Development and clinical consequences of white matter lesions in Fabry disease: a systematic review

Körver, Simon; Vergouwe, Magda; Hollak, Carla E. M.; van Schaik, Ivo N.; Langeveld, Mirjam

Published in:
Molecular genetics and metabolism

DOI:
10.1016/j.ymgme.2018.08.014

Published: 01/01/2018

Document Version
Version created as part of publication process; publisher's layout; not normally made publicly available

Citation for pulished version (APA):
Körver, S., Vergouwe, M., Hollak, C. E. M., van Schaik, I. N., & Langeveld, M. (2018). Development and clinical consequences of white matter lesions in Fabry disease: a systematic review. *Molecular genetics and metabolism*, *125*(3), 205-216. https://doi.org/10.1016/j.ymgme.2018.08.014

Molecular Genetics and Metabolism xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

Development and clinical consequences of white matter lesions in Fabry disease: a systematic review

Simon Körver[a,1], Magda Vergouwe[a,1], Carla E.M. Hollak[a], Ivo N. van Schaik[b], Mirjam Langeveld[a,*]

[a] Amsterdam UMC, University of Amsterdam, Department of Endocrinology and Metabolism, Meibergdreef 9, Amsterdam, the Netherlands
[b] Amsterdam UMC, University of Amsterdam, Department of Neurology, Meibergdreef 9, Amsterdam, the Netherlands

ARTICLE INFO

Keywords:
Lysosomal Storage Diseases
Fabry Disease
White matter lesions
Leukoaraiosis
MRI
Cerebral Small Vessel Disease
Systematic review

ABSTRACT

Background: Fabry disease (FD) is a rare lysosomal storage disorder that might result in, amongst other complications, early stroke and white matter lesions (WMLs). More insight in WMLs in FD could clarify the role of WMLs in the disease presentation and prognosis in FD. In this systematic review we assessed the prevalence, severity, location and course of WMLs in FD. We also systematically reviewed the evidence on the relation between WMLs, disease characteristics and clinical parameters.

Methods: We searched Pubmed, EMBASE and CINAHL (inception to Feb 2018) and identified articles reporting on FD and WMLs assessed with MRI. Prevalence and severity were assessed for all patients combined and divided by sex.

Results: Out of 904 studies a total of 46 studies were included in the analyses. WMLs were present in 46% of patients with FD (581 out of 1276 patients, corrected mean age: 38.8 years, range 11.8–79.3) and increased with age. A total of 16.4% of patients (31 out of 189 patients, corrected mean age: 41.1 years, range 35.8–43.3 years) showed substantial confluent WMLs. Men and women showed comparable prevalence and severity of WMLs. However, men were significantly younger at time of WML assessment. Patients with classical FD had a higher chance on WMLs compared to non-classical patients.

Progression of WMLs was seen in 24.6% of patients (49 out of 199 patients) during 38.1 months follow-up. Progression was seen in both men and women, with and without enzyme replacement therapy, but at an earlier age in men. Stroke seemed to be related to WMLs, but cerebrovascular risk factors, cardiac and renal (dys) function did not. Pathology in the brain in FD seemed to extend beyond the WMLs into the normal appearing white matter.

Conclusions: A significant group of FD patients has substantial WMLs and male patients develop WMLs earlier compared to female patients. WMLs could be used in clinical trials to evaluate possible treatment effects on the brain. Future studies should focus on longitudinal follow-up using modern imaging techniques, focusing on the clinical consequences of WMLs. In addition, ischemic and non-ischemic pathways resulting in WML development should be studied.

1. Introduction

Fabry disease (FD; OMIM 301500) is an X-inherited lysosomal storage disease. A mutation in the GLA-gene causes a deficiency of the enzyme α-galactosidase A (enzyme commission no. 3.2.1.22), resulting in accumulation of globotriaosylceramide (Gb3) and its derivatives in

Abbreviations: CBF, cerebral blood flow; DWI, diffusion weighted imaging; ERT, enzyme replacement therapy; FA, fractional anisotropy; FD, Fabry disease; Gb3, globotriaosylceramide; MD, mean diffusivity; MSSI, Mainz severity score index; MRI, magnetic resonance imaging; NAWM, normal appearing white matter; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCTs, randomized controlled trials; T, Tesla; TIA, transient ischemic attack; WMLL, white matter lesion load; WML(s), white matter lesion(s)

* Corresponding author at: Amsterdam UMC, Department of Internal Medicine, Div Endocrinology and Metabolism, Room F5-166, PO box 22660, 1100 DD Amsterdam, the Netherlands.

E-mail addresses: s.korver@amc.uva.nl (S. Körver), c.e.hollak@amc.uva.nl (C.E.M. Hollak), i.n.vanschaik@amc.uva.nl (I.N. van Schaik), m.langeveld@amc.uva.nl (M. Langeveld).

[1] Authors contributed equally.

https://doi.org/10.1016/j.ymgme.2018.08.014
Received 1 August 2018; Received in revised form 29 August 2018; Accepted 30 August 2018

various cell types. FD is a multi-organ disease and disease manifestations occur predominantly in kidney, heart and brain [1,2]. To detect and monitor organ involvement systematic follow-up of patients is strongly recommended. This should include MRI brain on a regular basis, since early cerebral manifestations of FD can be asymptomatic but might warrant treatment [2]. These cerebral manifestations are early (transient ischemic attack) TIA, stroke, lacunar infarctions and white matter lesions (WMLs) [1,3]. Despite many reports on WMLs, information on the development and consequences are scarce.

As FD is an X-linked disorder, men are generally more severely affected and develop disease complications earlier in life then women. In addition, disease severity is variable between patients who can traditionally be classified as having classical or non-classical FD. Men with a classical phenotype typically have no residual enzyme activity and affected family members generally have earlier and more widespread disease manifestations and complications compared to non-classical patients [1]. Interestingly, differences in the development of WMLs between men and women have so far not been found [4,5]. This may be the result of lack of statistical power, lack of correction for age differences, or because no distinction is made between patients with classical and non-classical disease. The latter is supported by the recent observation of a higher prevalence of WMLs in men with classical disease versus those with non-classical FD [1]. This emphasizes the need to classify patients by sex, age and and phenotype, when studying cerebral involvement in FD.

Detection of WMLs can also have diagnostic implications: in some diseases other than FD, the specific location and distribution of WMLs suggests a specific underlying disease, such as corpus callosum involvement in multiple sclerosis [6]. This has so far not been established for FD: WML distribution in FD has been described as aspecific and multifocal [7]. Moreover, despite the status of WMLs as an early marker of cerebral involvement in FD [8], their clinical consequences and response to enzyme replacement therapy (ERT) have been rarely addressed in follow-up studies.

In view of the paucity of analyses on this topic, the following points of interest were raised. Firstly, more insight in the prevalence, severity and course of WMLs may help to identify patients who are likely to develop WMLs. Secondly, a detailed exploration of the location of WMLs by magnetic resonance imaging (MRI) may possibly assist in the diagnosis of FD. Lastly, the relationship between WMLs and occurrence and severity of FD complications can help to identify whether WMLs can be used as a prognostic factor and/or parameter to evaluate treatment efficacy. Hence, in this systematic review we assessed the prevalence, severity, location and course of WMLs in FD as well as the relation between WMLs, disease characteristics and clinical parameters.

2. Methods

For this systematic review we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [9].

2.1. Data sources and search

We searched Pubmed, EMBASE and CINAHL from inception to the 15th of February 2018. No restrictions were applied on language or publication date. The search included synonyms of “Fabry disease” and “White matter lesions”. To include studies that did not use a synonym of WMLs in the title or abstract but might report on WMLs in full text we used terms related to MRI brain and other cerebral manifestations of FD, see Supplementary File A for the search terms used. The search strategy was adapted for each database to increase sensitivity. Reference lists of reviews and included studies were checked and did not identify missing studies.

2.2. Study selection

Randomized controlled trials (RCTs) and cohort studies (≥ 5 included patients) were included, using MRI brain to report on WMLs in adults and children with FD. Excluded were: 1) Case-series since these are prone for publication bias [10], 2) Studies screening for FD in high risk populations (e.g. in a young stroke cohort), 3) Studies focusing on a group of patients with one specific mutation. Studies reported as congress abstracts only were included for the calculation of the prevalence of WMLs.

The most relevant report of consecutive studies in the same cohort was included. If studies reported on the same or an overlapping cohort, but provided information on different research questions, both studies were included.

Two reviewers (SK and MV) independently screened all titles and abstracts using Covidence, an online article screening tool [11]. Reviewers resolved disagreement by discussion, if necessary a third reviewer (ML) was consulted.

2.3. Data extraction

Two reviewers (SK and MV) individually extracted data using a standardized report form. The following data were extracted: number of patients in the study, sex, phenotype, age, treatment status, previous TIA or Stroke, MRI sequence used to identify WMLs, MRI field strength (Tesla (T)), definition that was used for WMLs and data reporting on WML frequency, severity, location and course and the relation of WMLs to clinical parameters and patients characteristics. Data were extracted for the whole study cohort and by disease phenotype and sex if specified. If data were reported for adults and children both groups were included separately. Primary outcome was the prevalence of WMLs. Secondary outcomes were WML severity, location and course. In addition, data on the relation of WMLs to clinical parameters and patient characteristics were extracted.

2.4. Definitions

We used the definitions for WMLs as provided by the authors of the individual articles. Prevalence was defined as the number of patients with WMLs on MRI divided by the number of patients who underwent a brain MRI. Severity was defined as the size or number of WMLs, WML volume or by using a WML rating scale (e.g. Fazekas). Location was defined as the region in which the WMLs were observed on MRI and was classified as periventricular, deep or subcortical or per anatomical or circulatory area. Course was defined as whether WMLs were progressive or stable over time as reported by a radiologist or quantitatively assessed on at least one follow-up MRI.

2.5. Statistical analysis

Data are presented as median and range or mean ± SD where appropriate. R (version 3.3.1) was used for statistical analysis. Prevalence of WMLs was calculated with and without information obtained from abstracts only (studies for which no full article is available). When combining variables (e.g. age or Fazekas score), correction for cohort size was performed by using the number of patients per study as a weight factor. These variables are referred to as “corrected mean age” and “corrected mean Fazekas score”. Prevalence of WMLs (present versus absent) and Fazekas scores (Fazekas ≥ 2 versus Fazekas < 2) in men and women were compared using the chi^2-test. Ages in studies reporting on the prevalence and/or severity of WMLs were considered non-normally distributed after visual inspection using histograms and Q-Q plots and the Shapiro-Wilk test and were compared using the Mann-Whitney *U* test.

3. Results

A total of 904 studies was identified through our search of which 256 were duplicates, see Supplementary File B for the PRISMA flow diagram. After screening for title and abstract 170 articles and 17 abstracts were assessed for eligibility. A total of 46 articles [1,3–5,12–53] and eight abstracts were included in the qualitative synthesis [54–61], see Supplementary Table A for an overview table of all articles.

3.1. MRI field strength and sequences

Different field strengths and MRI sequences were used in the assessment of WMLs. Of the 46 studies, 25 (54.3%) reported both field strength and sequence(s) used to assess WMLs and eight (17.4%) reported neither. MRI field strengths of 0.5–3 T were reported for 27 studies and sequences used to assess WMLs were reported for 36 studies. Most used field strength was 1.5 T and most used sequence was the fluid attenuation inversion recovery (FLAIR) sequence. For details see Supplementary Table A.

3.2. Prevalence of WMLs

Thirty-one articles [1,3,4,12–39] and eight abstracts [54–61] assessed the prevalence of WMLs in FD in a total of 1577 patients, of which 1276 patients were described in the articles (Table 1). Since abstracts often did not provide information on patient characteristics these were only extracted from the articles. Corrected mean age of patients was 38.8 years (range 11.8–79.3 years). A total of 372 patients (33.6%) were treated with ERT and 76 patients (12.7%) had a history of TIA and/or stroke (TIA/stroke data missing in 46.8% of patients).

WMLs were present in 45.5% of all patients (581 out of 1276 patients). When including abstracts WML prevalence was 44.8% (707 out of 1577 patients). The prevalence of WMLs visually increased with age (Fig. 1). One cohort with six geriatric patients (mean age: 79.3 years (range: 75–87 years), prevalence WMLs: 50%) was removed for visual purposes as their average age extended the x-axis with 20 years.

In approximately half of the 1276 patients, sex was reported (309 men and 317 women). None of the pediatric cohorts provided the prevalence of WMLs divided by sex (Fig. 2). One cohort with five geriatric women (mean age: 80.2 years (range 75–87 years), prevalence WMLs: 40%) was removed for visual purposes as their average age extended the x-axis with 20 years.

WML prevalence was 46.9% in men at a corrected mean age of 36.4 years and 41.0% in women at a corrected mean age of 43.1 years (Table 2). No differences were found when comparing prevalence of WMLs between men and women ($\chi^2(1) = 2.0$, $p = .15$). However comparing uncorrected age showed that men were younger at time of WML assessment compared to women (U = 10, $p < .0001$).

Table 1
Characteristics of patients with reported prevalence of WMLs.

	All patients*	Sex known	
		Men†	Women†
Patients (including abstracts), n	1577	368	346
Patients (articles only), n	1276	309	317
Patient characteristics (articles only)#			
Patients per article, median (range)	26 (6–283)	15 (4–52)	15 (4–57)
Number of patients with age reported, n	930	261	302
Corrected age (years), mean (range)	38.8 (11.8–79.3)	36.4 (27.4–41.9)	43.1 (35.0–80.2)
Number of patients with ERT use reported$, n	1106	188	147
Number of patients on ERT, n (%)	372 (33.6%)	96 (51.1%)	60 (40.8%)
History of TIA and/or stroke reported, n	597	172	193
History of TIA and/or stroke, n (%)	76 (12.7%)	29 (16.9%)	35 (18.1%)

*Includes mixed cohorts, pediatric cohorts, men only cohorts and women only cohorts, †Includes all articles from the "All patients" group that presented data on prevalence of WMLs divided by sex, #Abstracts often did not provide information on ERT use, TIA or stroke and age and were subsequently not included in the patient characteristics, $Two articles were published before the availability of ERT. These patients were classified as not using ERT.
ERT = Enzyme Replacement Therapy, WMLs = White matter lesions, TIA = transient ischemic attack.

3.3. Severity

Twenty-six studies assessed WML severity [3–5,13,14,17–21,23,26–28,31,32,34–37,39–44]. Methods used to assess WML severity were the Fazekas scale, subjective assessment, white matter lesion number and/or size and white matter lesion volume.

3.3.1. Fazekas scale

The original Fazekas scale describes WML severity in deep and periventricular white matter [62]. It ranges from 0 (no WMLs) to 3 (confluent WMLs) for both locations, resulting in a total score from 0 to 6. A modified version of the Fazekas scale is often used, primarily focusing on deep white matter lesions, resulting in a score from 0 (no deep WMLs) to 3 (confluent deep WMLs), with a score of ≥ 2 considered as the presence of significant WMLs (Fig. 3). The Fazekas scale was used in eleven studies, in a total of 405 patients with FD of which seven studies used the modified scale ($n = 212$; Table 3).

The corrected mean Fazekas score was 0.76 ($n = 185$, range: 0.53–1.90; Fig. 4) at a corrected mean age of 42.1 years (range: 35.8–46.0). A score of ≥ 2 was found in 16.4% of the patients (31 out of 189 patients). Equal percentages were found in men and women, respectively 16.9% (11 out of 65 men) and 16.1% (18 out of 112 women), ($\chi^2(1) = 0.0$, $p = 1.0$) at a corrected mean age of 35.8 years for men and 43.6 years for women. Importantly, when comparing uncorrected mean age men were younger at the time of assessment compared to women (U = 1, $p = .016$).

3.3.2. Size and number of white matter lesions

Seven studies reported lesions number and/or size [3,14,17,19,21,39,44]. The three studies measuring WML size used different methods, complicating comparability (Supplementary Table B). Methods varied from measuring total length of all lesions to WML diameter per lesion normalized for head size. Five studies reported the number of lesions, with lesion counts ranging from a single lesion to > 10 lesions (Supplementary Table B).

3.3.3. White matter lesion volume

Six studies (on four different cohorts) reported total WML volume [5,20,27,40–42], in 279 patients with a corrected mean age of 39.5 years (range 36.5–46.0 years) (Table 4). In the largest cohort, a mixed group of 223 patients, men and women showed comparable mean WML volumes (4.7 ml in men, 4.9 ml in women) [5]. Again, in this study men were significantly younger compared to women.

3.4. Location

Twelve studies reported the location of WMLs [3,14,18,19,22,26,27,35–37,39,44]. WML locations were classified as periventricular, deep and subcortical or by specific anatomical or circulatory area.

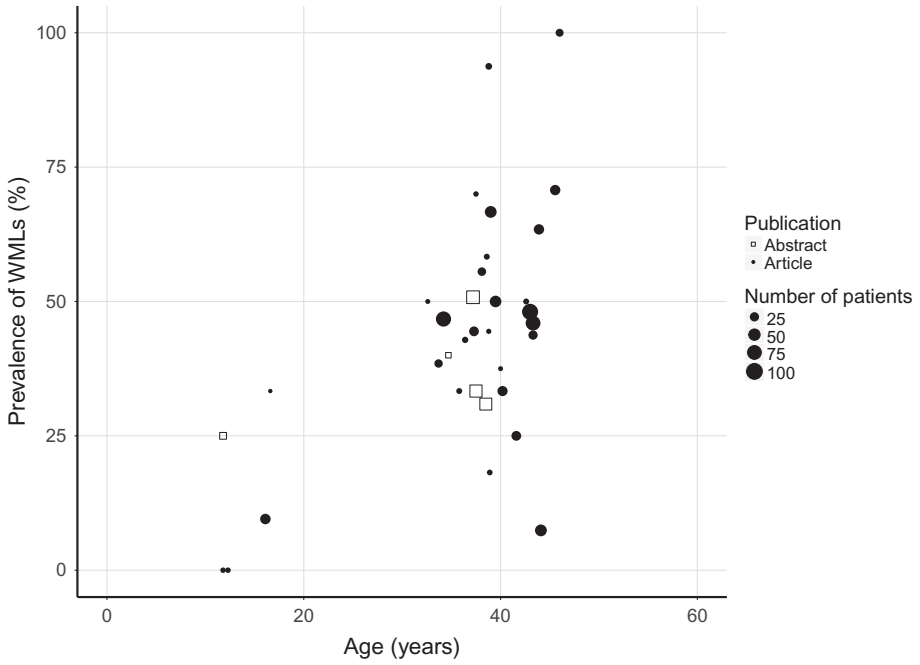

Fig. 1. Prevalence of white matter lesions (WMLs) per study in relation to age.

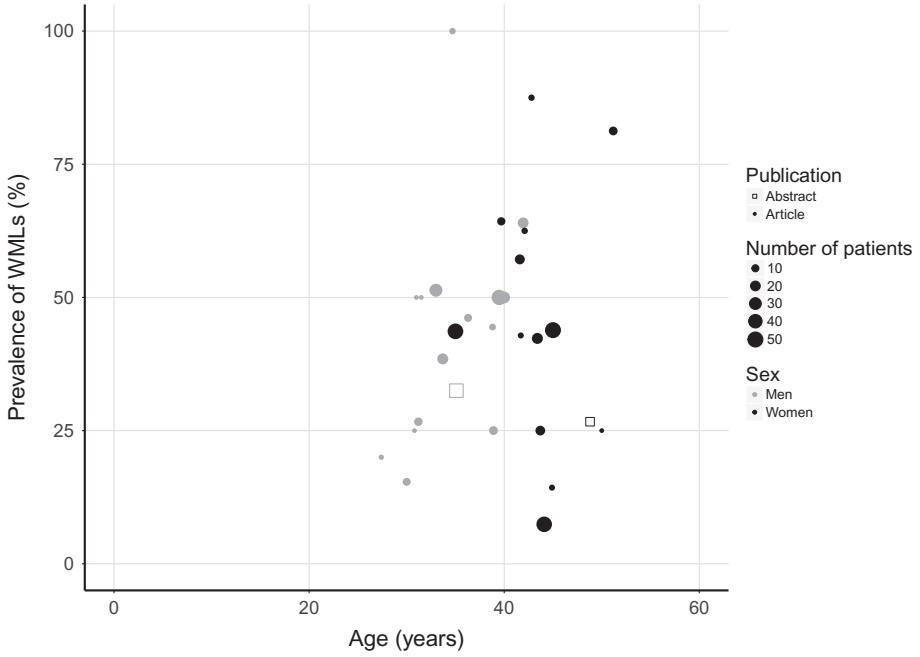

Fig. 2. Prevalence of white matter lesions (WMLs) per study, divided by sex in relation to age.

3.4.1. Periventricular, deep and subcortical WMLs

In eight publications the location of WMLs was described as periventricular, deep and/or subcortical [3,14,18,19,22,36,37,44], two of which report on the same cohort during one and two year follow-up [19,44]. Periventricular WMLs were found in all eight articles [3,14,18,19,22,36,37,44], with periventricular involvement ranging from 21% [36] to 100% [22] of included patients. Deep WMLs were found in seven studies [3,14,18,19,36,37,44], with deep white matter involvement ranging from 25% [19] to 100% [36] of included patients. Subcortical lesions were described in two cohorts [18,44].

3.4.2. Specific anatomical and circulatory areas

Seven studies located WMLs according to anatomical areas and two studies according to circulatory areas (Supplementary Table C). White matter involvement occurred in the anterior, middle as well as the posterior circulation, and WMLs were mostly found in the frontal, parietal and temporal lobes. The brainstem, cerebellum and grey matter were less frequently affected.

Since some patients with FD are initially misdiagnosed as having multiple sclerosis one study used corpus callosum involvement to differentiate between 117 multiple sclerosis patients and a mixed cohort of 104 FD patients [35]. Only 3% of FD patients had WMLs in the corpus callosum compared to 90% of the multiple sclerosis patients. This finding may assist in the differential diagnosis of these disorders.

Table 2
Prevalence of WMLs.

	All patients*	Sex known	
		Men†	Women†
Number of patients with WMLs (articles only), n	581	145	130
WML prevalence (articles only), %	45.5%	46.9%	41.0%
Number of patients with WMLs (including abstracts), n	707	168	139
WML prevalence (including abstracts), %	44.8%	45.7%	40.2%

*Includes mixed cohorts, pediatric cohorts, men only cohorts and women only cohorts, †Includes all articles from the "All patients" group that presented data on prevalence of WMLs divided by sex
WML(s) = White matter lesion(s)

3.5. Course

Eleven studies assessed the course of WMLs over time [3,12,14,16,23,26,29,30,32,41,44] either by assessment of a radiologist or by quantitative measurement using volume or diameter.

3.5.1. Assessment by radiologist

In ten studies WMLs were reported as progressive or stable, in a total of 241 patients (corrected mean baseline age: 37.4 years, range: 11.8–46.1) (Table 5).

A total of 24.6% of patients showed progression of WMLs (49 out of 199 patients) and 75.4% of patients had stable WMLs (150 out of 199 patients) over a corrected mean follow-up time of 38.1 months (range: 6–96 months). A higher percentage of patients on ERT showed progression versus untreated patients (21.6%, 30 out of 139 patients versus 13.9%, 5 out of 36 patients respectively), most likely because untreated patients had milder disease. Men and women showed comparable rates of progression (20.7% of men over a corrected mean follow-up time of 24.9 months (17 out of 82 men, corrected mean baseline age: 34.5 years) versus 23.1% of women over a corrected mean follow-up time of 46.1 months (15 out of 65 women, corrected mean baseline age: 42.1 years)). Again men were significantly younger compared to women when comparing uncorrected baseline age (U = 0, p = .004). Uncorrected mean follow-up time was not different between men and women (U = 10, p = .41).

3.5.2. Quantitatively measured course

Two studies assessed WMLs quantitatively over time [14,41]. In one study, a mixed cohort of 14 patients (4 men, 10 on ERT), significant progression of the median white matter lesion load (WMLL) from 0.12 ml to 1.03 ml was found [41]. The second study, a post-hoc analysis of a RCT comparing agalsidase-beta (Fabrazyme; Genzyme Corp., Cambridge, Massachusetts, USA) showed significant progression of WML diameter in both treated and untreated patients (n = 41, 38 men, 25 treated, mean follow-up time 27 months) [14].

3.6. Relation of white matter lesions to cerebral parameters

To gain more insight in the pathophysiology of WML development in FD, 18 studies assessed the relation between WMLs and other cerebral parameters (Supplementary Table D).

3.6.1. Brain metabolism, cerebral blood flow and diffusion of water molecules

Twelve studies used imaging techniques to quantify water molecule diffusivity, brain metabolism and cerebral blood flow (CBF) (Supplementary Table D).

Hypometabolic areas were found in correspondence with infarctions and hemorrhages, but also in deep and periventricular white matter of patients with and without WMLs, compared to controls. N-acetylaspartate, a nervous system-specific metabolite of which decreases have been linked to neuronal damage [63], was found to be decreased in areas with WMLs. In some patients, these areas extended into the normal appearing white matter (NAWM). Moreover, regions of increased CBF showed a similar pattern, extending from areas with WMLs into the NAWM. It was therefore hypothesized that microstructural alterations happen in areas with WMLs but also in adjacent areas with NAWM.

Diffusion weighted imaging (DWI), an imaging technique using random motion of water molecules, was performed in six studies in five different cohorts, in a total of 111 patients (corrected mean age: 41.9 years, range: 38.1–46.0, 58 men) (Supplementary Table D). Motion of water molecules can be influenced by changes in structural organization, permeability and cellularity of brain tissue [64]. Derivative variables are mean diffusivity (MD), the average random molecular diffusion rate and fractional anisotropy (FA), as well as the preferred direction of diffusion [65]. Increased MD and decreased FA can be the result of cell damage (increasing random diffusion, and thereby MD) and decreased fiber integrity (decreasing anisotropy and thereby FA) [66]. Increased MD was found in men and women with FD compared to controls, especially in the temporal, frontal and parietal white matter. Three studies showed reduced FA in men and women with FD compared to controls, with no clear regional preference. In contrast, two studies assessing the same cohort, did not find reduction of FA compared to controls.

In five out of six studies increased MD and/or decreased FA were found both in areas with WMLs and in NAWM [27,28,45,46,48]. One of these reported a positive relation between MD and the WMLL, and a negative relation between FA and the WMLL [48].

3.6.2. Other cerebral parameters

In FD patients with microbleeds WMLs were more often present,

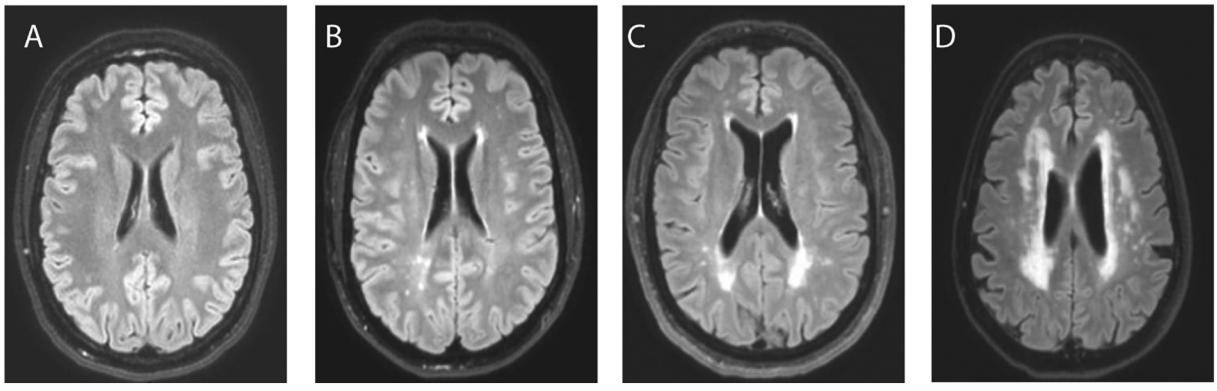

Fig. 3. Modified Fazekas scale in Dutch patients with Fabry disease. A Fazekas score 0, B Fazekas score 1, C Fazekas score 2, D Fazekas score 3.

Table 3
Fazekas score per study.

First author, groups (sex)	Patients per study, n (men)	Age (years), median or mean ± SD (range)	Faz score, mean	Faz 0	Faz 1	Faz 2	Faz 3	Faz 4	Faz 5	Faz 6
Fazekas (0–3), modified										
Paavilianen et al. [28], All	12 (4)	38.6 ± 17.8 (16–68)	1.00	5 (41.7%)	3 (25.0%)	3 (25.0%)	1 (8.3%)	–	–	–
Men	4	31.6 ± 16.1 (17–54)	0.75	2 (50.0%)	1 (25.0%)	1 (25.0%)	0 (0.0%)	–	–	–
Women	8	42.1 ± 18.6 (16–68)	1.13	3 (37.5%)	2 (25.0%)	2 (25.0%)	1 (12.5%)	–	–	–
Üçeyler et al. [31], All	87 (30)	43.3 (16–73)	0.53	47 (54.0%)	35 (40.2%)	4 (4.6%)	1 (1.1%)	–	–	–
Men	30	40.0 (16–40[$])	0.63	15 (50.0%)	12 (40.0%)	2 (6.7%)	1 (3.3%)	–	–	–
Women	57	45.0 (16–73)	0.47	32 (56.1%)	23 (40.4%)	2 (3.5%)	0 (0.0%)	–	–	–
Korsholm et al. [32], All	39 (13)	40.2 ± 14.7 (10–66)	0.56	27 (69.2%)	5 (12.8%)	7 (17.9%)	1 (2.6%)	–	–	–
Men	13	30.0 ± 10.6 (10–47)	0.31	11 (84.6%)	0 (0.0%)	2 (15.4%)	0 (0.0%)	–	–	–
Women	26	43.4 ± 13.9 (15–66)	0.69	15 (57.7%)	5 (19.2%)	5 (19.2%)	1 (3.8%)	–	–	–
Azevedo et al. [37], All	12 (5)	35.8 ± 12.8	0.75	8 (66.7%)	1 (8.3%)	1 (8.3%)	2 (16.7%)	–	–	–
Men	5	27.4 ± 11.5	0.60	4 (80.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	–	–	–
Women	7	41.7 ± 10.6	0.86	4 (57.1%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	–	–	–
Fellgiebel et al. [4], All	27 (13)	38.1 (12–69)	–	12 (44.4%)	6 (22.2%)	9 (33.3%)	*	–	–	–
Men	13	36.3 ± 9.9 (12–51)	–	7 (53.8%)	2 (15.4%)	4 (30.8%)	*	–	–	–
Women	14	39.7 ± 13.5 (19–69)	–	5 (35.7%)	4 (28.6%)	5 (35.7%)	*	–	–	–
Lee et al. [34], All (Mixed)	12 (4)	42.6 ± 14.3 (18–61)	0.67	6 (50.0%)	4 (33.3%)	2 (16.7%)	0 (0.0%)	–	–	–
Duning et al. [27], All (Mixed)	23 (12)	46.0 (29–61)	1.9	–	–	–	–	–	–	–
Fazekas (0–6), original										
Cocozza et al. [36], All (Mixed)	32 (12)	43.3 ± 12.2 (20–68)	0.66	18 (56.3%)	11 (34.4%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Gavazzi et al. [13], All	16 (8)	38.8 ± 13.9 (17–58)	2.06	1 (6.3%)	8 (50.0%)	3 (18.8%)	0 (0.0%)	2 (12.5%)	1 (6.3%)	1 (6.3%)
Men	8	34.7 ± 10.0 (22–58)	2.13	0 (0.0%)	4 (50.0%)	2 (25.0%)	0 (0.0%)	1 (12.5%)	1 (12.5%)	0 (0.0%)
Women	8	42.8 ± 16.6 (17–58)	2.00	1 (12.5%)	4 (50.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)	0 (0.0%)	1 (12.5%)
Buechner et al. [23], All	41 (25)	45.6 (19–74)	–	12 (29.3%)	6 (14.6%)	23 (56.1%)	#	#	#	#
Men	25	41.9 ± 10.8 (21–62)	–	9 (36.0%)	3 (12.0%)	13 (52.0%)	#	#	#	#
Women	16	51.2 ± 18.0 (19–74)	–	3 (18.8%)	3 (18.8%)	10 (62.5%)	#	#	#	#
Cocozza et al. [35], All (Mixed)	104 (40)	43.0 ± 13.4 (13–72)	2.3	–	–	–	–	–	–	–

* Fazekas score 2 and 3 were grouped, [#] Fazekas 2–6 were grouped, [$]Adopted from the original article. However, it was considered unlikely that median and maximum age were both 40 years.
Faz = Fazekas, − = Not available

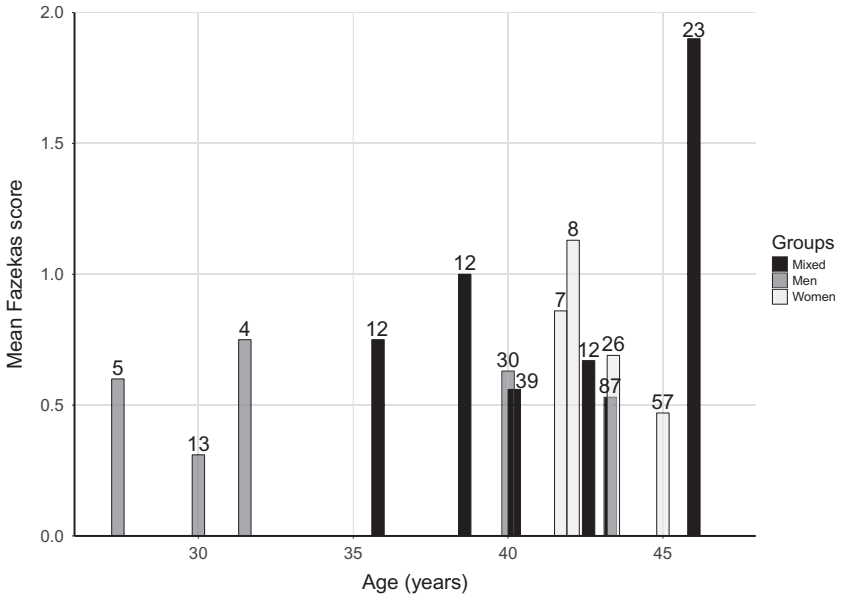

Fig. 4. Mean Fazekas score per study in relation to age. Whole study cohorts are labeled as "Mixed" and if available as sex divided subgroups. Number of patients is displayed at the top of each bar.

Table 4
White matter lesion volume per study.

First author, group (Sex)	Patients per study, n (men)	Age (years), median/ mean	Volume WMLs (ml), mean	Volume WMLs (ml), range
Marino et al. [20], All	8 (4)	40.0	2.8	0.9–18.2
Men	4	31.0	1.1	0.9–3.5
Women	4	50.0	4.6	18.2
Rost et al. [5], All	223 (91)	39.2	4.7	0.3–61.2
Men	91	34.7	4.7	–
Women	132	42.3	4.9	–
Duning et al. [27], All (Mixed)	23 (12)	46.0	3.0	–
Fellgiebel et al. [40,42], All (Mixed)	25 (10)	36.5	2.0	0–24.1
Lelieveld et al. [41]*, All (Mixed)	14 (4)	46.1	1.0	0–2.8

* Provided eight-year follow-up data on 14 patients from the earlier studies by Fellgiebel et al [40,42]. WMLs = white matter lesions, ml = milliliter, – = Not available

compared to patients without microbleeds (Supplementary Table D). No strong relation was found between the diameter of large intracranial arteries and WMLs. Moreover, studies reported no relation between WMLL and hippocampal volume and atrophy, white and grey matter volume, functional connectivity of the motor cortex and between presence of WMLs and increased motor cortex excitability. In one study an abnormal pattern of brain activation was found during a simple motor task (finger tapping) in 16 FD patients compared to healthy control subjects [13]. While no relation was established between the WMLL and motor functions, the sensorimotor cortex activation contralateral of the tapping fingers correlated with the WMLL.

3.7. Relation of white matter lesions to patient characteristics and clinical parameters

Twenty-four studies assessed the relation of WMLs to patient characteristics and clinical parameters [1,3–5,14,17,19,21,22,25–27,29,31,32,40,41,44,48–53].

3.7.1. White matter lesions, TIA and/or stroke

Two follow-up studies reported that WML severity at baseline was related to progression of WML severity during follow-up, both in treated and untreated patients [14,41].

The majority of seven studies [3,5,14,31,32,41,48] supported a positive relation between WMLs and TIA and/or stroke: a higher prevalence of TIA and/or stroke in patients with WMLs was found [3,32], while a follow-up study reported that patients with a history of stroke had more WMLs at baseline and developed more WMLs [14]. A large mixed cohort study on 223 patients (91 men) showed that stroke was related to the WMLL in a multivariate model but TIA was not [5]. No relation between TIA and/or stroke and WMLs was reported in three articles [31,41,48], but the largest (n = 87) did not formally test the relation [31] and the two other studies were relatively small.

3.7.2. Age, sex and phenotype

Six studies reported that patients with WMLs are significantly older compared to patients without WMLs [4,17,22,26,29,50] and twelve studies showed a positive relation between age and presence of WMLs or WMLL [1,3,5,14,21,25,40,41,44,48,52,53].

The four studies that assessed the relation between sex and WMLs did not find differences between men and women in the presence of WMLs or WMLL [4,5,21,53]. However, in the largest study men were significantly younger compared to women, while WMLL was comparable [5].

Only one study, a mixed cohort including 283 patients with MRI of the brain, assessed subgroups divided by both sex and phenotype [1]. Men as well as women with classical disease were more likely to have WMLs compared to men with non-classical disease. MRIs of 42 pediatric patients were also assessed and all four pediatric patients with WMLs (3 boys, 1 girl) had classical FD.

3.7.3. Cerebrovascular risk factors

Five studies assessed the relation between cerebrovascular risk factors and WMLs [3–5,26,52]. No relation was found between the presence of WMLs and cholesterol-level [52], hypertension [3,52] or smoking [3] or between WMLL and smoking [5]. In a fourth study, a mixed cohort with 27 patients (13 men), there were no differences in WMLL between men and women and no differences in history of hypertension, serum LDL-cholesterol, smoking or APOE-4 frequency [4]. In the last study, a mixed cohort with 10 pediatric and 36 adult patients showed that patients with WMLs had more vascular risk factors (defined as a history of hypertension, dyslipidemia, diabetes and/or smoking), compared to patients without WMLs [26].

3.7.4. Renal and cardiac involvement and the Mainz Severity Score Index

Seven studies assessed the relation between renal involvement and WMLs [3,5,14,26,31,41,48]. No relation was found between WMLL and renal function [14,41], WMLL or presence of WMLs and renal dysfunction/complications [3,5,26,31,48] or WMLL and decreasing estimated glomerular filtration rate during follow-up [14].

Five studies assessed the relation between cardiac involvement and WMLs [5,14,26,41,48]. No relation was found between the WMLL and cardiovascular dysfunction [48], WMLL or presence of WMLs and hypertrophic cardiomyopathy [5,26,41] or WMLL and arrhythmias [5,41]. One follow-up study reported a relation between the left ventricular posterior wall thickness and WMLL at baseline and during follow-up [14].

Of two studies reporting on the Mainz Severity Score Index (MSSI) in relation to WMLs, one article found no significant differences between patients with WMLs and patients without WMLs on MSSI-scores [26]. The second study found that WMLL and MSSI-scores were moderately related [50].

3.7.5. Relations to other clinical parameters and patient characteristics

Ten studies assessed the relation between other clinical parameters, patient characteristics and WMLs (Supplementary Table E). No relation between WMLL and neuropsychological test scores or depression frequency and severity was found. However, during follow-up a relation was found between increased WMLL and decreased performance on an executive task.

The presence of WMLs was not related to residual enzyme activity, nor to the presence of antibodies against recombinant agalsidase A. On the other hand, high lysoGb3 level, a biomarker in FD, was related to an increased risk of developing WMLs in men. Subsequently, reduction in lysoGb3 and Gb3 predicted a decreased risk of WML development in the first year of treatment in both men and women with FD. Finally, some genetic polymorphisms related to cerebral ischemia in the general population were related to presence of WMLs in FD while others were not.

4. Discussion

WMLs are present in almost half of the patients with FD and their prevalence increases with age. In the majority of FD patients a mild WMLL is found (Fazekas 0–1), but 16% of FD patients have a substantial WMLL with (beginning) confluent WMLs (Fazekas ≥ 2). In the general population WMLs are commonly found, especially in the elderly [67]. However, the prevalence and severity of WMLs reported in FD

Table 5
Radiological assessment of white matter lesion course per study.

First author, groups (Sex)	Patients in study, n (men)	Patients in follow-up, n	Age at first MRI (years), median/mean	Patients on ERT, n	Follow-up time (months), mean	Progression, n (n no ERT, n ERT)	Stable, n (n no ERT, n ERT)
Buechner et al. [23], All	41 (25)	24 (13)	41.7	15	30 m	9 (4 no ERT, 5 ERT)	15 (5 no ERT, 10 ERT)
Men	25	13	37.2	10	17 m	4 (1 no ERT, 3 ERT)	9 (2 no ERT, 7 ERT)
Women	16	11	47.1	5	44 m	5 (3 no ERT, 2 ERT)	6 (3 no ERT, 3 ERT)
Ortu et al. [12], All	11 (4)	9 (2)	40.8	9	12 m	0 (0 no ERT, 0 ERT)	9 (0 no ERT, 9 ERT)
Men	4	2	26.5	2	12 m	0 (0 no ERT, 0 ERT)	2 (0 no ERT, 2 ERT)
Women	7	7	44.9	7	12 m	0 (0 no ERT, 0 ERT)	7 (0 no ERT, 7 ERT)
Korsholm et al. [32], All	40 (14)	34 (12)	39.2	29	47 m	3 (0 no ERT, 3 ERT)	31 (5 no ERT, 26 ERT)
Men	14	12	29.5	11	52 m	0 (0 no ERT, 0 ERT)	12 (1 no ERT, 11 ERT)
Women	26	22	44.5	18	45 m	3 (0 no ERT, 3 ERT)	19 (4 no ERT, 15 ERT)
Rombach et al. [29], All	63 (32)	56 (27)	39.4	56	–	21 (0 no ERT, 21 ERT)	35 (0 no ERT, 35 ERT)
Men	30	25	37.3	25	37 m	12 (0 no ERT, 12 ERT)	13 (0 no ERT, 13 ERT)
Women	27	25	46.6	25	48 m	7 (0 no ERT, 7 ERT)	18 (0 no ERT, 18 ERT)
Pediatric (Mixed)	6 (2)	6 (2)	16.6	6	–	2 (0 no ERT, 2 ERT)	4 (0 no ERT, 4 ERT)
Jardim et al. [44], All	8 (7)	6 (5)	35.0	6	24 m	1 (0 no ERT, 1 ERT)	3 (0 no ERT, 3 ERT)[$]
Men	7	5	32.8	5	24 m	1 (0 no ERT, 1 ERT)	3 (0 no ERT, 3 ERT)[$]
Woman	1	1	46.0	1	24 m	0 (0 no ERT, 0 ERT)	0 (0 no ERT, 0 ERT)[$]
Reisin et al. [26], All (Mixed)	46 (18)	22 (? + 3)	–	–	–	5 (1 no ERT, 4 ERT)	17 (17 unknown)
Pediatric (Mixed)	10 (3)	10 (3)	11.8	1	–	1 (0 no ERT, 1 ERT)	9 (9 no ERT, 0 ERT)
Borgwardt et al. [30], Pediatric (Mixed)	10 (6)	10 (6)	12.3	10	–	0 (0 no ERT, 0 ERT)	10 (0 no ERT, 10 ERT)
Lelieveld et al. [41], All (Mixed)	25 (10)	14 (4)	46.1	10	96 m	10 (10 unknown)	4 (4 unknown)
Crutchfield et al. [3], Men	52 (52)	40 (40)	–	0	–	4 +? * (4 +? no ERT, 0 ERT)	9 +? * (9 +? no ERT, 0 ERT)
Moore et al. [16], Men	26 (26)	26 (26)	33.7	14	6 m	0 (0 no ERT, 0 ERT)	26 (12 no ERT, 14 ERT)[#]

$ Description in study: “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.” The patients with fluctuating and disappearing WMLs were removed from the analysis. * Description in study: “Patients who had lesions and who were studied multiple times usually had increased lesion load on subsequent testing.” This study was excluded from further analyses, # Description in study: “There was no significant progression of the lesion burden over the 6-month trial period.” Patients were classified as being stable.
- = Not available, m = months, unknown = ERT status unknown

corresponds to that found in individuals in the general population that are at least one to three decades older [67,68].

When combining all studies, prevalence, severity and progression of WMLs are comparable in men and women. However, men were significantly younger compared to women at time of the WML assessment (approximately 6–7 years), supporting the concept that men are more severely affected than women, since WMLs tend to progress over time. Perhaps an even larger difference exist as most studies in the general population point to an increased risk of WMLs in women [68]. It is likely that phenotype plays a role as well: classically affected males have faster disease progression than classical females or non-classical patients. Most studies did not take phenotype into consideration, but a single report dividing patients by sex and phenotype suggests that indeed phenotype does play a role in the risk of WML development in FD [1].

To establish their role as a biomarker of cerebral involvement in FD, WMLs should be linked to clinically relevant endpoints. In the general population WMLs are related to stroke, cognitive dysfunction and mortality [69]. We found that, despite not uniformly shown in every study, WMLs and WMLL are most probably related to the occurrence of stroke in FD. Of importance is whether there is a link between high WMLL and cognitive dysfunction. This is currently being investigated at our center. In contrast, renal and cardiac disease were not found to be related to the presence and severity of WMLs. Conversely, decreased renal function is related to increased WMLL in the general population [70]. It is possible that men with classical FD (who are prone to develop kidney failure) have a higher WMLL, since studies did not incorporate phenotype in their analyses and studies lacked power to detect this relation. Of clinical importance is the fact that two studies found no relation between arrhythmias and WMLs, because supraventricular rhythm disturbances, in particular atrial fibrillation, is a risk factor for ischemic stroke.

No specific location and distribution of WMLs can be established in FD: the frontoparietal and temporal white matter are most often affected and both the periventricular and deep white matter are involved. Despite early reports that the posterior circulatory areas are most severely affected in FD, this was not confirmed by analysis of the location and distribution. A major feature of posterior circulation alterations in FD, an increased basilar artery diameter, was also not related to WML development in FD. It is expected in FD that WMLs originate from pathological changes of the small cerebral vessels, and that large vessel abnormalities might play little to no role in the origin of WMLs. In the general population both periventricular and deep WMLs have been attributed to small vessels pathology, but with regional differences in pathology [71,72].

Follow-up of WML development was performed in a minority of studies, despite the possible role of WMLs as biomarker for cerebral involvement in FD. We found that a quarter of patients show progression of WMLs during three years follow-up irrespective of sex and treatment status. Evaluating the effect of ERT on WMLs is unreliable due to four points: 1) most follow-up cohorts are subgroups of bigger cohort studies and no background characteristics are provided for these subgroups, 2) there is a treatment bias, with more severely affected patients being treated earlier, 3) there are very little follow-up data of untreated patients, 4) most RCTs comparing ERT to a placebo did not incorporate WML development. In a post-hoc analysis of a RCT comparing agalsidase-beta to a placebo, significant progression of WML diameter was seen, comparable in the treated versus untreated group [14]. Most of these patients were male, with advanced FD. In patients under 50 years old less progression of WML diameter and a more stable WMLL was found in the agalsidase-beta group compared to the placebo group. However, the subgroup included only 38% of the original patient cohort and the analysis of this subgroup was not predefined. A consensus document on treatment in FD stated that ERT "may be considered" for the treatment of WMLs (evidence class IIB) [73], a conclusion that cannot be changed after this systematic review. Unfortunately, none of the future, ongoing or recently published trials mention cerebral MRIs or WMLs as their primary or secondary outcome on ClinicalTrial.gov, except for a German observational prospective cohort study of patients treated with chaperone therapy [74].

In the general population, hypertension is considered the biggest risk factor for WML development, next to age [75]. Surprisingly, only one of five articles reported a relation between cerebrovascular risk factors and WMLs in FD. Since the frequency of hypertension is similar to the general population (Korver et al., unpublished analysis based upon Arends [76]), the WMLs we see in the majority of younger patients with FD probably have a different pathological origin. Naturally, vascular risk factors are still very important to address in patients with FD, especially as with treatment and supportive care patients become older.

The pathophysiology of WML in FD is probably complex. Glycosphingolipid accumulation in the smooth muscle cell of the vessel wall may lead to a less compliant vascular wall due to fibrosis and impairment of autoregulation of cerebral perfusion [66,77]. The shear stress due to a hyperdynamic circulation and an incompliant vessel wall might then lead to endothelial dysfunction. Combined with storage in the endothelium, especially prevalent in classical male patients, increases in reactive oxygen species and pro-thrombotic/pro-inflammatory cytokines as well as upregulation of the renin–angiotensin system are the result [77,78]. Changes in regional metabolism, cerebral blood flow, MD and FA were found beyond the borders of the WMLs. As was previously hypothesized [66], this might indicate a pathological continuum extending into the NAWM, compatible with findings in the general population [75,79]. In addition to the described vascular/perfusion pathology, non-ischemic contributors to WML development that have been found in the general population are glial dysfunction, neuroinflammation, blood-brain barrier disruption and genetic predisposition and these factors may also contribute to WML development in FD [79]. Post mortem studies in FD have shown widespread glycosphingolipid accumulation in the brain itself [80–82]. Swelling of neurons, axons and glial cells was also noted [81,82]. One post mortem study in a man with progressive cognitive complaints and severe WMLs on MRI showed astrocytic swelling and increased astrocytic processes, indicating glial dysfunction in FD [82]. Moreover, increased protein levels have been found in the cerebral spinal fluid of FD patients that were described as having aseptic meningitis and in patients misdiagnosed as having multiple sclerosis [83,84]. This could indicate blood-brain barrier dysfunction. In the Fabry mouse a disruption of the autophagy-lysosome pathway has been described in the brain, possibly adding to axonal pathology [85]. A study by Altarescu et al. [52] showed that a number of genetic polymorphisms contributed to the risk of WML development in FD patients.

Pathology studies in cell or mouse models and brain tissue samples obtained post mortem could further explore potential pathways resulting in WML development in FD.

Some included studies extensively described the definition and criteria to determine WMLs, while most did not. It might therefore be possible that some lacunar infarctions were classified as WMLs. We did not exclude studies with limited description of WML methods since: 1) we would be left with a small group of studies, 2) we expect that WMLs and lacunar infarctions might represent a spectrum of cerebral disease and have similar pathology in FD and 3) the differentiation between WMLs and lacunar infarctions is difficult, even with extensive definitions [86]. However, we do encourage future studies to provide well defined definitions and criteria for WMLs.

In this study we systematically reviewed WMLs in FD. It is clear that many unresolved questions remain, which have been summarized in Table 6 including proposals for future research directions.

5. Conclusions

A significant group of FD patients has confluent WMLs and a substantial WMLL, which progresses over time. As expected, men with FD start developing WMLs earlier compared to women and patients with classical disease are more severely affected compared to non-classical patients. WMLs seem to be related to stroke, represent cerebral small vessel dysfunction but systematic studies fail that address influence of

Table 6
Main findings and future research directions on WMLs in FD.

Topic	Main findings	Future research directions
Prevalence	• WMLs were present in 46% of patients with FD at 39 years of age and their number increased with age • Men with FD develop WMLs at a younger age compared to women with FD • Patients with classical FD appear to have a higher risk of WML development compared to patients with non-classical FD	• Strengthen the findings on the relations between phenotype, sex of FD patients and prevalence of WMLs • Correct for age when comparing subgroups of FD patients with WMLs • Avoid using only "presence" or "absence" of WMLs, since this provides minimal information and decreases power to detect risk factors
Severity	• 16% of patients with FD had a substantial amount of WMLs • Men with FD develop a higher WMLL at a younger age compared to women with FD	• Further explore the relation between phenotype and WML severity • Use well established scales or volumetric measurements of WMLL to assess WML severity
Location	• No clear pathognomonic location or distribution of WMLs in FD was found • WMLs were present in both the periventricular and deep white matter	• Include WML location and distribution since local differences in underlying pathology and consequences of WMLs might be present
Course	• WMLs progressed in 1/4th of patients with FD over three years follow-up • WMLs progressed in both men and women, with and without ERT • Men with FD show progression of WMLs at a younger age compared to women	• Report patient characteristics of (sub)groups in longitudinal studies • Report on the course of WMLs in untreated patients • Include WMLs as outcome parameters in trials evaluating (new) treatments • Use quantifiable methods of WML assessment
Clinical relations and consequences: brain parameters	• There might be changes in metabolism and CBF in areas with WMLs extending into the NAWM • Loss of cellular integrity and/or increased interstitial water content seem to be present, even in FD patients without WMLs • WMLs seemed to be related to stroke	• Explore whether changes in NAWM precede WML formation using longitudinal follow-up combining structural MRI modern imaging techniques • Confirm the relation between stroke (subtypes) and WML (severity) in longitudinal studies • Study the relationship between the presence of WMLs and clinical consequences (e.g. cognitive functioning) • Study model organisms to explore pathways resulting in WML development in FD
Clinical relations and consequences: other	• Renal and cardiac (dys)function did not seem to be (strongly) related to the amount of WMLs in FD • Cerebrovascular risk factors did not seem to be (strongly) related to the amount of WMLs in FD	• Identify factors contributing to risk of WML development in FD

WMLs = white matter lesions, WMLL = white matter lesion load, ERT = enzyme replacement therapy, CBF = cerebral blood flow, NAWM = normal appearing white matter.

treatment as well as important clinical outcomes such as cognitive function. Traditional cerebrovascular risk factors probably have a minor effect on development of WMLs in patients. Future studies should focus on longitudinal follow-up using modern imaging techniques, with emphasis on the clinical consequences of WMLs and use of WMLs in treatment trials. Last but not least, ischemic and non-ischemic pathways resulting in WML development should be studied.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2018.08.014.

Competing interests

SK and MV report no disclosures. CH and ML report that Sphinx (through AMC-research BV) is involved in pre-marketing studies with Sanofi-Genzyme, Protalix and Idorsia; they do not have any other financial relationship with pharmaceutical companies. IS chairs a steering committee for CSL Behring and received departmental honoraria for serving on scientific advisory boards for CSL Behring. All lecturing and consulting fees for INS were donated to the Stichting Klinische Neurologie, a local foundation that supports research in the field of neurological disorders.

Funding

The study was funded by the Academic Medical Center (innovation grant 2014). There is no role of the funding body in the design of the study, collection analysis and interpretation of data, or in writing the manuscript.

Authors' contributions

SK and MV conceptualized the study design, completed the search on Pubmed, Embase and Cochrane, completed acquisition, analyses and interpretation of data on white matter lesions and had major contributions to the first draft of manuscript.

CH and ML conceptualized the study design, interpreted data, provided study supervision and critical revision of the manuscript.

IS interpreted data, provided study supervision and critical revision of the manuscript

All authors read and approved the final manuscript.

Acknowledgements

None.

References

[1] M. Arends, et al., Characterization of classical and nonclassical fabry disease: A multicenter study, J. Am. Soc. Nephrol. 28 (5) (2017) 1631–1641.
[2] R. Schiffmann, et al., Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference, Kidney Int. 91 (2) (2017) 284–293.
[3] K.E. Crutchfield, et al., Quantitative analysis of cerebral vasculopathy in patients with Fabry disease, Neurology 50 (6) (1998) 1746–1749.
[4] A. Fellgiebel, et al., White matter lesion severity in male and female patients with Fabry disease, Neurology 65 (4) (2005) 600–602.
[5] N.S. Rost, et al., Determinants of white matter hyperintensity burden in patients with Fabry disease, Neurology 86 (20) (2016) 1880–1886.
[6] A.L. Traboulsee, D.K. Li, The role of MRI in the diagnosis of multiple sclerosis, Adv. Neurol. 98 (2006) 125–146.
[7] R. Schiffmann, M.S. van der Knaap, Invited Article: An MRI-based approach to the diagnosis of white matter disorders, Neurology 72 (8) (2009) 750–759.
[8] E. Kolodny, et al., Cerebrovascular involvement in Fabry disease: current status of knowledge, Stroke 46 (1) (2015) 302–313.
[9] D. Moher, et al., Preferred reporting items for systematic reviews and meta-analyses: The prisma statement, Ann. Intern. Med. 151 (4) (2009) 264–269.
[10] T. Nissen, R. Wynn, The clinical case report: a review of its merits and limitations, BMC Res. Notes 7 (2014) 264.
[11] Covidence systematic review software, Veritas Health Innovation, Available from www.covidence.org.
[12] E. Ortu, et al., Primary motor cortex hyperexcitability in Fabry's disease, Clin.

Neurophysiol. 124 (7) (2013) 1381–1389.
[13] C. Gavazzi, et al., Subcortical damage and cortical functional changes in men and women with Fabry disease: a multifaceted MR study, Radiology 241 (2) (2006) 492–500.
[14] A. Fellgiebel, et al., Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease, Cerebrovasc. Dis. 38 (6) (2014) 448–456.
[15] G. Tedeschi, et al., Diffuse central neuronal involvement in Fabry disease: a proton MRS imaging study, Neurology 52 (8) (1999) 1663–1667.
[16] D.F. Moore, et al., Enzyme replacement reverses abnormal cerebrovascular responses in Fabry disease, BMC Neurol. 2 (2002) 4.
[17] D.F. Moore, et al., White matter lesions in Fabry disease occur in 'prior' selectively hypometabolic and hyperperfused brain regions, Brain Res. Bull. 62 (3) (2003) 231–240.
[18] J. Takanashi, et al., T1 hyperintensity in the pulvinar: key imaging feature for diagnosis of Fabry disease, AJNR Am. J. Neuroradiol. 24 (5) (2003) 916–921.
[19] L. Jardim, et al., CNS involvement in Fabry disease: clinical and imaging studies before and after 12 months of enzyme replacement therapy, J. Inherit. Metab. Dis. 27 (2) (2004) 229–240.
[20] S. Marino, et al., Diffuse structural and metabolic brain changes in Fabry disease, J. Neurol. 253 (4) (2006) 434–440.
[21] L. Ginsberg, et al., Magnetic resonance imaging changes in Fabry disease, Acta Paediatr. Suppl. 95 (451) (2006) 57–62.
[22] M. Low, et al., Neurology of Fabry disease, Intern. Med. J. 37 (7) (2007) 436–447.
[23] S. Buechner, et al., Central nervous system involvement in Anderson-Fabry disease: a clinical and MRI retrospective study, J. Neurol. Neurosurg. Psychiatry 79 (11) (2008) 1249–1254.
[24] A.P. Burlina, et al., The pulvinar sign: frequency and clinical correlations in Fabry disease, J. Neurol. 255 (5) (2008) 738–744.
[25] S.M. Rombach, et al., Plasma globotriaosylsphingosine: diagnostic value and relation to clinical manifestations of Fabry disease, Biochim. Biophys. Acta 1802 (9) (2010) 741–748.
[26] R.C. Reisin, et al., Brain MRI findings in patients with Fabry disease, J. Neurol. Sci. 305 (1–2) (2011) 41–44.
[27] T. Duning, et al., Brainstem involvement as a cause of central sleep apnea: pattern of microstructural cerebral damage in patients with cerebral microangiopathy, PLoS One 8 (4) (2013) e60304.
[28] T. Paavilainen, et al., Diffusion tensor imaging and brain volumetry in Fabry disease patients, Neuroradiology 55 (5) (2013) 551–558.
[29] S.M. Rombach, et al., Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain, Orphanet J. Rare Dis. 8 (2013) 47.
[30] L. Borgwardt, et al., Fabry disease in children: agalsidase-beta enzyme replacement therapy, Clin. Genet. 83 (5) (2013) 432–438.
[31] N. Üçeyler, et al., Increased Arterial Diameters in the Posterior Cerebral Circulation in Men with Fabry Disease, PLoS One 9 (1) (2014) e87054.
[32] K. Korsholm, et al., Positron emission tomography and magnetic resonance imaging of the brain in fabry disease: a nationwide, long-time, Prospective Follow-Up, PLOS ONE 10 (12) (2015) e0143940.
[33] Y. Kono, et al., Characteristics of cerebral microbleeds in patients with fabry disease, J. Stroke Cerebrovasc. Dis. 25 (6) (2016) 1320–1325.
[34] H.-J. Lee, et al., A comparison of central nervous system involvement in patients with classical Fabry disease or the later-onset subtype with the IVS4 + 919G > A mutation, BMC Neurol. 17 (1) (2017) 25.
[35] S. Cocozza, et al., Corpus callosum involvement: a useful clue for differentiating Fabry Disease from Multiple Sclerosis, Neuroradiology 59 (6) (2017) 563–570.
[36] S. Cocozza, et al., Alterations of functional connectivity of the motor cortex in Fabry disease: An RS-fMRI study, Neurology 88 (19) (2017) 1822–1829.
[37] E. Azevedo, et al., Functional transcranial Doppler: presymptomatic changes in Fabry disease, Eur. Neurol. 67 (6) (2012) 331–337.
[38] F. Barbey, et al., Fabry disease in a geriatric population, Clin. Genet. 88 (5) (2015) 499–501.
[39] S. Gupta, et al., The relationship of vascular glycolipid storage to clinical manifestations of Fabry disease: a cross-sectional study of a large cohort of clinically affected heterozygous women, Medicine (Baltimore) 84 (5) (2005) 261–268.
[40] A. Fellgiebel, et al., Diagnostic utility of different MRI and MR angiography measures in Fabry disease, Neurology 72 (1) (2009) 63–68.
[41] I.M. Lelieveld, et al., Eight-year follow-up of neuropsychiatric symptoms and brain structural changes in fabry disease, PLoS One 10 (9) (2015) e0137603.
[42] A. Fellgiebel, et al., Hippocampal atrophy as a surrogate of neuronal involvement in Fabry disease, J. Inherit. Metab. Dis. 35 (2) (2012) 363–367.
[43] D.F. Moore, et al., Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy, Circulation 104 (13) (2001) 1506–1512.
[44] L.B. Jardim, et al., White matter lesions in Fabry disease before and after enzyme replacement therapy: a 2-year follow-up, Arq. Neuropsiquiatr. 64 (3b) (2006) 711–717.
[45] D.F. Moore, R. Schiffmann, A.M. Ulug, Elevated CNS average diffusion constant in Fabry disease, Acta Paediatr. Suppl. 91 (439) (2002) 67–68.
[46] A. Fellgiebel, et al., Pattern of microstructural brain tissue alterations in Fabry disease: a diffusion-tensor imaging study, J. Neurol. 253 (6) (2006) 780–787.
[47] S. Cocozza, et al., Default mode network modifications in Fabry disease: A resting-state fMRI study with structural correlations, Hum. Brain Mapp. 39 (4) (2018) 1755–1764.
[48] J. Albrecht, et al., Voxel based analyses of diffusion tensor imaging in Fabry disease. Journal of Neurology, Neurosurgery &amp, Psychiatry 78 (9) (2007) 964–969.
[49] M. Ries, et al., Neuropathic and cerebrovascular correlates of hearing loss in Fabry disease, Brain 130 (Pt 1) (2007) 143–150.
[50] I. Schermuly, et al., Neuropsychiatric symptoms and brain structural alterations in Fabry disease, Eur. J. Neurol. 18 (2) (2011) 347–353.
[51] S.M. Rombach, et al., Long-term effect of antibodies against infused alpha-galactosidase A in Fabry disease on plasma and urinary (lyso)Gb3 reduction and treatment outcome, PLoS One 7 (10) (2012) e47805.
[52] G. Altarescu, D.F. Moore, R. Schiffmann, Effect of genetic modifiers on cerebral lesions in Fabry disease, Neurology 64 (12) (2005) 2148–2150.
[53] Ginsberg, L., Nervous system manifestations of Fabry disease: data from FOS – the Fabry Outcome Survey, in Fabry Disease: Perspectives from 5 Years of FOS, A. Mehta, M. Beck, and G. Sunder-Plassmann, Editors Oxford PharmaGenesis: Oxford.
[54] C. Mendes, et al., MRI Findings in Anderson- Fabry disease(AFD), Mol. Genet. Metab. 102 (2) (2010) S29.
[55] Y. Ouyang, et al., Characteristics of clinical manifestations in Chinese Fabry patients, 49th ERA-EDTA Congress, Nephrology Dialysis Transplantation, Paris, France, 2012, p. ii426.
[56] P. Pablo, et al., Fabry disease brain MRI findings in adults and children, Neuroradiology (2014) 459–460.
[57] S. Shankar, et al., Fabry disease: Correlation of progression of white matter disease and severity of neurological manifestations with the pulvinar sign, Mol. Genet. Metab. (2009) S40.
[58] C.M. Lourenco, et al., "Night, night, sleep tight?": Sleep disorders in Fabry disease, recognizing an overlooked feature of a complex lysosomal disorder, Mol. Genet. Metab. 114 (2) (2015) S75–S76.
[59] E. Hanson, et al., Multiparametric 3.0 Tesla MRI of the Brain in Fabry Disease, Mol. Genet. Metab. 105 (2) (2011) S33.
[60] C. Lourenco, et al., Evaluation of plasma globotriaosylsphingosine in patients with anderson-fabry disease in Brazil on enzyme replacement therapy with Agalsidase Alfa, Mol. Genet. Metab. 105 (2) (2012) S44.
[61] C. Marchesoni, et al., Brain MRI findings in Fabry Disease, J. Neurol. Sci. 333 (2013) e179–e180.
[62] F. Fazekas, et al., MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJR Am. J. Roentgenol. 149 (2) (1987) 351–356.
[63] J.R. Moffett, et al., N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology, Prog. Neurobiol. 81 (2) (2007) 89–131.
[64] Bammer, R., Basic principles of diffusion-weighted imaging. Eur. J. Radiol. 45(3): p. 169–184.
[65] J.M. Soares, et al., A hitchhiker's guide to diffusion tensor imaging, Front. Neurosci. 7 (2013) 31.
[66] A. Fellgiebel, et al., Quantification of brain tissue alterations in Fabry disease using diffusion-tensor imaging, Acta Paediatr. 96 (455) (2007) 33–36.
[67] F.E. de Leeuw, et al., Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study, J. Neurol. Neurosurg. Psychiatry 70 (1) (2001) 9–14.
[68] P. Sachdev, X. Chen, W. Wen, White matter hyperintensities in mid-adult life, Curr. Opin. Psychiatry 21 (3) (2008) 268–274.
[69] A. Chutinet, N.S. Rost, White matter disease as a biomarker for long-term cerebrovascular disease and dementia, Curr. Treat. Opt. Cardiovas. Med. 16 (3) (2014) 292.
[70] M. Khatri, et al., Chronic kidney disease is associated with white matter hyperintensity volume: The Northern Manhattan Study (NOMAS), Stroke 38 (12) (2007) 3121–3126.
[71] F. Fazekas, R. Schmidt, P. Scheltens, Pathophysiologic mechanisms in the development of age-related white matter changes of the brain, Dement. Geriatr. Cogn. Disord. 9 (Suppl. 1) (1998) 2–5.
[72] Shim, Y.S., et al., Pathological correlates of white matter hyperintensities on MRI. Dement. Geriatr. Cogn. Disord., 2015. 39(0): p. 92–104.
[73] M. Biegstraaten, et al., Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document, Orphanet J. Rare Dis. 10 (2015) 36.
[74] U.S. National Library of Medicine. Clinicaltrials.gov Database. [2018, May 14]; Available from: https://clinicaltrials.gov/ct2/results?cond=Fabry+Disease&term=&cntry=&state=&city=&dist=.
[75] Y. Shi, J.M. Wardlaw, Update on cerebral small vessel disease: a dynamic whole-brain disease, Stroke Vascular Neurol. 1 (3) (2016) 83.
[76] M. Arends, et al., Retrospective study of long-term outcomes of enzyme replacement therapy in Fabry disease: Analysis of prognostic factors, PLoS One 12 (8) (2017) e0182379.
[77] S.M. Rombach, et al., Vasculopathy in patients with Fabry disease: Current controversies and research directions, Mol. Genet. Metab. 99 (2) (2010) 99–108.
[78] M.J. Hilz, et al., Reduced cerebral blood flow velocity and impaired cerebral autoregulation in patients with Fabry disease, J. Neurol. 251 (5) (2004) 564–570.
[79] S.B. Wharton, et al., Age-associated white matter lesions: the MRC Cognitive Function and Ageing Study, Brain Pathol. 25 (1) (2015) 35–43.
[80] Schiffmann, R., et al., Pathological findings in a patient with Fabry disease who died after 2.5 years of enzyme replacement. Virchows Archiv: an international journal of pathology, 2006. 448(3): p. 337–343.
[81] T. Tabira, et al., Neuropathological and biochemical studies in Fabry's disease, Acta Neuropathol. 30 (4) (1974) 345–354.

[82] R. Okeda, M. Nisihara, An autopsy case of Fabry disease with neuropathological investigation of the pathogenesis of associated dementia, Neuropathology 28 (5) (2008) 532–540.
[83] T. Böttcher, et al., Fabry Disease – Underestimated in the Differential Diagnosis of Multiple Sclerosis? PLoS One 8 (8) (2013) e71894.
[84] O. Lidove, et al., Aseptic meningitis and ischaemic stroke in Fabry disease, Int. J. Clin. Pract. 63 (11) (2009) 1663–1667.
[85] M.P. Nelson, et al., Autophagy-lysosome pathway associated neuropathology and axonal degeneration in the brains of alpha-galactosidase A-deficient mice, Acta Neuropathol. Commun. 2 (2014) 20.
[86] E.E. Smith, et al., Prevention of stroke in patients with silent cerebrovascular disease: A scientific statement for healthcare professionals from the american heart association/american stroke association, Stroke 48 (2) (2017) e44–e71.