Molecular Genetics and Metabolism Reports 38 (2024) 101044

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

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

Use of T1 mapping in cardiac MRI for the follow-up of Fabry disease in a pediatric population☆

Oscar Werner [a,b,*], Lydia Ichay [c], Nabila Djouadi [c], Fernando Vetromile [e], Marie Vincenti [a], Sophie Guillaumont [a], Dominique P. Germain [d], Marc Fila [c]

[a] Pediatric Cardiology and Pulmonology Department, M3C Regional Reference Center, Montpellier University Hospital, Montpellier, France
[b] Pediatric Imaging Department, Montpellier University Hospital, Montpellier, France
[c] Pediatric nephrology department, Montpellier University Hospital, Montpellier, France
[d] French Referral Center for Fabry disease, Division of Medical Genetics, University of Versailles and APHP – Paris Saclay University, Garches, France
[e] Nephrology Department, Montpellier University Hospital, Montpellier, France

ARTICLE INFO

Keywords:
Fabry disease
ERT
Cardiac MRI
T1 mapping

ABSTRACT

Background: Fabry disease (FD) is a rare X-linked lysosomal disorder caused by pathogenic variants in the alpha-galactosidase-A gene (*GLA*). Life threatening complications in adulthood include chronic kidney failure, strokes and the cardiac involvement which is the leading cause of mortality. Usually, it presents with hypertrophic cardiomyopathy, together with arrhythmia and conduction abnormalities. An early indicator is decreased T1 value on cardiac magnetic resonance (CMR). Enzyme replacement therapy (ERT) is effective on some extra-cardiac symptoms but its effect on cardiac lesions depends on the level of initial myocardial lesions. CMR is routinely used to monitor cardiac involvement in FD due to its capacity for tissular characterization. However, there is a lack of data on the pediatric population to understand how to integrate CMR into early therapeutic decisions.

Method: Monocentric longitudinal study carried out at Montpellier University Hospital from 2016 to 2022. All pediatric patients with FD were evaluated over time with clinical, biological, and cardiac imaging (CMR, echocardiography).

Results: Out of the six patients included, (3 males), five were treated with ERT during the study. Low T1 values were observed in 4 patients. The normalization of T1 values was observed after 4 years of ERT in 3 patients.

Conclusion: Due to the lack of strong clinical and biological markers of FD in pediatric patients, initiation and follow-up of ERT efficacy remain challenging. CMR with T1-mapping, a noninvasive method, could play a role in the evaluation of early cardiac impairment in young patients at diagnosis and during follow-up with or without ERT.

1. Introduction

Fabry disease (FD, OMIM 301500) is a rare X-linked lysosomal disorder caused by pathogenic variants in the alpha-galactosidase A gene (*GLA*) and is characterized by an accumulation of globotriaosylceramide (GL-3) and other glycolipids in lysosomes and body fluids [1]. This multisystem disease involves principally the kidney, the central nervous system, and the heart leading to chronic kidney disease (CKD), cerebrovascular events, and progressive hypertrophic cardiomyopathy with arrhythmias and conduction defects [1]. The prognosis lies in the severity of the cardiac involvement which has become the leading cause of mortality (40%) [2]. Usually, FD presents in the third decade of life with hypertrophic cardiomyopathy (up to 88% of men with classical FD), valvular disease, or conduction abnormalities that can be complicated by heart failure and arrhythmia. In rarer cases, some aortic dilatation may be seen (in about 30% of male patients with FD). Organ

Abbreviations: FD, Fabry disease; GL-3, globotriaosylceramide; CKD, chronic kidney disease; ERT, Enzyme replacement therapy; CMR, cardiac magnetic resonance; HRQoL, Health related quality of life; TTE, Transthoracic echocardiography; LVEF, left ventricular ejection fraction; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy.

☆ "All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

* Corresponding author at: Pediatric and Congenital Cardiology Department, Montpellier University Hospital, Montpellier, France.
E-mail address: oscarwerner@hotmail.fr (O. Werner).

https://doi.org/10.1016/j.ymgmr.2023.101044
Received 3 October 2023; Received in revised form 20 December 2023; Accepted 20 December 2023

manifestation are associated with the accumulation of GL-3 in specific types of cardiac cells (myocytes, endothelial cells, and valvular fibroblast) [2]. This storage is also present in the other organs and begins early in life. Some authors suggest that this process begins even before birth [3,4].

Enzyme replacement therapy (ERT) has shown a positive effect to prevent the decline of the glomerular filtration rate especially when started early in life [5–7]. ERT may also reduce GL-3 accumulation in cardiac cells and a reduction of left ventricular mass and cardiac wall thickness has been observed [7]. ERT is effective in the early phase of storage but seems to have limited efficacy in the late stage of the disease especially when the process of inflammation and fibrosis is initiated [4,7]. Considering that, an early ERT initiation can prevent organ damage and delay both morbidity and mortality in patients with FD, this is in favor of a shift from treatment to prevention of organ damage with the aim to maintain organ function. Guidelines for the introduction of ERT have been recently updated in France and ERT should be considered in male patients with FD from 7 to 8 years old and in symptomatic pediatric female patients with skewed and unfavorable X-linked inactivation [8]. The risk of adverse events occurrence such as hypersensitivity to ERT, the psychological impact of a long-life treatment in pediatric patients, and the cost of the treatment have to be taken into account before treating asymptomatic patients [8].

To date, only a few noninvasive biomarkers (plasma GL-3 and microalbuminuria) are available in pediatric patients with FD to monitor the organ's impairment and the efficacy of the ERT. Most biological (GFR, proteinuria) and radiological features (echocardiography and cerebral MRI) remain in the normal range in pediatric patients with FD. A study carried out on pediatric patients with iterative renal biopsies showed a clear reduction in GL-3 deposits in the podocytes after 1 to 5 years of ERT. However, it is an invasive technique that cannot be performed routinely. The validation of non-invasive techniques allowing the monitoring of the efficacy of ERT is a research avenue, particularly in pediatric patients.

Outside of EKG and echocardiography which are usually normal in our young patients, cardiac magnetic resonance (CMR) has been proposed as a key exam in the evaluation and the understanding of FD. In the adult population, presenting with unexplained cardiomyopathy, CMR gives strong and specific arguments for FD: low T1 values, elevated T2 values, late gadolinium enhancement, and normal extracellular volumes [2,4]. Mapping sequences can detect the early stage of sphingolipid storage presenting as isolated decreased T1-values [4,9–11] and could potentially be used to guide the ERT prescription in this pre-hypertrophic phase of the cardiac involvement of FD.

To date, there is a lack of data in the pediatric population to understand how to integrate CMR and especially mapping sequences in early therapeutic decisions. This cross-sectional study aims to describe the evolution of a pediatric cohort of FD and to specify the place of CMR in the follow-up.

2. Patients and methods

This work was a monocentric longitudinal study carried out in Montpellier University Hospital from October 2016 to January 2022 on pediatric patients with a genetically proven diagnosis of FD. The following parameters were assessed for each patient at FD diagnosis, at ERT initiation (if treated), and at the last follow-up:

- *Clinical and general characteristics:* sex, age, weight, height, body mass index (BMI), arterial pressure, specific FD symptoms (cutaneous, neurologic, digestive, and ophthalmologic).
- *Kidney function* was assessed using analysis: Schwartz 2012 formula, albuminuria/urinary creatinine ratio, proteinuria/urinary creatinine ratio and GL-3 level.
- *The health-related Quality of life* (HRQoL) with the PedsQL score: this instrument is a generic pediatric HRQoL instrument, designed for children aged from 2 to 18 years, developed from a large cohort of healthy children as well as children with acute or chronic health conditions The PedsQL questionnaire has four multidimensional scales: physical functioning, emotional functioning, social functioning, and school functioning. The three summary scores are the total scale score (23 items), the physical health summary score (8 items), and the psychosocial health summary score (15 items). Items are reversed scored and linearly transformed to a 0–100 scale, with higher scores indicating a better HRQoL.
- *Cardiologic assessment:*

EKG: Heart rate, arrhythmia and conduction disorder.

Transthoracic echocardiography (TTE): left ventricular end fraction (LVEF), Left ventricular wall thickness, left ventricular end-diastolic diameter.

CMR: T1, T2 mapping values, LVEF, indexed left ventricular (LV) mass, indexed LV end-diastolic volume (iLVEDV), indexed LV end-systolic volume (iLVESV), late gadolinium enhancement (LGE).

- *-CMR protocol:*

CMR examinations were performed on a 1.5 T Aera® unit (Siemens Healthineers) with a cardiac 32 channel cardiac coil for signal reception and electrocardiographic (EKG) gating. Cardiac function assessment was performed using cine-MRI sequences obtained with retrospectively EKG-gated balanced steady-state-free precession (SSFP) sequences in the long axis and short axis providing full coverage of the LV. Native T1 mapping was performed using short-axis planes in all patients. Modified Look-Locker inversion recovery (MOLLI®) technique was used to evaluate T1 values. We conducted measurements in the septal, lateral, and inferior segments at both the base (S1-S6) and medioventricular portions (S7-S12) of the myocardium. Subsequently, we calculated the T1 mapping values for both the basal and medioventricular regions. The mean value, derived as the average between the basal and medioventricular measurements, is then juxtaposed with the mean T1 value for a healthy reference. The apical short axis slice (S12-S16) was not used because of the quality of the signal as this level where the myocardium is very thin.

The normal values of T1 and T2 have initially been determined on a healthy pediatric population aged from 8 to 18 years old part of an ongoing clinical trial (QUALIMYORYTHM NCT04712136). As recommended, we provided the normal values accompanied by the mean and standard deviation, along with sex-specific cutoffs [9]. The T1 values were considered “low” under 1SD from the normal.

Delayed contrast-enhanced images were captured 10 min post-gadolinium injection, maintaining identical positions to the cine images. Evaluation of each LV segment was conducted to assess the presence of LGE in accordance with recommended guidelines.

- *Ethics:*

The study was conducted in compliance with the Good Clinical Practices protocol and declaration of Helsinki principles and was approved by the local Ethics Committee of the University Hospital of Arnaud de Villeneuve – Montpellier, France (IRB-MTP_2022_12_202201284). Oral informed consent was obtained from each patient.

3. Results

Six patients (3 males and 3 females) with genetically confirmed FD, were included in this study. The diagnosis of Fabry disease was made at a median age of 11,5 years (min 4 years, max 16 years). The mean follow-up was 5 years. ERT was started in 5 patients with a mean time on ERT of 30 months (min 6 months – max 4 years) at the last follow-up. Cinical data for each patient were summarized in Table 1.

Patient 1 was a female with a rare presentation of FD. She had a

Table 1
Patient characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at diagnosis (years)	12	12	4	10	11	16
Sex (F/M)	F	F	M	M	M	F
GLA gene variant	Hemizygous - p. R227X	Heterozygous p. R227X	Hémizygous - P. R112C	Hemizygous p.Ala250Val / p.Ala352Asp.	Hemizygous p. N215S	Heterozygous p. N215S
Alpha galactosidase A activity ()	0.1µkat/kg prot (N: 10–19)	5µkat/kg prot (N:10–19)	0.32 µmol/L/h (N:2.6–10.3)	0.28 µmol/L/h (N:2.6–10.3)	0.6 µmol/L/h (N:2.6–10.3)	3.38 µmol/L/h (N; 2.6–10.3)
Duration of follow up (years)	6	5	12	4	2	2
ERT onset date/ Time under treatment (months)	Novembre 2018/ 40	April 2021/ 11	April 2017/ 60	July 2019/ 32	April 2021/ 11	No
Age at ERT onset (years)	15	15	10	17	12	–
LysoGL-3 at onset (nmol/L)	38,4	5	65	60,8	6,4	0.6
HRQoL (/100)	46.25	61	MD	52	98.75	82
UPr/UCr (mg/mmol)	10.9	41.3	8.9	7.1	10.7	3.9
Ualb/UCr (mg/mmol)	0.4	22.1	0.2	0.4	1	0.4
GFR (mL/min/1,73m^2)	121	141	112	119	127	105
Acroparesthesia, dysesthesia, pain	Yes	Yes	Yes	Yes	No	No
Heat /cold exercise intolerance	Yes	Yes	Yes	Yes	No	No
Hypohidrosis, anhidrosis	Yes	No	Yes	Yes	No	No
Hearing loss	No	No	No	No	No	No
Angiokeratoma	Yes	No	No	yes	No	No
Corneal whorms cornea verticillatta	No	No	No	No	No	No
Gastrointestinal symptoms	Yes	Yes	Yes	Yes	No	No

*UPr/UCr: proteinuria/urinary creatinine ratio; Ualb/Ucr: Albuminuria/urinary creatinine ratio. GFR: glomerular filtration rate estimated with 2012 Schwartz formula. ERT: enzyme replacement therapy; HTQoL: Health-related quality of life; GFR: Glomerular filtration rate.

drastically decreased alpha-galactosidase activity because of an unfavorable skewed X chromosome inactivation. She has an elevated level of GL-3 and symptoms that occurred before the age of 10. ERT was started in November 2018. The evolution of CMR T1, GL-3 level, and quality of life score are described in Fig. 1.

Patient 2, was the sister of Patient 1. She was not treated until 2021 because of the absence of symptoms of FD. T1 values at this time were at lower limit. The occurrence of acroparesthesia, significant albuminuria, and the diminution of T1 mapping values during the follow-up prompted to start ERT in 2021 (Fig. 1). Her GL-3 level was only slightly increased before the start of the ERT (5 nmol/L).

Patients 3 and 4, both males with a phenotype of classic FD, exhibited an association of typical clinical symptoms and biological analysis related to FD (acroparaesthesia, abdominal pain, and headache), elevated GL-3, and low T1 mapping. The evolution of T1, GL-3 level, and Quality of Life score are described in Figs. 2.

Patient 5, male, presented with a genetically proven late onset FD with a familial history of early severe cardiac and renal impairment. After a multidisciplinary discussion, according to the parents and the patient requests, ERT was started despite the absence of symptoms and no biological or imaging patterns. The evolution of T1, GL-3 level, and Quality of Life score are described in Figs. 2.

Patient 6, is the sister of Patient 5. As usually in pediatric patient with late onset FD, she is not treated due to absent symptoms, no cardiac lesion, and a first CMR evaluation that was normal.

Importantly, outside of the T1 mapping results, the CMRs revealed no other abnormality of volume, myocardial thickness, late gadolinium enhancement, or T2 mapping time in any of the 6 patients (Table 2).

4. Discussion

This study is the first to describe the integration of CMR and mapping sequences in the follow-up of a pediatric population with FD. This prospective observational study aimed to describe the utility of multimodality imaging to help with the therapeutic decision and follow-up of this specific population. CMR is considered routine care in the FD adult population, as a method of diagnosis of early cardiac involvement as well as in the follow-up of patients [4,12,13]. The pediatric population is more challenging because it is heterogenous ranging from symptomatic patients to less severe forms diagnosed through familial screening [14]. Since the storage process begins during the fetal period, it is interesting to carefully evaluate before ERT initiation the level of myocardial GL-3 accumulation that may be part of patients' prognosis. A CMR exam can be performed in children without sedation from 6 years old depending on his/her maturity. To improve the tolerance of a CMR, one should focus on qualitative T2, T1 weighted and mapping sequences as no left ventricle hypertrophy is expected to be found in the early stage of the disease. Lesions of fibrosis can occur earlier than the hypertrophy (up to 60% of adult patients with FDs) [14]. Performing a late gadolinium enhancement sequence can be useful with the aim of predicting cardiac events [15].

T1 mapping sequences are crucial as they help in the diagnosis of idiopathic cardiomyopathy. A cut-off value has been fixed around 900 msec but in practice, every engine of every brand has its specific cut-off value depending on the field strength (1,5 or 3 Tesla) or the sequence characteristics. It has to be determined with a control population to be used in clinical practice [4,10].

In confirmed cases, CMR could be used to evaluate the evolution of the myocardial GL-3 accumulation. Nordin et al. described, this process as a progressive mechanism. Our work intends to illustrate it with the evolution of the T1 values especially in Patient n°2 (Figure n°2) with a significant reduction/decrease of the values before ERT initiation [13]. The use of CMR seems to be particularly relevant in female patients because of the possible discordance between the symptoms and the level of plasma GL-3 that can stay in the low range. Moreover, since there is a lack of consensus on the timing of the introduction of ERT in pediatric patients. The use of a non-invasive method to document organ accumulation of glycosphingolipids may be helpful to the decision of ERT initiation [8]. For Patient n°2, CMR data was integrated into the decision-making process as an argument for a cardiac impairment. In the absence of well-defined cut-off values in pediatric population, a dynamic approach of the T1 mapping values could be helpful in these patients. Furthers studies should focus on defining *Z*-scores of T1 normal values in FD pediatric patients.

The ERT has shown benefits in FD adult and pediatric population, but its efficacy on constituted myocardial lesions is debated [7,13,16]. The ERT has its maximum efficacy in the early storage phase and the positive evolution of T1 values in Patients 1, 3, and 4 seems to be in line with these results. The presence of myocardium hypertrophy, inflammation (elevated T2 values), and/or constituted fibrotic scares (late gadolinium

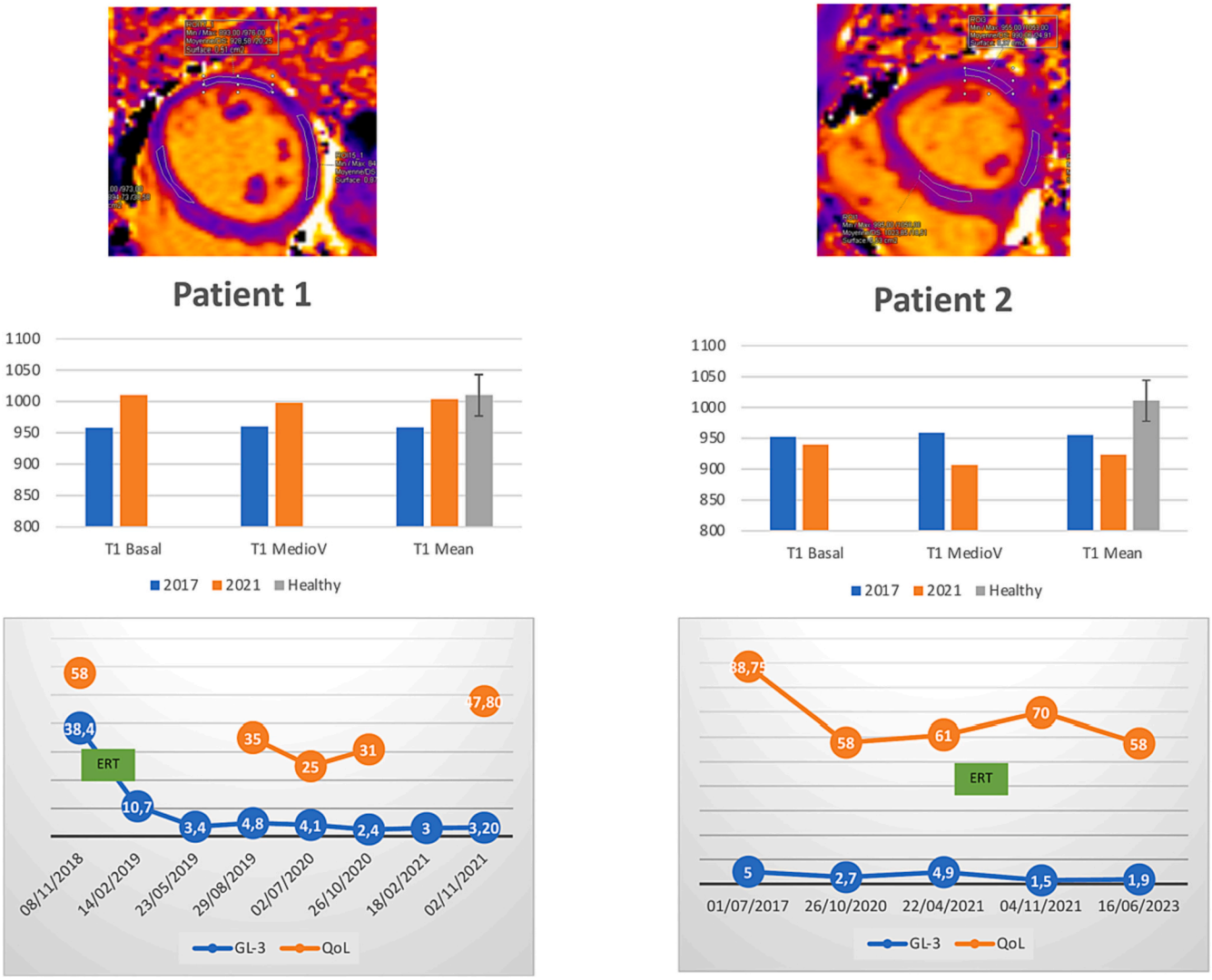

Fig. 1. Summary evolution of clinical, biological, and imaging results of patients 1 and 2.
A (2021),b (2019), and c (2021): T1 mapping sequences (MOLLI) at the mid ventricule level
Middle figures: systematic positive evolution of health-related quality of life and biologic level of GL-3 in reaction to the introduction of the ERT.
Lower figures: Evolution of the mean T1 mapping between the first (blue) and the second (orange) CMR with values in the normal range compared to healthy patients (green)
ERT: *Enzyme replacement therapy; QoL: Quality of life.*

enhancement) seems to compromise the positive effect of ERT on cardiac lesions [13]. This is in favor of extensive familial screening [14] and early therapeutic initiation with regular follow-up. The improvement of the cardiac prognosis may also depend on the dose and regimen of ERT that is used. [8,17,18].

The use of other imaging techniques could be also discussed. Trans thoracic echocardiography (TTE) is also in constant evolution and it seems that Speckle tracking imaging with the global longitudinal strain (GLS) could be an interesting parameter to explore [19]. The GLS explores the potential for distortion of the myocardial muscle. Every aggression of the myocardium can lead to an early modification of the strain rate. The storage process of FD seems to have an early negative impact on myocardial function (even before the hypertrophic phase) with a correlation with lower T1 values in CMR [20]. TTE could be used in pediatric populations in centers having difficulties of access to CMR, or when there are challenges with the acceptance of CMR by the child.

Considering our results and the limited literature on pediatric population, there is a strong need for prospective research on the subject, especially on the long-term benefit of an early prescription of ERT considering the potential side effects. Integrating multimodal imaging such as CMR and TTE in the outcome's measures are interesting options in view of the lack of strong clinical indicators in this paucisymptomatic population.

5. Conclusion

Due to the lack of strong clinical and biological markers of FD in pediatric patients, initiation and follow-up of ERT efficacy remain challenging. CMR could play a role in the evaluation of early organ impairment in these patients. Our work on a small cohort of pediatric patients suggests some promising results in the use of cardiac T1 mapping as a noninvasive method to assess the cardiac impairment at diagnosis and during the follow-up with or without ERT.

Fundings

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

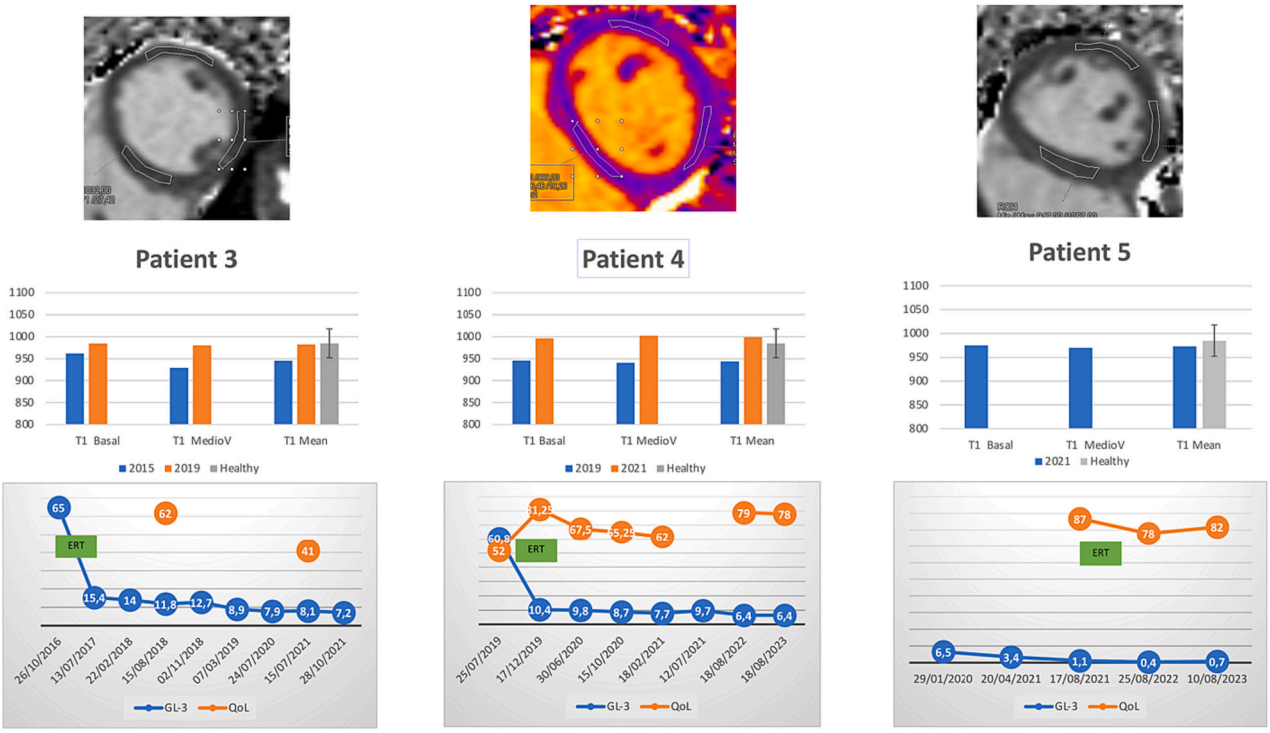

Fig. 2. Summary evolution of clinical, biological, and imaging results of Patient 2.
CMR images (2021): T1 mapping sequence in short axis slice at the mid ventricle level.
Middle figure:
QoL: Negative evolution of the health-related quality of life motivating the introduction of the ERT.
GL-3: values slightly increased before the introduction of ERT
Lower figure: Lowering of the T1 values between the first (2017) and the second (2021) exam motivating the introduction of ERT.
ERT: Enzyme *replacement therapy; QoL: Quality of life.*

Table 2
Initial CMR evaluation.

	Indexed end diastolic volume (mL/m2)	Indexed End systolic volume (mL/m2)	LVEF (%)	LVH	Indexed myocardic mass (g/m2)	T1 (msec)	T2 (msec)	LGE
Patient 1	67 (N: 78,7 +/− 10,7)	30 (N: 28,9 +/− 6,1)	64 (N: 63,2 ±6,3)	No	32 (N: 48,2±8,2)	959	ND*	No
Patient 2	71 (N: 78,7 +/− 10,7)	35,5 (N: 28,9 +/− 6,1)	59 (N: 63,2 ±6,3)	No	37 (N: 48,2±8,2)	955	ND*	No
Patient 3	77,5 (N: 81,9 ±12,9)	41 (N: 28,2 ±6,7)	62 (N: 65,7 ±4,9)	No	54 (N:52,1±10,6)	945	47,5	No
Patient 4	73,5 (N: 93,5 ±9,5)	32,5 (N: 36 ±7,1)	60 (N: 61,8 ±4,3)	No	43 (N: 67,6±7,7)	944	ND*	No
Patient 5	66 (N: 81,9 ±12,9)	31 (N: 28,2 ±6,7)	63 (N: 65,7 ±4,9)	No	26 (N:52,1±10,6)	972	43,5	No
Patient 6	63 (N: 80,7 ±9,5)	35,5 (N: 29 ±7,5)	64 (N:64,3±7,3)	No	38 (N:51,2±7,3)	980	46	No

LVEF: Left ventricle ejection fraction; LVH: left ventricular hypertrophy; LGE: Late gadolinium enhancement;N: normal range; ND: No data.

Author statement

The authors declare that they did not use any AI or and AI-assisted technologies in the writing process of this article.

CRediT authorship contribution statement

Oscar Werner: Conceptualization, Data curation, Validation, Writing – original draft, Writing – review & editing. **Lydia Ichay:** Data curation, Investigation, Validation. **Nabila Djouadi:** Validation. **Fernando Vetromile:** Data curation, Validation. **Marie Vincenti:** Conceptualization, Data curation, Validation. **Sophie Guillaumont:** Conceptualization, Data curation, Validation. **Dominique P. Germain:** Validation, Writing – original draft, Writing – review & editing. **Marc Fila:** Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

D.P.G. is a consultant for Amicus, Sanofi-Genzyme and Shire. He has received speaker's honoraria from Amicus, Sanofi-Genzyme and Shire.

Data availability

Data will be made available on request.

Acknowledgement

Thanks to patients and families for accepting to participate to this study.

References

[1] A. Ortiz, D.P. Germain, R.J. Desnick, J. Politei, M. Mauer, A. Burlina, et al., Fabry disease revisited: management and treatment recommendations for adult patients, Mol. Genet. Metab. 123 (4) (2018) 416–427.
[2] M. Pieroni, J.C. Moon, E. Arbustini, R. Barriales-Villa, A. Camporeale, A. C. Vujkovac, et al., Cardiac involvement in Fabry disease, J. Am. Coll. Cardiol. 77 (7) (2021) 922–936.
[3] A.C. Vedder, A. Strijland, M.A. vd Bergh Weerman, S. Florquin, Aerts JMFG, Hollak CEM, Manifestations of Fabry disease in placental tissue, J. Inherit. Metab. Dis. 29 (1) (2006) 106–111.
[4] J.B. Augusto, N. Johner, D. Shah, S. Nordin, K.D. Knott, S. Rosmini, et al., The myocardial phenotype of Fabry disease pre-hypertrophy and pre-detectable storage, Eur. Heart J. Cardiovasc. Imaging 22 (7) (2021) 790–799.
[5] S.J. van der Veen, S. Körver, A. Hirsch, C.E.M. Hollak, F.A. Wijburg, M.M. Brands, et al., Early start of enzyme replacement therapy in pediatric male patients with classical Fabry disease is associated with attenuated disease progression, Mol. Genet. Metab. 135 (2) (2022) 163–169.
[6] C.A. Stamerra, M. De Feo, V. Castelli, M. d'Angelo, A. Cimini, D. Grassi, et al., Effects of agalsidase-β administration on vascular function and blood pressure in familial Anderson–Fabry disease, Eur. J. Hum. Genet. 29 (2) (2021) 218–224.
[7] M. Spada, R. Baron, P.M. Elliott, B. Falissard, M.J. Hilz, L. Monserrat, et al., The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease – a systematic literature review by a European panel of experts, Mol. Genet. Metab. 126 (3) (2019) 212–223.
[8] D.P. Germain, A. Fouilhoux, S. Decramer, M. Tardieu, P. Pillet, M. Fila, et al., Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients, Clin. Genet. 96 (2) (2019) 107–117.
[9] D.R. Messroghli, J.C. Moon, V.M. Ferreira, L. Grosse-Wortmann, T. He, P. Kellman, et al., Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI), J. Cardiovasc. Magn. Reson. 19 (1) (2017) 75.
[10] E. Deborde, B. Dubourg, S. Bejar, A.C. Brehin, S. Normant, P. Michelin, et al., Differentiation between Fabry disease and hypertrophic cardiomyopathy with cardiac T1 mapping, Diagn. Interv. Imaging 101 (2) (2020) 59–67.
[11] A. Hagège, P. Réant, G. Habib, T. Damy, G. Barone-Rochette, G. Soulat, et al., Fabry disease in cardiology practice: literature review and expert point of view, Arch. Cardiovasc. Dis. 112 (4) (2019) 278–287.
[12] R. Perry, R. Shah, M. Saiedi, S. Patil, A. Ganesan, A. Linhart, et al., The role of cardiac imaging in the diagnosis and management of Anderson-Fabry disease, JACC Cardiovasc. Imaging 12 (7) (2019) 1230–1242.
[13] S. Nordin, R. Kozor, R. Vijapurapu, J.B. Augusto, K.D. Knott, G. Captur, et al., Myocardial storage, inflammation, and cardiac phenotype in Fabry disease after one year of enzyme replacement therapy, Circ. Cardiovasc. Imaging 12 (12) (2019), e009430.
[14] D.P. Germain, S. Moiseev, F. Suárez-Obando, F. Al Ismaili, H. Al Khawaja, G. Altarescu, et al., The benefits and challenges of family genetic testing in rare genetic diseases-lessons from Fabry disease, Mol Genet Genomic Med. 9 (5) (2021), e1666.
[15] F. Weidemann, M. Beer, M. Kralewski, J. Siwy, C. Kampmann, Early detection of organ involvement in Fabry disease by biomarker assessment in conjunction with LGE cardiac MRI: results from the SOPHIA study, Mol. Genet. Metab. 126 (2) (2019) 169–182.
[16] R. Parini, G. Pintos-Morell, J.B. Hennermann, T.R. Hsu, N. Karabul, V. Kalampoki, et al., Analysis of renal and cardiac outcomes in male participants in the Fabry outcome survey starting agalsidase alfa enzyme replacement therapy before and after 18 years of age, Drug Des. Devel. Ther. 14 (2020) 2149–2158.
[17] D.P. Germain, F. Weidemann, A. Abiose, M.R. Patel, M. Cizmarik, J.A. Cole, et al., Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: data from the Fabry registry, Genet. Med. 15 (12) (2013) 958–965.
[18] C. Kampmann, A. Perrin, M. Beck, Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: cardiac outcomes after 10 years' treatment, Orphanet J. Rare Dis. 10 (1) (2015) 125.
[19] P.T. Levy, A. Machefsky, A.A. Sanchez, M.D. Patel, S. Rogal, S. Fowler, et al., Reference ranges of left ventricular strain measures by two-dimensional speckle-tracking echocardiography in children: a systematic review and meta-analysis, J. Am. Soc. Echocardiogr. 29 (3) (2016) 209–225.e6.
[20] R. Vijapurapu, S. Nordin, S. Baig, B. Liu, S. Rosmini, J. Augusto, et al., Global longitudinal strain, myocardial storage and hypertrophy in Fabry disease, Heart. 105 (6) (2019) 470–476.