116	7 (15.9)	3 (12.5)	1.000	0.046
Obesity	7 (14.0)	3 (6.8)	0.327	0.116	7 (15.9)	2 (8.3)	0.476	0.107

*Significance on Student t-test for age variable and Fisher exact test for the remaining variables. Values denote mean ± standard deviation or number (percentage). WMLs = white matter lesions. + Cohen's d value for age and Phi coefficient for the remaining variables [9].

Table 2 - Point-biserial correlation coefficients (r_{pd}) between age and others risk factors

Variables	Age			
	FD patients over 17 years old (n=94)		FD patients over 39 years old (n=68)	
	r_{pd}	*p*	r_{pd}	*p*
WMLs	0.496	**<0.001**	0.419	**<0.001**
Depression	0.207	**0.045**	0.124	0.315
Anxiety	0.216	**0.036**	0.102	0.408
Hypertension	0.580	**<0.001**	0.526	**<0.001**
Diabetes	0.226	**0.029**	0.101	0.414
Obesity	0.121	0.244	0.004	0.976

WMLs = white matter lesions

From the univariate logistic regression, anxiety, and hypertension present a significant association with the presence of WMLs in FD patients older than 17 years old. However, when adjusted by age no variable presents a significant association with the presence of WMLs (Table 3). In FD patients older than 39 years old, the anxiety variable, even after being adjusted to age, remains significant (Table 3).

Table 3 - Logistic regression models to predict the presence of WMLs in FD patients

Variables	Univariate Logistic Regression			Multivariate Logistic Regression – Adjusted to age		
	Odds Ratio	95% CI	*p*	Odds Ratio	95 % CI	*p*
FD patients over 17 years old (n=94)						
Anxiety	3.000	1.157-7.776	**0.024**	2.315	0.808-6.637	0.118
Age	-	-	-	1.077	1.039-1.115	**<0.001**
Hypertension	4.879	1.831-13.000	**0.002**	1.487	0.451-4.901	0.514
Age	-	-	-	1.071	1.030-1.114	**0.001**
FD patients over 39 years old (n=68)						
Anxiety	3.800	1.113-12.976	**0.033**	4.475	1.143-17.514	**0.031**
Age	-	-	-	1.117	1.043-1.195	**0.002**
Hypertension	3.600	1.201-10.794	**0.022**	1.459	0.397-5.367	0.570
Age	-	-	-	1.097	1.023-1.176	**0.010**

Discussion

As shown in previous studies [10], increased age was significantly associated with the presence of WMLs. However, although age is the strongest known risk factor for the onset of WMLs, it is not an inevitable consequence of aging. The results here reported support the importance of assessing the anxiety symptoms in FD and its potential correlation with WMLs. Of note, although anxiety and depression can occur together [11], in concord with previously observed [12] no significant association was found between depression and WMLs. Further studies in larger cohorts of patients are warranted to untangle if anxiety is a risk factor or a consequence of WMLs.

Ethics committee and informed consent:

This current research has been submitted to the local ethics committee and all patients gave their informed consent.

Acknowledgments:

This work has been supported by FCT – Fundação para a Ciência e Tecnologia within the R&D Units Project Scope: UIDB/00319/2020 and UIDB/00013/2020.

References:

1. Azevedo O, Gago MF, Miltenberger-Miltenyi G, Robles AR, Costa MA, Pereira O, et al. Natural history of the late-onset phenotype of Fabry disease due to the p. F113L mutation. Molecular genetics and metabolism reports. 2020;22:100565. https://doi.org/10.1016/j.ymgmr.2020.100565
2. de Vrueh R, Baekelandt E, de Haan J. Priority medicines for Europe and the world: "a public health approach to innovation." WHO Background Paper 6.19. Rare Diseases2013. Available from: http://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf.
3. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke. 2003;34(5):1126-9. https://doi.org/10.1161/01.STR.0000068408.82115.D2
4. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. New England Journal of Medicine. 2003;348(13):1215-22. https://doi.org/10.1056/NEJMoa022066
5. Organization oH. Global action plan on the public health response to dementia 2017–2025.2017. Available from: https://www.who.int/mental_health/neurology/dementia/action_plan_2017_2025/en/.
6. van Bloemendaal L, Ijzerman RG, Jennifer S, Barkhof F, Diamant M, Veltman DJ, et al. Alterations in white matter volume and integrity in obesity and type 2 diabetes. . Metabolic brain disease. 2016;31(3):621-9. https://doi.org/10.1007/s11011-016-9792-3
7. Johansson M, Stomrud E, Lindberg O, Westman E, Johansson PM, van Westen D, et al. Apathy and anxiety are early markers of Alzheimer's disease. Neurobiology of aging. 2020;85:74-82. https://doi.org/10.1016/j.neurobiolaging.2019.10.008
8. De Leeuw FE, de Groot JC, Oudkerk M, Witteman JCM, Hofman A, Van Gijn J, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. Brain. 2002;125(4):765-72. https://doi.org/10.1093/brain/awf077
9. Cohen J. Statistical power analysis for the behavioral sciences: Academic press; 2013. https://doi.org/10.4324/9780203771587
10. Körver S VM, Hollak CE, van Schaik IN, Langeveld M. Development and clinical consequences of white matter lesions in Fabry disease: a systematic review. Molecular genetics and metabolism. 2018;125(3):205-16. https://doi.org/10.1016/j.ymgme.2018.08.014
11. JW. T. Depression and anxiety. The Medical Journal of Australia. 2013;199(6): S28-S31. https://doi.org/10.5694/mja12.10628
12. Körver S GG, Hollak CE, van Schaik IN, Longo MG, Lima MR, et al. Depressive symptoms in Fabry disease: the importance of coping, subjective health perception and pain. Orphanet journal of rare diseases. 2020;5(1). https://doi.org/10.1186/s13023-020-1307-y