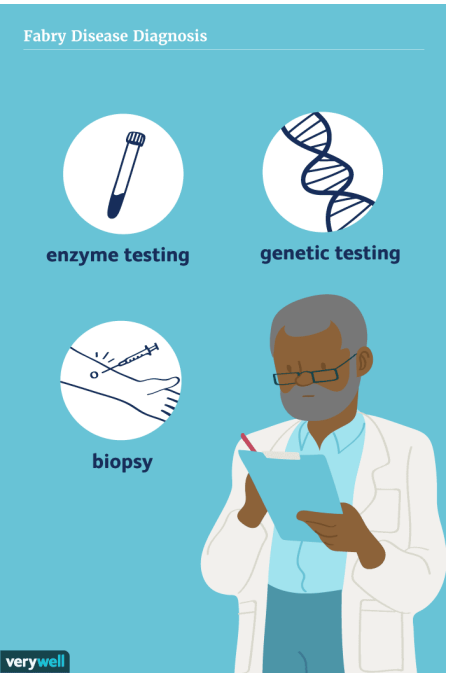


Fabry disease

Mojgan Mortazavi

Professor of nephrology

Isfahan Kidney diseases research center /Isfahan university of medical sciences

Panel members:

Diana taheri: Professor of pathology

Yousof Gheisari. Assiciate Professor of biologic products

Rasool Soltani: Assiciate Professor of clinical pharmacy

2 CASE PRESENTATION

A 37 years old man came with CC of lower limb edema.

PMH:

Proteinuria from 10 years ago

Phy.Exam:

Normal

Lab Exam:

Positive data : Cr=1.4 mg/dl. U/A=pro+++. Urine protein 24h=1800mg

Kidney biopsy:

Clinical History : A 37 y/o man with non-nephrotic range of proteinuria
Laboratory findings: Cr: 1.42 mg/dl , 24hr Pro: 1800 mg, U/A : Pr: +++

GROSS :

The specimen is received in formalin, labeled as " Kidney biopsy", consists of a piece of pale-tan cylindrical tissue measuring 1.5 cm in length and 0.2cm in diameter.

Submitted in toto in one block .

Serial sections prepared. Stained by H&E, Masson's Trichrome, PAS and JMS methods.

MICROSCOPY:

Microscopic examination shows one needle-shaped fragments of cortical kidney tissue with the following histopathological changes :

-Glomeruli: Up to 14 glomeruli in serial sections are identified. One of them shows sglobal sclerosis. Mild mesangial matrix expansion and hypercellularity in some glomeruli is seen. GBM shows normal thickness and shape. Podocytes show expanded cytoplasm with pale and foamy appearance. No endocapillary proliferation is seen. There is no evidence of crescent. No glomerulitis is identified. Glomerular size is increased.

-Tubules and interstitium: Mild focal interstitial infiltration of inflammatory cells including lymphocytes is seen. Mild focal tubular atrophy and proportional interstitial fibrosis involving less than 10% of the specimen are identified. Intraluminal RBC/WBC casts not seen.

-Vessels : Unremarkable

IMMUNOFLUORESCENCE STUDY(#98-459):

Frozen sections reveal 8 glomeruli with following immune reaction with the following antisera:

Polyvalent(G.A.M): Negative
IgG: Negative
IgA: Negative
IgM: Negative
Kappa: Negative
Lambda: Negative
C3c: 1+, mesangium
C4c: Negative
C1q: Negative
Fibrinogen: Negative

ELECTRON MICROSCOPY STUDY: Please see our ref EM#98-234

DIAGNOSIS:

" KIDNEY NEEDLE BIOPSY":

-HISTOPATHOLOGIC AND ELECTRON MICROSCOPIC FINDINGS ARE COMPATIBLE WITH FABRY DISEASE

COMMENT:

Fabry disease is a lysosomal storage disorder caused by genetic deficiency in alpha-galactosidase leading to accumulation of globotriaosylceramide in many cell types. In males with residual alpha-Gal activity, signs and symptoms may be restricted to kidney (renal variant) and lack the classic features of the disease. For definite diagnosis, genetic study is recommended.

پاتولوژیست : دکتر فاطمه نیلی احمد آبادی دستیار : دکترفتحی

تهران - انتهای بلوار کشاورز - کدپستی 14197/3314 تلفن: 021-61192502 ایمونوهیستوشیمی : 021-61192558

Clinical History: A 37 year old man with subnephrothic range of proteinuria since chidhood.

Material recieved:
From Imam khomeini hospital / path. lab, in gloutaraldehyde fixative, submitted in one resin embedded block for electron microscopic examination.
Thick sections of entire specimen stained by toluidene-blue revealed kidney tissue containing 2glomeruli and following histopathological findings:

- Glomeruli: Large podocytes with lamellated round densely stained inclusions.
- Tubules and interstitium: Resorptive droplets in some tubular epithelial cell.

Ultrastructural Findings on Thin Sections:

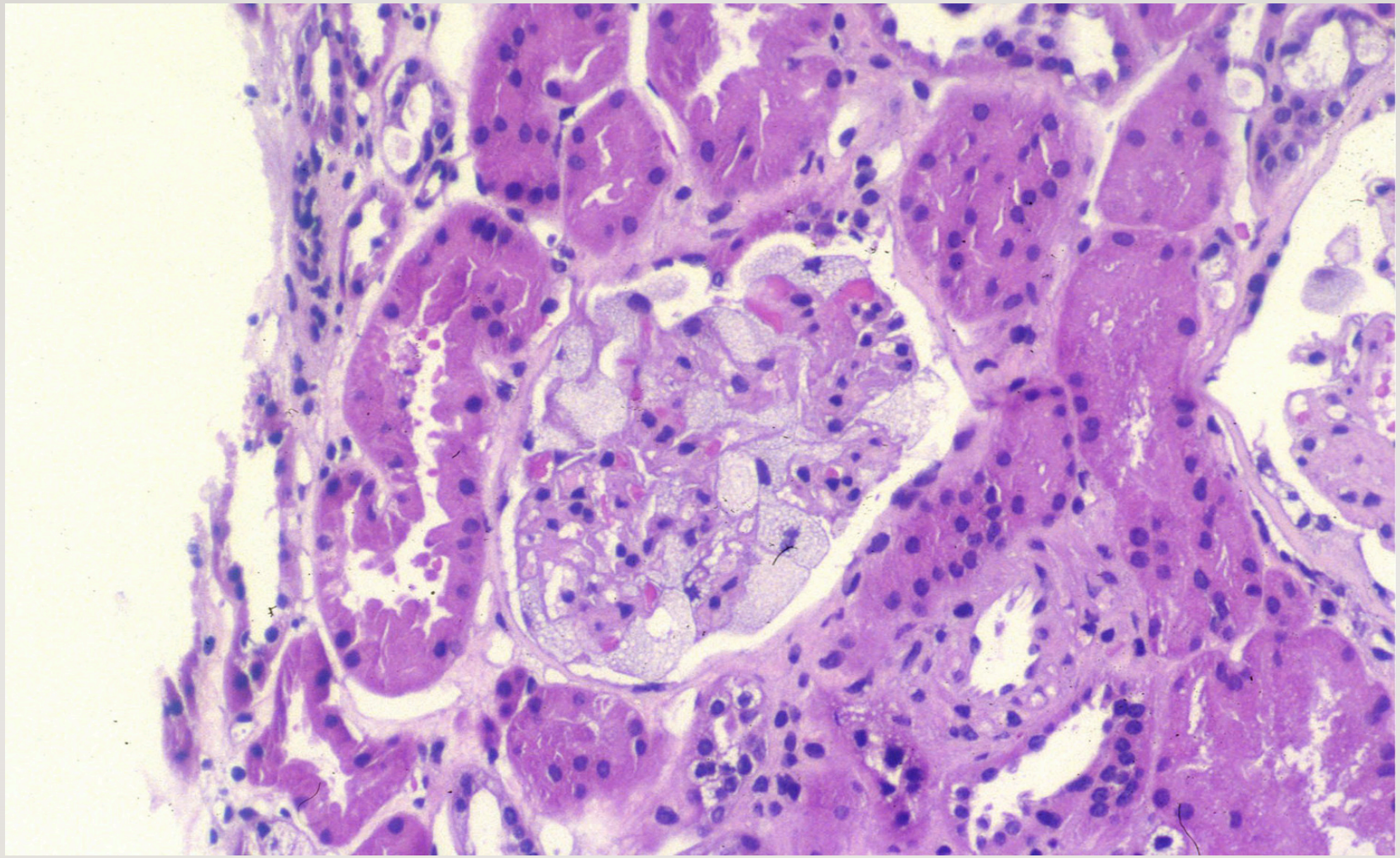
- Global efffacement of visceral foot processes.
- Large podocytes with cytoplasmic lamellated zebra-body like inclusions.
- Segmental thickening of GBM.
- Segmental GBM wrinkling / duplication and remodeling.
- Expansion of GBM-like mesangial matrix and mesangial hypercellularity.
- No subepithelial, mesangial paramesangial and subendothelial electron dense deposits.

DIAGNOSIS:
ULTRASTRUCTURAL FINDINGS ARE COMPATIBLE WITH FABRY DISEASE.

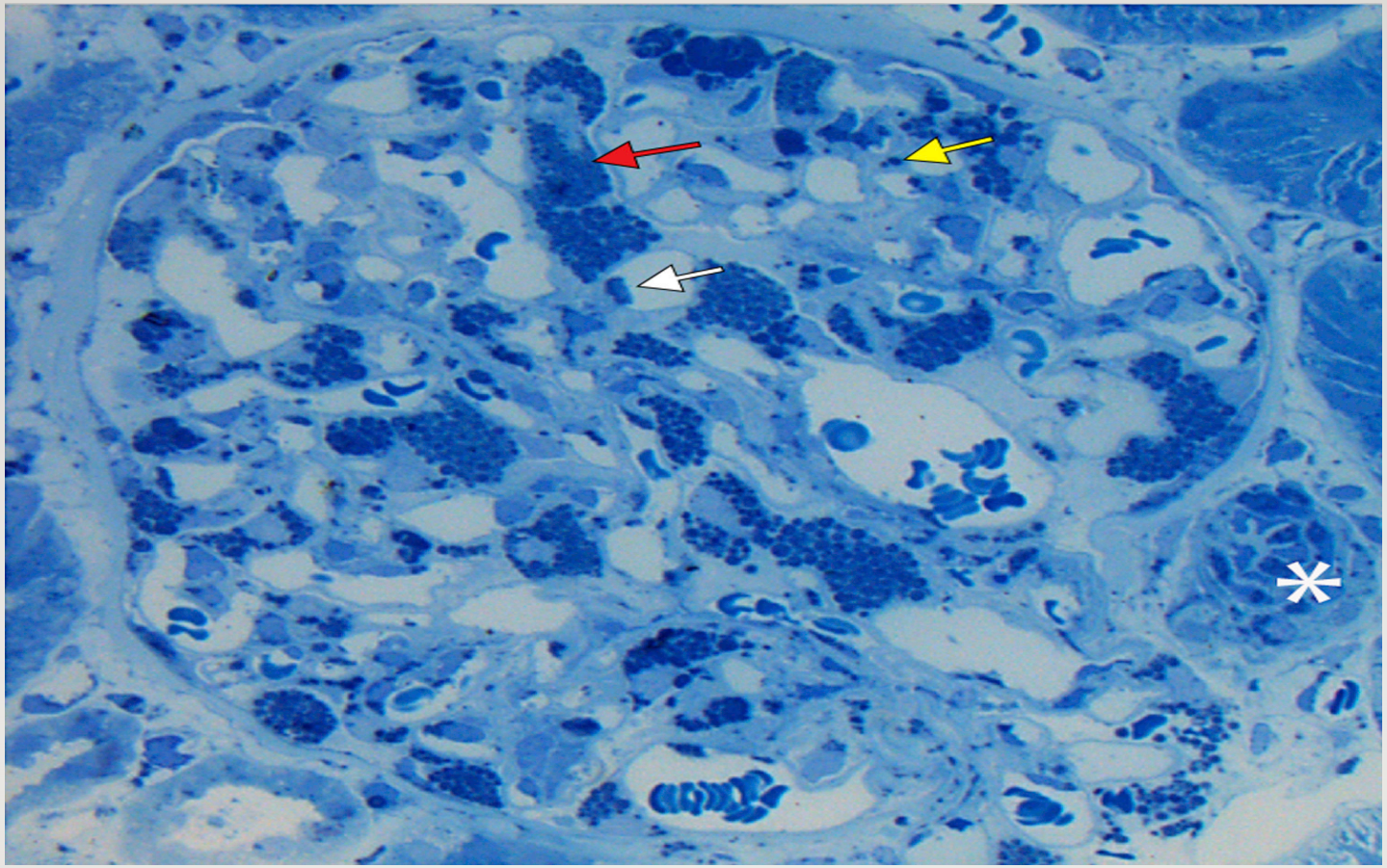
دستیار : ____

پاتولوژیست : دکتر فاطمه نیلی احمد آبادی

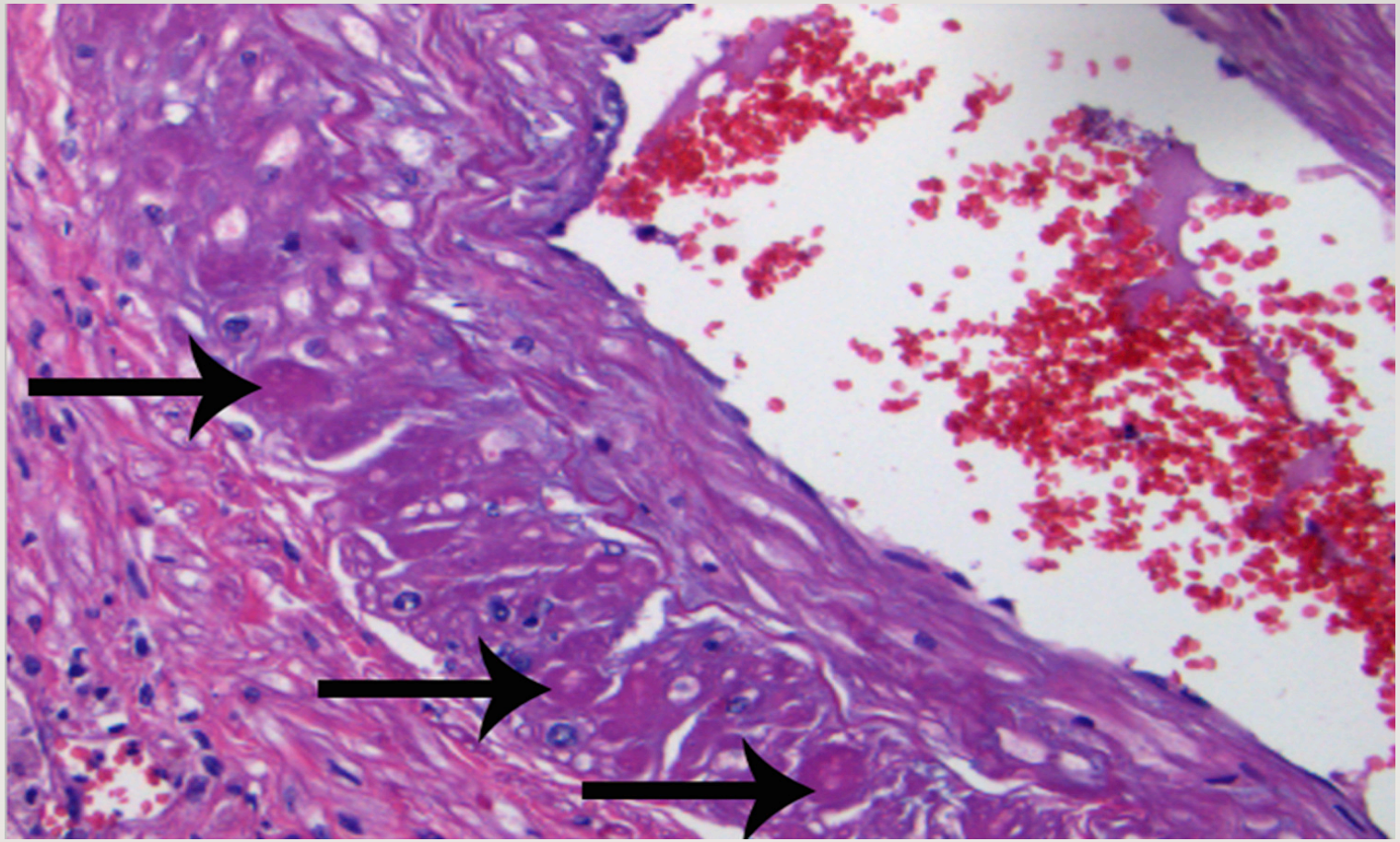
5



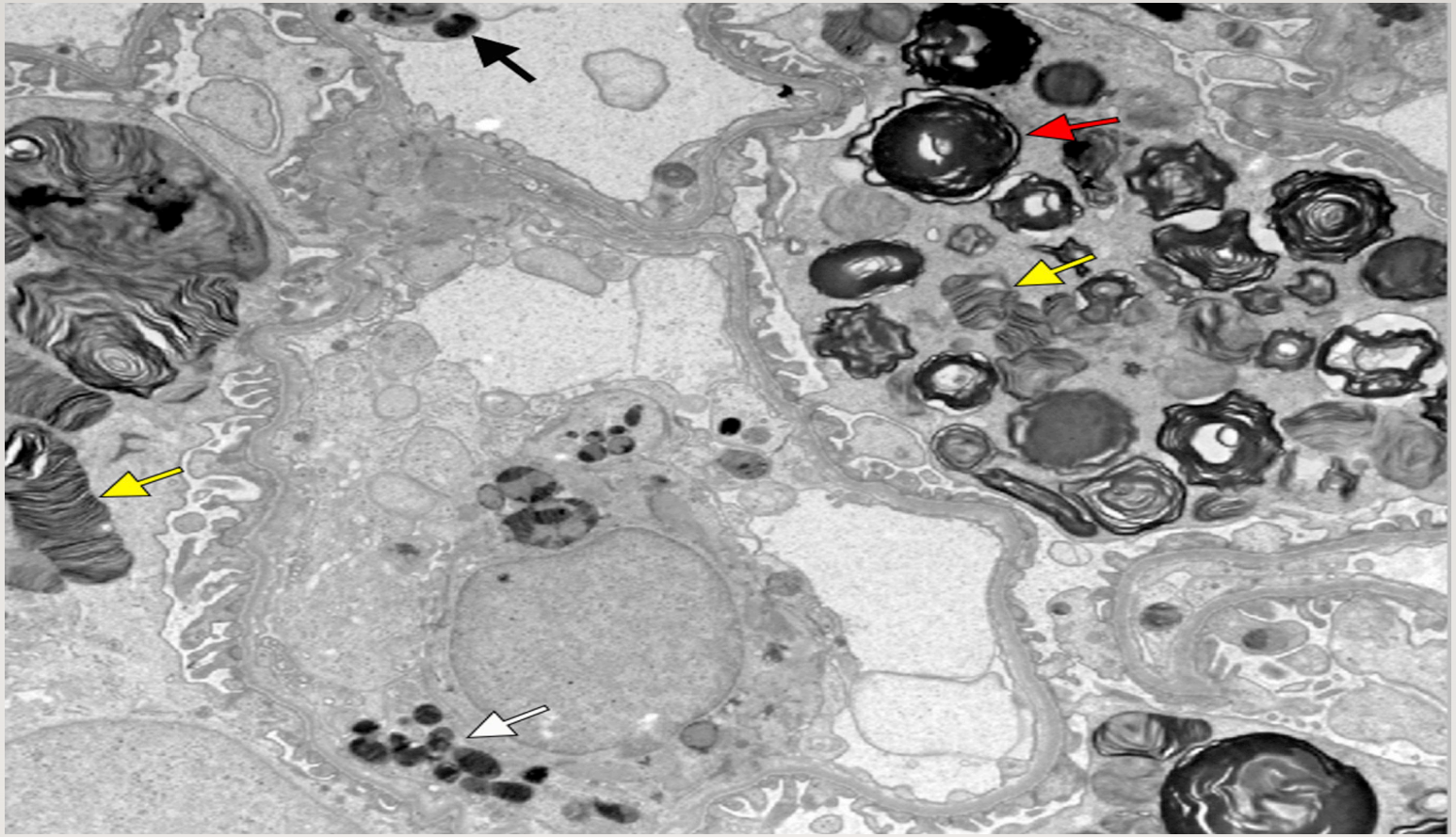
Fabry nephropathy with prominent vacuolization of podocytes (hematoxylin and eosin stain).



Fabry nephropathy with darkly stained round inclusions in podocytes (red arrow), mesangial cells (yellow arrow), and endothelial cells (white arrow) in a glomerulus. There is an arteriole with Fabry inclusions in smooth muscle cells (asterisk; toluidine blue stain).



Fabry nephropathy with deposition of hyaline-like material in the media of an interlobular artery (arrows), consistent with Fabry arteriopathy (periodic acid–Schiff stain).



Fabry nephropathy with typical Fabry glycosphingolipid inclusions shaped as multilamellated myelin figures (red arrow) and zebra bodies (yellow arrows) in podocytes. There are also smaller inclusions in endothelial cells (black arrow) and mesangial cells (white arrow; electron microscopy).

9

Q J Med 2010; **103**:641–659
doi:10.1093/qjmed/hcq117 Advance Access Publication 21 July 2010

Review

QJM

Fabry disease: a review of current management strategies

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From the [1]Lysosomal Storage Disorders Unit, Department of Haematology, Royal Free Hospital and University College London School of Medicine, London, UK, [2]Children's Hospital, University of Mainz, Mainz, Germany, [3]Department of Metabolic Diseases, ZNA Middelheim General Hospital, Antwerp, Belgium, [4]Department of Dermatology, Università Cattolica del Sacro Cuore, Rome, Italy, [5]Department of Medicine, Turku University Hospital, Turku, Finland, [6]Paediatric Metabolic Unit, Addenbrooke's Hospital, Cambridge, UK, [7]Albrecht-Kossel-Institute for Neuroregeneration, Medical Faculty, University of Rostock, Rostock, Germany, [8]Department of Internal Medicine, Complejo Hospitalario, Universitario de Vigo, Hospital Xeral de Vigo, Vigo, Spain, [9]Department of Adult Metabolic Diseases, Salford Royal NHS Foundation Trust, Salford, UK and [10]Division of Medical Genetics, Hôpital Raymond Poincaré (AP-HP), University of Versailles, St. Quentin en Yvelines, 92380 Garches, France

Address correspondence to Professor A. Mehta, Lysosomal Storage Disorders Unit, Department of Academic

INTRODUCTION

- Fabry disease is an X-linked inherited condition due to the absence or reduction of a-galactosidase activity in lysosomes, that results in accumulation of globotriaosylceramide (Gb3) and related neutral glycosphingolipids.
- Manifestations of Fabry disease include serious and progressive impairment of renal and cardiac function.
- In addition, patients experience pain, gastrointestinal disturbance, transient ischaemic attacks and strokes.

11 INTRODUCTION

- Additional effects on the skin, eyes, ears, lungs and bones are often seen.
- The first symptoms of classic Fabry disease usually appear in childhood.
- Despite being X-linked, females can suffer the same severity of symptoms as males, and life expectancy is reduced in both females and males.

12 INTRODUCTION

- The second most common LSD after Gaucher disease is Fabry disease, with a worldwide prevalence of approximately 1 in 40 000 to 1 in 117000 live births for the classic form of the disease.
- Wide variations in the prevalence of Fabry disease have been reported in different countries, and with increasing awareness and screening, it is likely that the actual prevalence may be higher than previously recorded, particularly when late-onset phenotypes are taken into account.

13 INTRODUCTION

- The mean age at onset of the signs and symptoms of Fabry disease has been reported between 3 and 10 years in males and 6–15 years in females.
- The later manifestations of Fabry disease (such as renal impairment, cerebrovascular disease and cardiomyopathy) result in a reduced life expectancy, to <50 years in men and <70 years in women.
- Furthermore, quality of life is reduced in both male and female patients, not only due to end-organ failure, but also to a range of other symptoms, including GI problems, pain, acroparaesthesia, depression and temperature intolerance.

INTRODUCTION

- Signs and symptoms that tend to develop later in adolescence and early adulthood are associated with end-organ failure and premature death.
- These include proteinuria and glomerulosclerosis, cardiac hypertrophy and arrhythmia, other cardiovascular disease and stroke.

Table 1 Typical signs and symptoms of Fabry disease according to age

Typical time at onset	Signs and symptoms
Childhood and adolescence (≤16 years)	• Neuropathic pain • Ophthalmological abnormalities (cornea verticillata and tortuous retinal blood vessels) • Hearing impairment • Dyshidrosis (hypohidrosis and hyperhidrosis) • Hypersensitivity to heat and cold • Gastrointestinal disturbances and abdominal pain • Lethargy and tiredness • Angiokeratomas • Onset of renal and cardiac signs, e.g. microalbuminuria, proteinuria, abnormal heart rate variability
Early adulthood (17–30 years)	• Extension of any of the above • Proteinuria and progressive renal failure • Cardiomyopathy • Transient ischaemic attacks, strokes • Facial dysmorphism
Later adulthood (age >30 years)	• Worsening of any of the above • Heart disease (e.g. left ventricular hypertrophy, angina, arrhythmia and dyspnoea) • Stroke and transient ischaemic attacks • Osteopenia and osteoporosis

16 DIAGNOSIS AND SCREENING

- Diagnosis of Fabry disease is often delayed by at least 3 years, and often by >20 years, after the onset of signs and symptoms.
- The reasons for this delay include the condition's rarity (and cor- responding lack of awareness among clinicians) and the diversity and non-specificity of presenting symptoms.

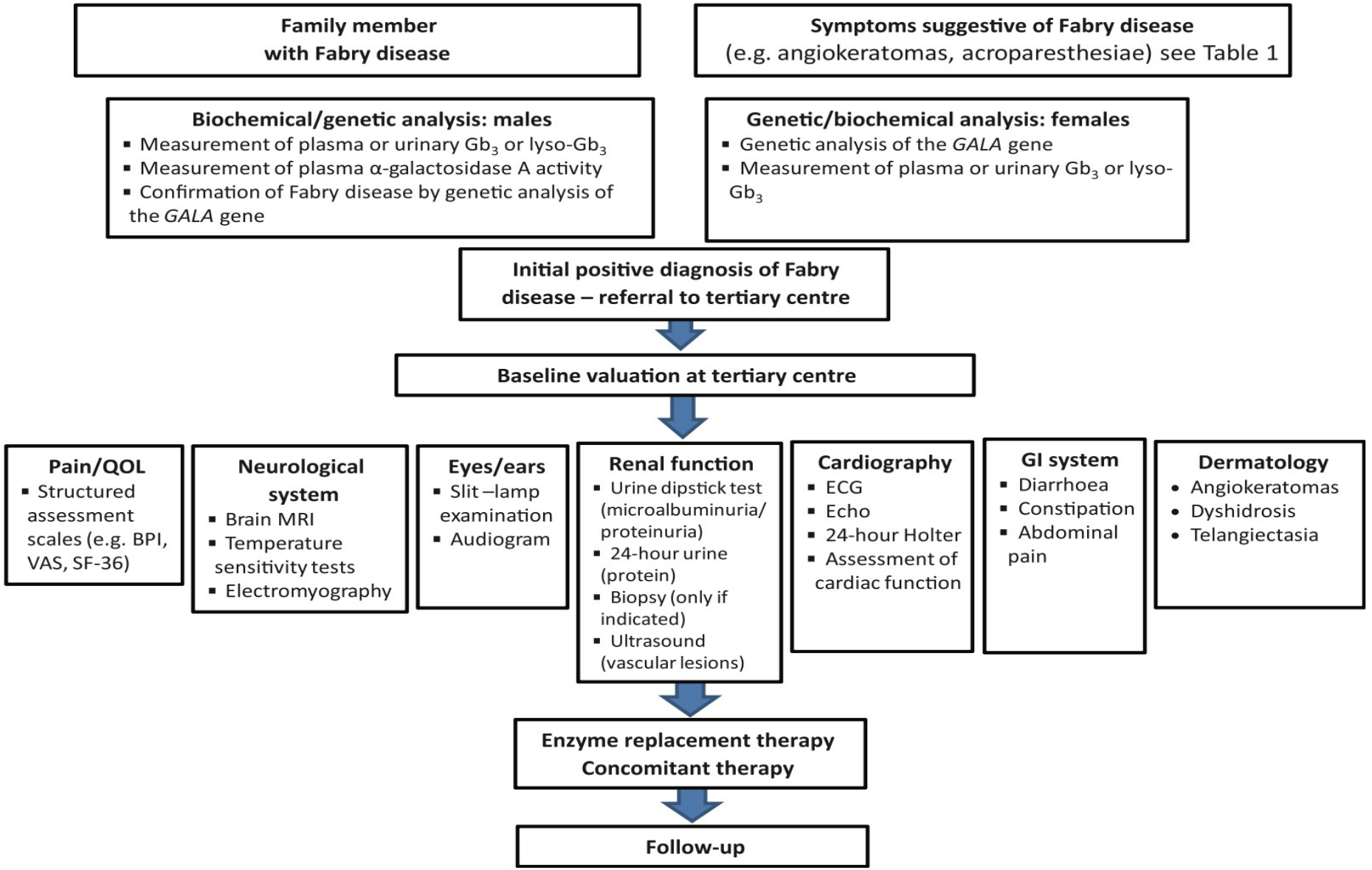
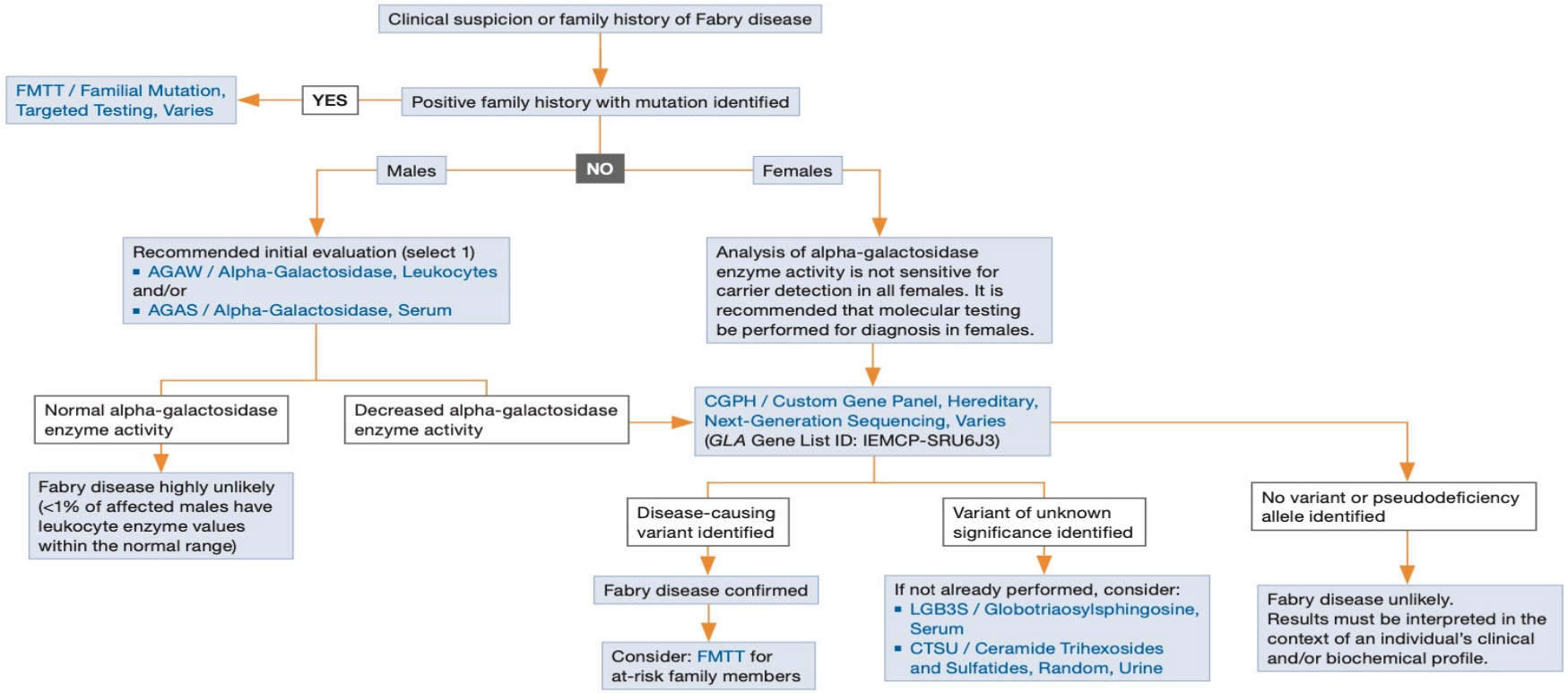


Figure 2. General algorithm for the diagnosis and assessment of patients with Fabry disease (see text for more detail). The initial point of presentation will vary depending on the first symptom. A particular specialist may therefore focus on just one aspect of the disease in the algorithm above before confirmation of the diagnosis and consideration of enzyme replacement therapy.

MAYO CLINIC LABORATORIES

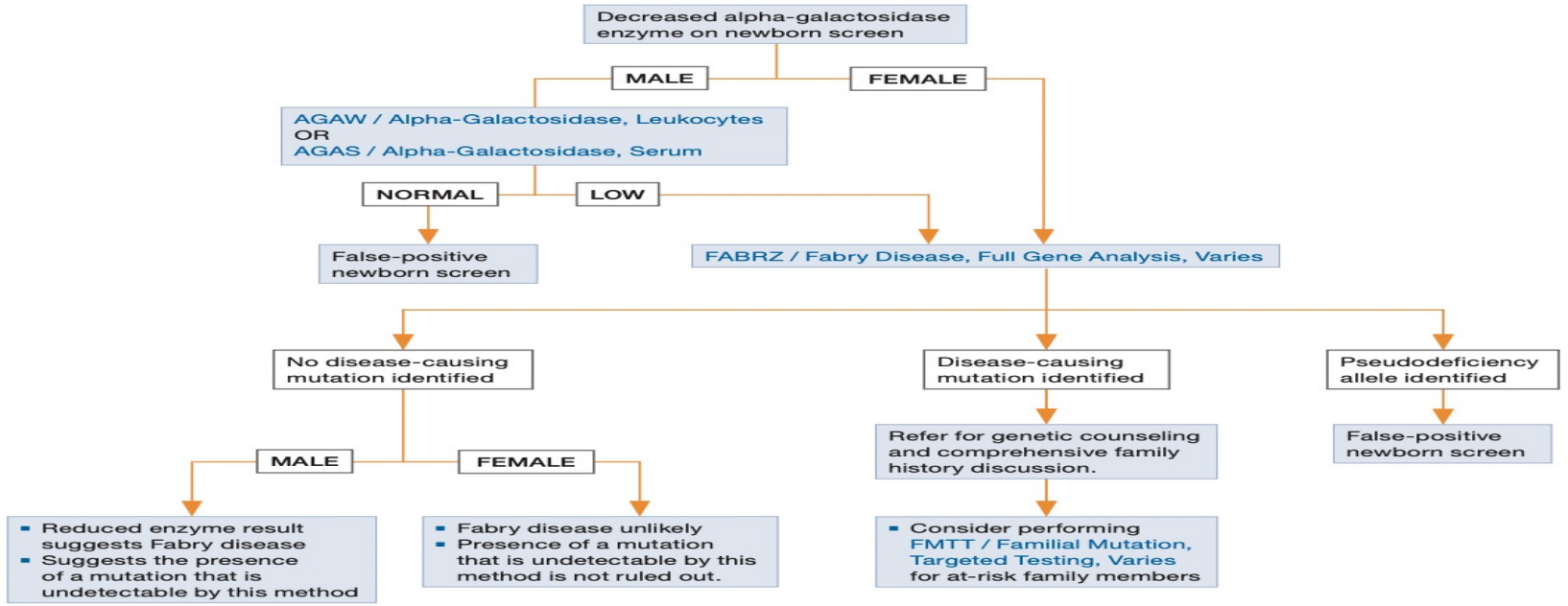
Fabry Disease Diagnostic Testing Algorithm



Clickable PDF
Click on blue tests to view test catalog information

MAYO CLINIC LABORATORIES

Fabry Disease: Newborn Screen-Positive Follow-up



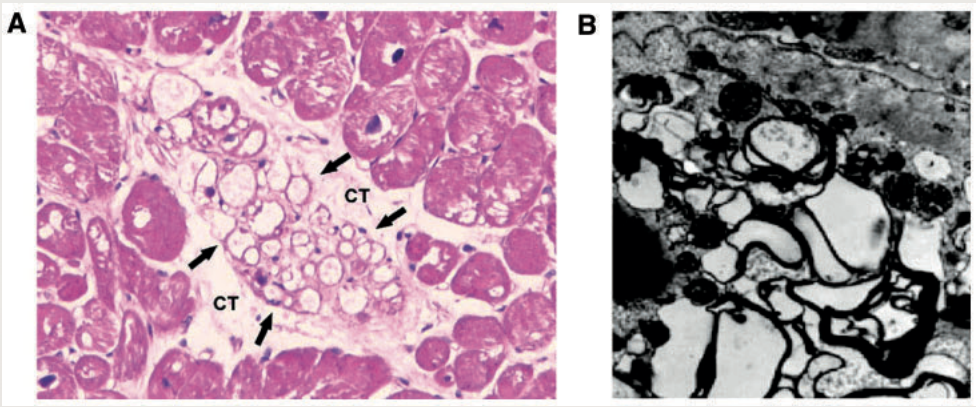
Clickable PDF

DIAGNOSIS AND SCREENING

- In males with left ventricular hypertrophy (LVH) or hypertrophic cardiomyopathy, 1–4% have been shown to have previously undiagnosed Fabry disease.
- Screening of female patients with hypertrophic cardiomyopathy has also detected a prevalence of Fabry disease of 1%

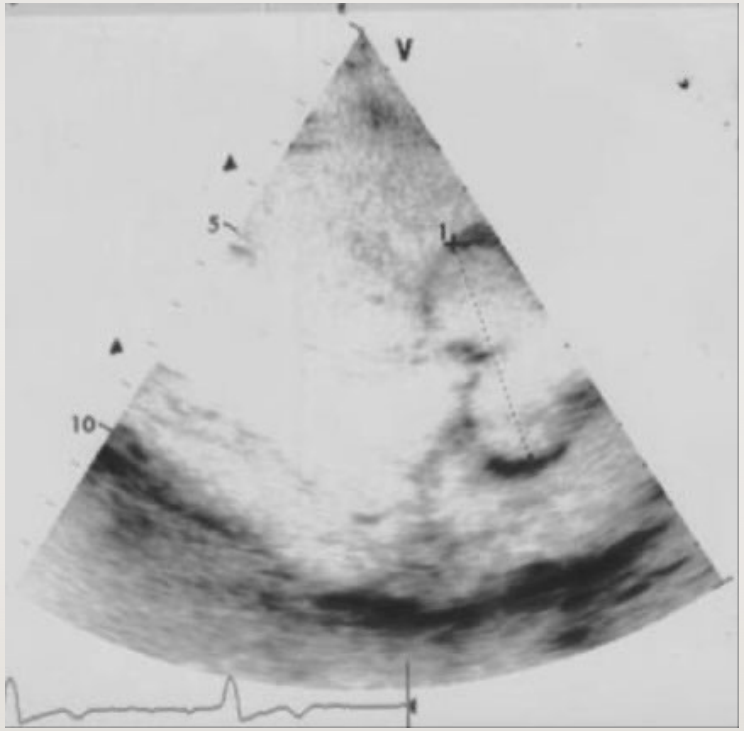
21

LEFT VENTRICULAR ENDOMYOCARDIAL BIOPSY SHOWING A FRAGMENT OF CONDUCTION TISSUE (CT) IN WHICH ALMOST THE ENTIRE CELL AREA IS OCCUPIED BY LARGE VACUOLES (ARROWS) WHEREAS IN THE WORKING MYOCARDIUM ONLY SMALL PERINUCLEAR VACUOLES ARE EVIDENT. (B): TRANSMISSION ELECTRONMICROSCOPY SHOWING THE VACUOLES TO CONSIST OF SINGLE MEMBRANE-BOUND MYELIN BODIES CONTAINING CONCENTRIC LAMELLAE SUGGESTIVE OF FABRY DISEASE. REPRODUCED WITH PERMISSION FROM FRUSTACI AND CHIMENTI.

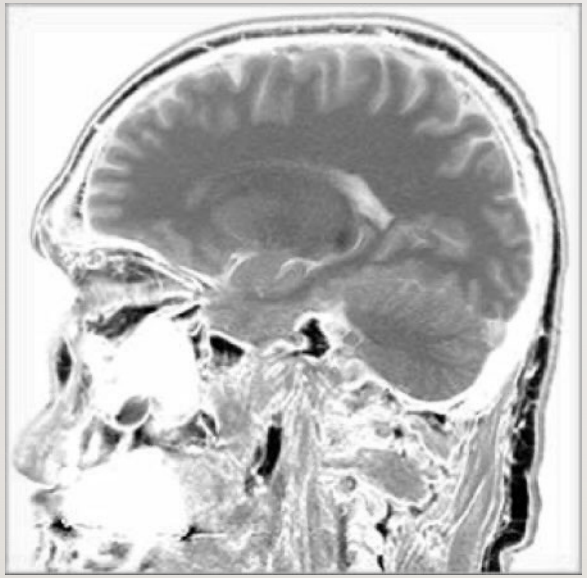


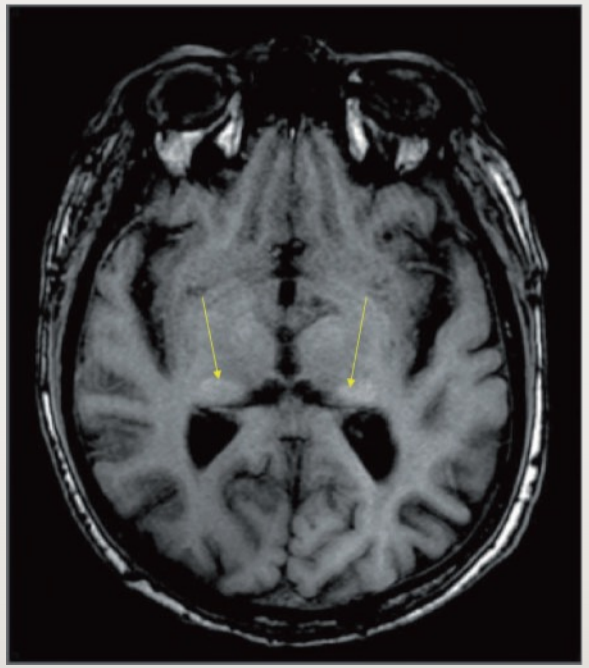
22

AORTIC ROOT DILATATION (47 MM) IN A 51-YEAR-OLD MALE PATIENT WITH FABRY DISEASE.7 COURTESY: OLIVIER DUBOURG AND DOMINIQUE P GERMAIN, UNIVERSITY OF VERSAILLES, FRANCE.

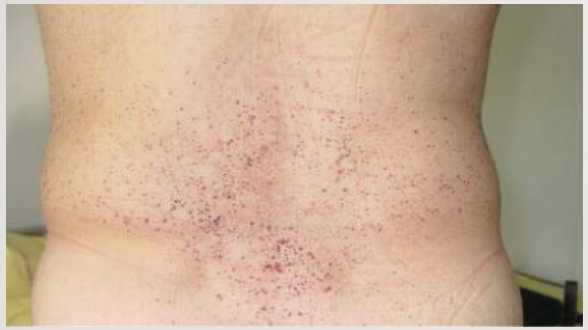


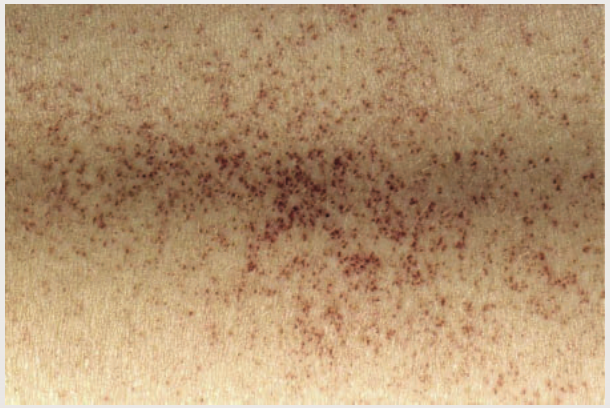
(A) T1 SAGITTAL IMAGE SHOWING A SLIGHT HYPERINTENSITY (YELLOW ARROWS) IN THE PULVINAR AREA OF A 46-YEAR-OLD MALE FABRY PATIENT. (B) T1 AXIAL IMAGE SHOW- ING A WELL-DEFINED SYMMETRIC HYPERINTENSITY (YELLOW ARROWS) OF BOTH PULVINAR NUCLEI OF A 46-YEAR OLD MALE FABRY PATIENT. COURTESY: FREDERIC COLAS, ROBERT CARLIER AND DOMINIQUE P GERMAIN, UNIVERSITY OF VERSAILLES, FRANCE.

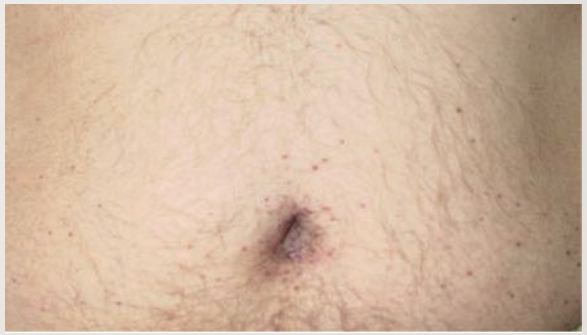




TYPICAL ANGIOKERATOMAS. COURTESY: DOMINIQUE P GERMAIN, UNIVERSITY OF VERSAILLES, FRANCE.



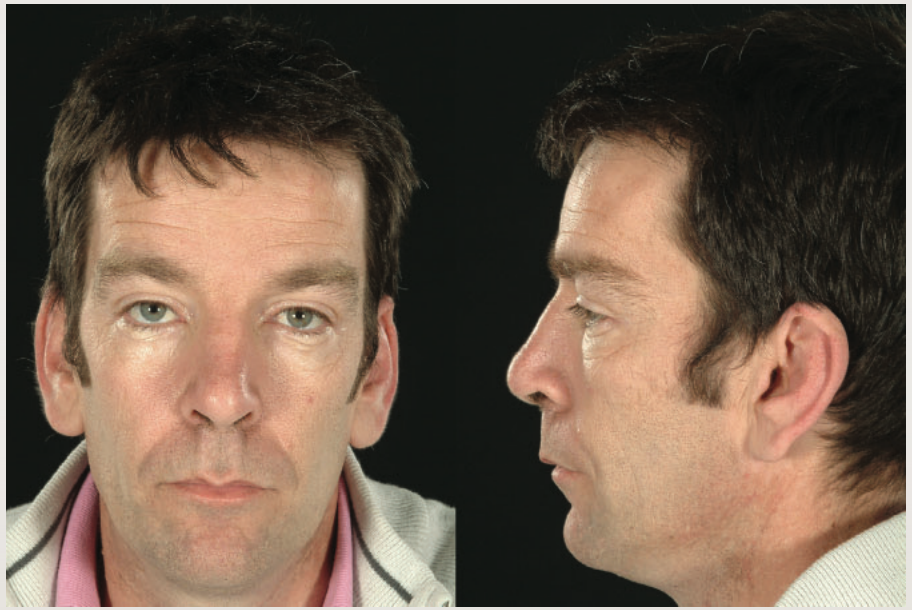




25 DEPRESSION AND REDUCED QUALITY OF LIFE

- Depression is a frequent and under-diagnosed problem among patients with Fabry disease.
- In a UK-based survey, as many as 46% of patients were found to have depression and 28% could be classified as having severe clinical depression.
- Most patients were previously undiagnosed for depression, highlighting the need for the correct assessment of depressive symptoms in patients with Fabry disease.

TYPICAL FACIAL DYSMORPHISM IN A PATIENT WITH FABRY DISEASE.
, SHOWING PROMINENT SUPRA ORBITAL RIDGES, BUSHY EYEBROWS, PERI-ORBITAL PUFFINESS, MILD PTOSIS, PROMINENT JAW LINE.



27 RENAL DISEASE

- Patients with Fabry disease who have established renal failure will require appropriate management of anaemia, renal bone disease and hypertension.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are useful as antiproteinuric agents and in the control of hypertension in patients with proteinuria.
- Many patients with Fabry disease and renal involvement who have not been given ERT may require dialysis or renal transplantation
- Transplanted kidneys remain free of Gb3 accumulation and 5-year organ survival is as good as in patients without Fabry disease.

28

Table 2 Effects of ERT on other signs and symptoms of Fabry disease

Effect	Enzyme	Reference
Amelioration of GI pain and diarrhoea at 6 months and 3 years of treatment	Agalsidase alfa Agalsidase beta	46 148
Improvement of acroparaesthesia at 24 months	Agalsidase alfa	152
Improvement of anhidrosis after 24 months	Agalsidase alfa	42,152
Improvement of pulmonary symptoms	Agalsidase beta	149
Improvement of hearing loss at 12 months	Agalsidase alfa	44
Significant decrease in cerebral hyperfusion vs. placebo after 6 months, although no impact on incidence of stroke or TIAs	Agalsidase alfa	150
Significant improvement (reduction) in elevated cerebral blood flow velocities after 18 months	Agalsidase alfa	151

Clinical Kidney Journal

ORIGINAL ARTICLE

Podocyturia in Fabry disease: a 10-year follow-up

Bojan Vujkovac [1], Irena Srebotnik Kirbiš [2], Tajda Keber[1], Andreja Cokan Vujkovac[1], Martin Tretjak[1] and Sandra Radoš Krnel[3]

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ABSTRACT

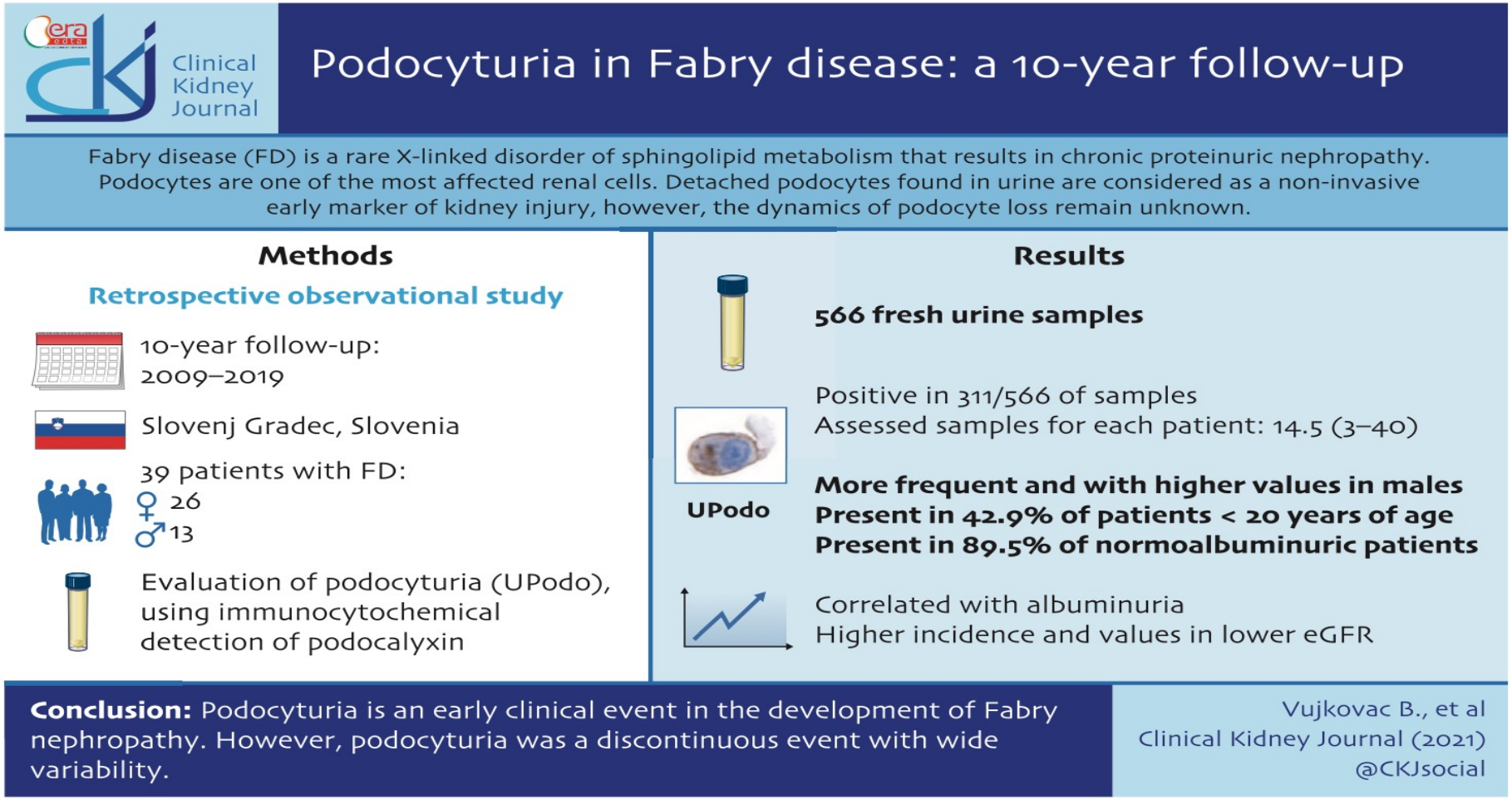
Background. Fabry disease (FD) is a rare X-linked disorder of sphingolipid metabolism that results in chronic proteinuric nephropathy. Podocytes are one of the most affected renal cells and play an important role in the development and progression of kidney disease. Detached podocytes found in urine (podocyturia) are considered as a non-invasive early marker of kidney injury; however, the dynamics of podocyte loss remains unknown.

Methods. In this 10-year follow-up study, podocyturia and other renal clinical data were evaluated in 39 patients with FD. From 2009 to 2019, podocyturia was assessed in 566 fresh urine samples from 13 male and 26 female FD patients using immunocytochemical detection of podocalyxin.

Results. Podocyturia (number of podocytes per 100 mL of urine) was found in 311/566 (54.9%) of the samples, more frequently (68.9 ± 21.9% versus 50.6 ± 25.9%; $P = 0.035$) and with higher values (364 ± 286 versus 182 ± 180 number of podocytes per gram of creatinine (Cr) in urine; $P = 0.020$) in males compared with females. The mean number of assessed samples for each patient was 14.5 (range 3–40) and the frequency of samples with podocyturia ranged from 0% to 100% (median 57%). Podocyturia was already present in 42.9% of patients <20 years of age and in 89.5% of normoalbuminuric patients. Podocyturia correlated with albuminuria (urine albumin:Cr ratio) ($r = 0.20$, $P < 0.001$) and a higher incidence and values of

30

GRAPHICAL ABSTRACT



Keywords: albuminuria, biomarkers, Fabry disease, immunocytochemistry, podocalyxin, podocyturia, proteinuria, renal function

Treatment

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DOI: 10.1002/jimd.12228

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REVIEW ARTICLE

JIMD SSIEM JOURNAL OF INHERITED METABOLIC DISEASE WILEY

Developments in the treatment of Fabry disease

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Abstract

Enzyme replacement therapy (ERT) with recombinant α-galactosidase A (r-αGAL A) for the treatment of Fabry disease has been available for over 15 years. Long-term treatment may slow down disease progression, but cardiac, renal, and cerebral complications still develop in most patients. In addition, lifelong intravenous treatment is burdensome. Therefore, several new treatment approaches have been explored over the past decade. Chaperone therapy (Migalastat; 1-deoxygalactonojirimycin) is the only other currently approved therapy for Fabry disease. This oral small molecule aims to improve enzyme activity of mutated α-galactosidase A and can only be used in patients with specific mutations. Treatments currently under evaluation in (pre)clinical trials are second generation enzyme replacement therapies (Pegunigalsidase-

TREATMENT

- Enzyme replacement therapy (ERT) with recombinant α-galactosidase A (r- αGAL A) for the treatment of Fabry disease has been available for over 15 years.
- Long-term treatment may slow down disease progression, but cardiac, renal, and cerebral complications still develop in most patients. In addition, lifelong intravenous treatment is burdensome. Therefore, several new treatment approaches have been explored over the past decade.
- Chaperone therapy (Migalastat; 1-deoxygalactonojirimycin) is the only other currently approved therapy for Fabry disease.

34 CHAPERONE THERAPY (MIGALASTAT; 1-DEOXYGALACTONOJIRIMYCIN)

- This oral small molecule aims to improve enzyme activity of mutated α-galactosidase A and can only be used in patients with specific mutations.
- Treatments currently under evaluation in (pre)clinical trials are:

1- second generation enzyme replacement therapies (Pegunigalsidase- alfa, Moss-aGal),

2-substrate reduction therapies (Venglustat and Lucerastat),

3-mRNA- and gene-based therapy.

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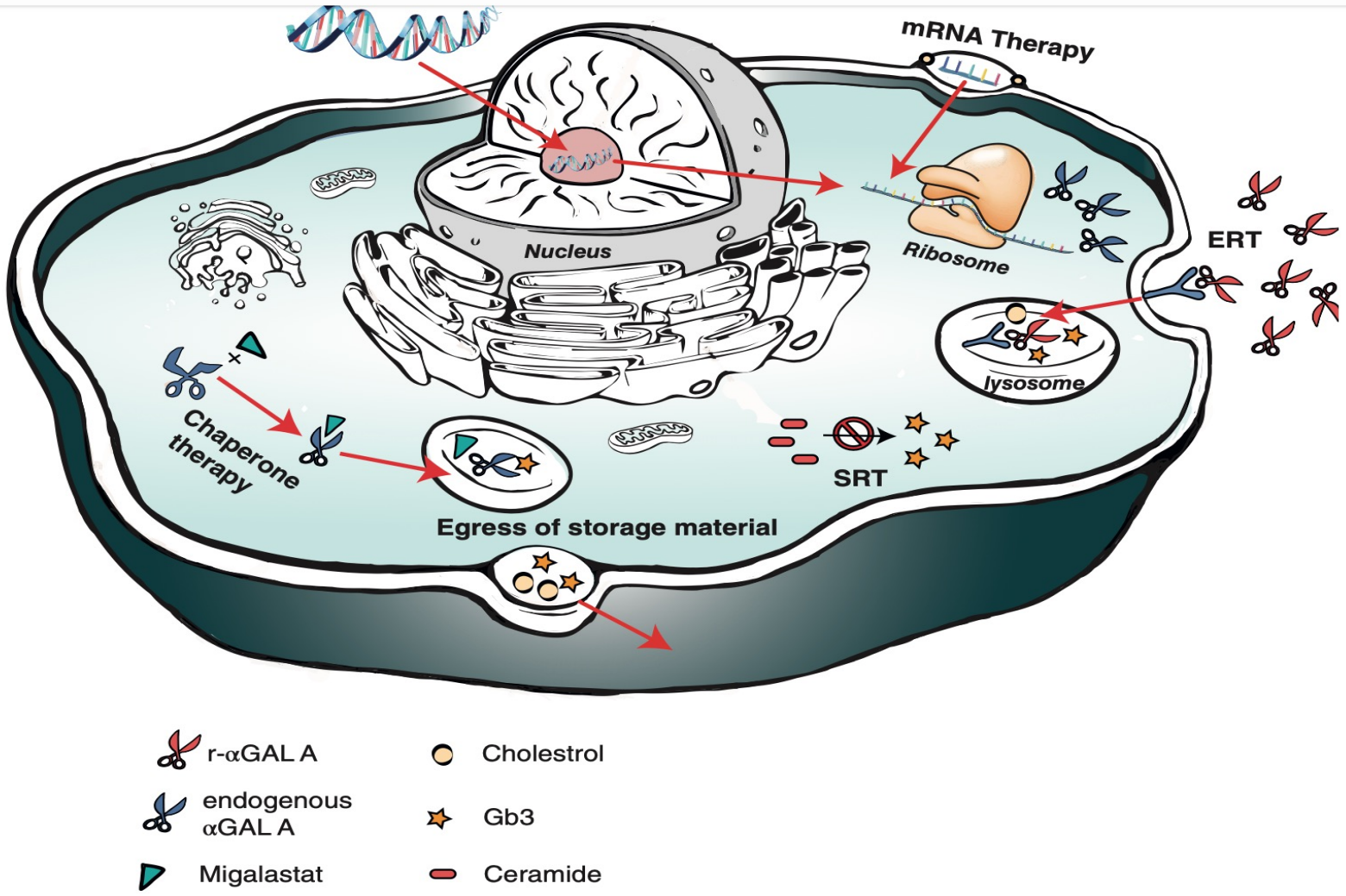


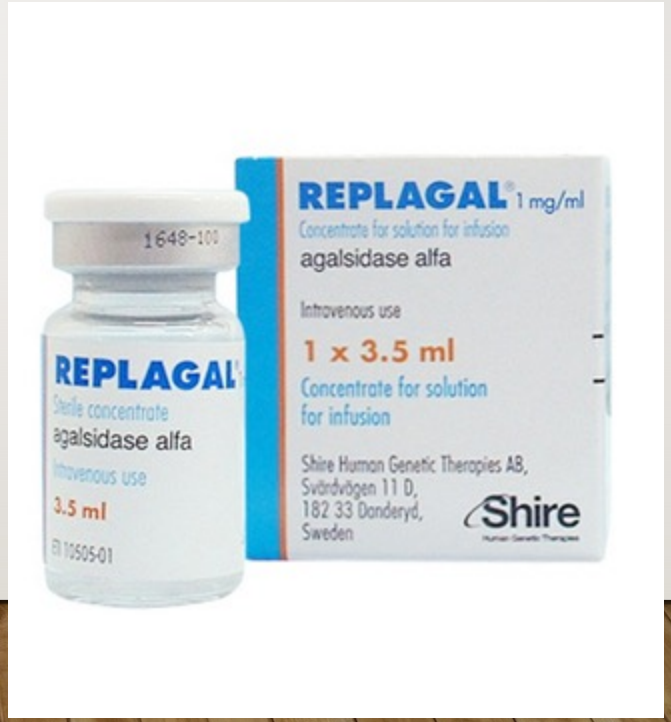
FIGURE 1 Overview of different approaches in treating Fabry disease; Enzyme replacement therapy (ERT) aims to restitute defective αGAL A. Chaperones bind to the active site of the unstable αGAL A to aid proper folding. Substrate reduction therapy targets the glycosphingolipid synthesis to reduce formation of Gb3 and its derivatives. Gene therapy aims to correct the underlying genetic defect of FD. MRNA therapy induces transient endogenous αGAL A production. The egress of Gb3 can potentially be stimulated by enhancing

TREATMENT OF FABRY DISEASE

RASOOL SOLTANI, PHARM.D., BCPS

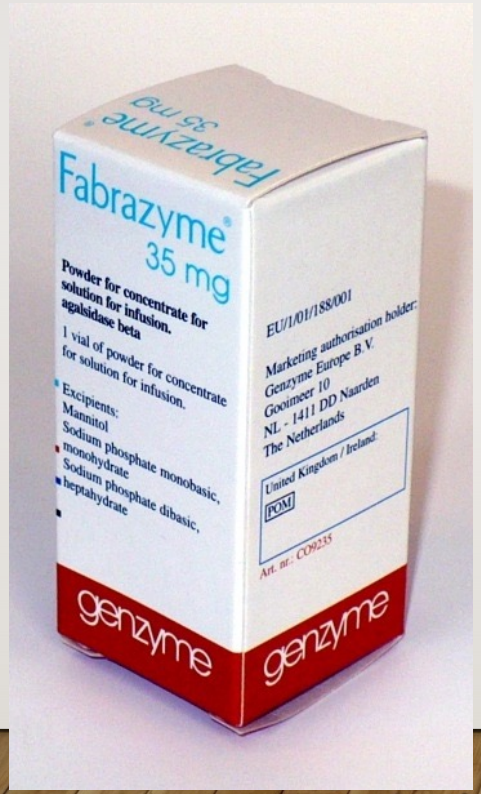
37 DRUGS FOR FABRY DISEASE

- Agalsidase alfa (Replagal)
- Agalsidase beta (Fabrazyme)
- Migalastat



38 FABRAZYME

- Agalsidase beta



39 FABRAZYME

- دوز:
  - 1 mg/kg هر 2 هفته
- نارسایی کلیوی: عدم نیاز به تعدیل دوز
- نارسایی کبدی: اطلاعاتی ذکر نشده است.

40 FABRAZYME

- تجویـز:
  - انفوزیون وریدی
  - فیلتر 0/2 میکرون
  - سرعت اولیه: حداکثر 0.25 mg/min
  - درصورت واکنش: کاهش سرعت یا قطع انفوزیون و پیش‌درمانی در دفعات بعد
  - پس از تأیید تحمل بیمار: افزایش سرعت به‌میزان 0.05 – 0.08 mg/min در هر بار
  - حداقل مدت انفوزیون: 1/5 ساعت

41 FABRAZYME

- عوارض:
  - هایپرتانسیون، ادم
  - راش
  - تهوع، استفراغ، درد شکمی، اسهال
  - ایجاد آنتی‌بادی (طی 3 ماه از شروع)
  - واکنش محل انفوزیون، واکنش‌های انفوزیون
  - پارستزی، لرز، سردرد
  - آرترالژی، درد پشت، میالژی
  - سرفه، عفونت‌های تنفسی، رینیت
  - آنافیلاکسی

42 FABRAZYME

- موارد احتیاط مصرف:
  - سابقهٔ حساسیت به دارو
  - بیماری قلبی

43 FABRAZYME

- تداخل‌های دارویی:
  - آمیوداروں
  - جنتامایسین
  - کلروکین
  - هیدروکسی‌کلروکین

44 MIGALASTAT

- اتصال و تثبیت فرم‌های خاصی از آلفا-گالاکتوزیداز
- بهبود ترافیک آنزیم به لیزوزوم

- First-line therapy in Fabry patients with amenable galactosidase alpha (*GLA*) gene variants

- منع مصرف در کلیرانس زیر 30 ml/min

45 MIGALASTAT

46

NOW
ABOUT OUR PATIENT:

(619) 781-2009

47

Patient Details
DOB: 09/21/1982
Age(y/m/d): 038/06/08
Gender: M
Patient ID:

Specimen Details
Date collected: 03/29/2021 0944 Local
Date received: 03/29/2021
Date entered: 03/29/2021
Date reported: 04/05/2021 1105 ET

Physician Details
Ordering: O [redacted]
Referring:
ID:
NPI: 1629507207

General Comments & Additional Information
Total Volume: Not Provided

Fasting: Yes

Ordered Items
Alpha-Galactosidase A

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL	LAB
Alpha-Galactosidase A					
Alpha-Galactosidase activity	**0.3**	**Low**	nmol/hr/mg prt	>35.5	01

****Please note reference interval change****

Interpretation — Affected — 01

The above enzyme activity is consistent with this patient being affected with alpha-galactosidase A deficiency. Alpha-galactosidase A deficiency is the underlying defect in the X-linked disorder Fabry disease. Genetic counseling for this family is recommended.

Director Review — 01

Jean-Leon Chong, PhD
Director, Biochemical Genetics
To discuss these results or other testing for inborn errors of metabolism, please contact our Biochemical Geneticists at 1-800-345-GENE(4363), LabCorp Genetics Customer Service, RTP, NC.

Methodology — 01

Alpha-galactosidase activity was measured against the artificial substrate 4-methylumbelliferyl-alpha-D-galactopyranoside by the method of Desnick RJ, et al. (Desnick RJ, Allen KY, Desnick SJ, Raman MK, Bernlohr RW, Krivit WJ Lab Clin Med, 81(2):157,1973)

Disclaimer: — 01

This test was developed and its performance characteristics determined by Labcorp. It has not been cleared or approved by the Food and Drug Administration.

01 TG LabCorp RTP
1912 TW Alexander Drive, RTP, NC 27709-0150
Dir: Anjen Chenn, MDPhD

For inquiries, the physician may contact **Branch: 800-859-6046 Lab: 858-668-3700**

Date Issued: 04/05/21 1525 ET

DUPLICATE FINAL REPORT

□ جواب اولیه (Preliminary): شامل جهش های با تطابق نسبی و یا دارای اهمیت ثانویه (مرتبط با بیماری های دیگر) که نیاز به بررسی توسط پزشک بالینی و اعلام نظر وی دارد. لازم به ذکر می باشد که این جواب قطعی نبوده و امکان دارد تغییر نماید.

■ جواب پس از بررسی اولیه (Revised): شامل جوابی که جهش توسط پزشک از نظر تطابق بالینی مورد تایید قرار گرفته است اما به روش سانگر در بیمار و خانواده تایید نشده است و یا جهش مناسبی یافت نگردیده است.

□ جواب نهایی (Final): شامل جوابی است که جهش یافت شده علاوه بر تایید توسط پزشک معالج، به روش سانگر در فرد بیمار و خانواده وی نیز بررسی و تایید گردیده است و برای جهش یافت شده امکان آزمایش ناقلی و تشخیص پیش از تولد برای خانواده و وابستگان آن ها وجود داشته و توصیه می گردد.

□ جواب منفی (Negative): جهشی منطبق با علایم بیماری یافت نگردیده و یا این که جهش پیدا شده مورد تایید پزشک معالج قرار نگرفته است. ممکن است جهش های غیر مرتبط با بیماری پیدا شده باشد که در جدول دوم ذکر شده است. منفی بودن جواب به معنی رد ژنتیکی بودن بیماری نمی باشد.

توجه به این نکته ضروری است که هر آزمایشی با میزانی از خطا همراه می باشد. همچنین آزمایش WES توانایی یافتن ناهنجاری های ژنتیکی شامل انواع copy number variation (CNV)، large deletion، duplication، بیماری های مرتبط با repeat expansion و انواع جهش های موجود در نواحی غیر اگزونی را ندارد و شاید با صلاحدید پزشک انجام آزمایشات دیگری نظیر array CGH و یا بررسی پنل ژن های مرتبط با تشخیص اولیه که تمام نواحی اگزون و اینترون را پوشش می دهد مفید باشد.**

REPORT GENETIC TESTING

گزارش آزمایش ژنتیک

مشخصات بیمار	مشخصات نمونه	مشخصات پزشک درخواست کننده
نام و نام [redacted]	نوع نمونه: خون محیطی حاوی ضد انعقاد K3-EDTA	نام و نام خانوادگی:
تاریخ تولد بیمار/سن: 39 سال	تاریخ نمونه گیری: 1400/03/02	بیمارستان/موسسه:
جنسیت: مذکر	تاریخ دریافت نمونه: 1400/03/02	آدرس:
کد بیمار: MOWES01	تاریخ جوابدهی: 1400/04/07	توضیحات:
نسبت فامیلی والدین: غریبه		

Type of request — نوع درخواست:

Mono (patient) Whole Exome Sequencing Test

Clinical Indication — دلایل کلینیکی:

بیمار با بیماری Fabry (بیماری Fabry با میکروسکوپ الکترونی تایید شده است).

Pedigree/Family Genetic Information — شجره/شرح سابقه بیماری در فامیل:

بیمار حاصل ازدواج غیرخویشاوندی می باشد. سابقه بیماری ژنتیکی در خانواده وجود ندارد.

Test Result Summary — خلاصه نتایج:

Primary/Diagnostic Sequence Variant(S) Detected: — موتاسیونهای دارای اهمیت تشخیصی بیشتر (اولیه):

Gene	Variant coordinates	dbSNP rsID[a]	Associated disease	Phenotype MIM number	Inheritance[b]	Zygosity[c]	ACMG/ClinVar Classificatio[d]
GLA	ChrX- 100652861 100652861 G A- NM_000169: exon7: c.C1226T: p.P409L	-	1: Fabry disease 2: Fabry disease, cardiac variant	1: 301500 2: 301500	XL	Hemi	Likely Pathogenic/NR

Incidental/Secondary Sequence Variant(S) Detected

- موتاسیونهای دارای اهمیت تشخیصی کمتر (ثانویه):

Gene	Variant coordinates	dbSNP rsID[a]	Associated disease	Phenotype MIM number	Inheritance[b]	Zygosity[c]	ACMG/ClinVar Classification[d]
PAH	Chr12- 103260378 103260378 G A- NM_000277: exon5: c.C505T: p.R169C	rs281865440	1: [Hyperphenylalaninemia, non-PKU mild] 2: Phenylketonuria	1: 261600 2: 261600	AR	Het	Pathogenic/Likely Pathogenic
COQ8A	Chr1- 227170697 227170697 C T- NM_020247: exon8: c.C1042T: p.R348X	rs771578775	Coenzyme Q10 deficiency, primary, 4	612016	AR	Het	Pathogenic/Pathogenic

a All variants with dbSNPrsID numbers have minor allele frequencies less than 0.5% unless otherwise stated
b AD=Autosomal Dominant; AR=Autosomal Recessive; XL=X-Linked; XLR=X-Linked Recessive; DR= Digenic Recessive
c Hom=Homozygous; Het=Heterozygous; Hem=Hemizygous; WT=Wild Type
d VUS=Variant of Uncertain Significance, R= Reported, NR= Not Reported

Current novel hemizygous mutation in *GLA* gene (NM_000169: exon7: c.C1226T) leads to amino acid change (p.P409L) which is likely pathogenic based on most predictors. This mutation still needs to be confirmed in patient and parents by Sanger sequencing.

Result Interpretation تفسیر نتایج:

GLA (GALACTOSIDASE, ALPHA; Cytogenetic Location: Xq22.1): This gene encodes a homodimeric glycoprotein that hydrolyses the terminal alpha-galactosyl moieties from glycolipids and glycoproteins. This enzyme predominantly hydrolyzes ceramide trihexoside, and it can catalyze the hydrolysis of melibiose into galactose and glucose. A variety of mutations in this gene affect the synthesis, processing, and stability of this enzyme, which causes Fabry disease, a rare lysosomal storage disorder that results from a failure to catabolize alpha-D-galactosyl glycolipid moieties.

Fabry Disease (FD): Rare X-linked sphingolipidosis disease where glycolipid accumulates in many tissues. The disease consists of an inborn error of glycosphingolipid catabolism. FD patients show systemic accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in the plasma and cellular lysosomes throughout the body. Clinical recognition in males results from characteristic skin lesions (angiokeratomas) over the lower trunk. Patients may show ocular deposits, febrile episodes, and burning pain in the extremities. Death results from renal failure, cardiac or cerebral complications of hypertension or other vascular disease. Heterozygous females may exhibit the disorder in an attenuated form, they are more likely to show corneal opacities.

Conclusion نتیجه گیری:

This test was performed to identify the most relevant mutations that might explain the disease in this patient. This mutation is in accordance with the patient's clinical presentation and still needs to be confirmed in patient and parents by Sanger sequencing.

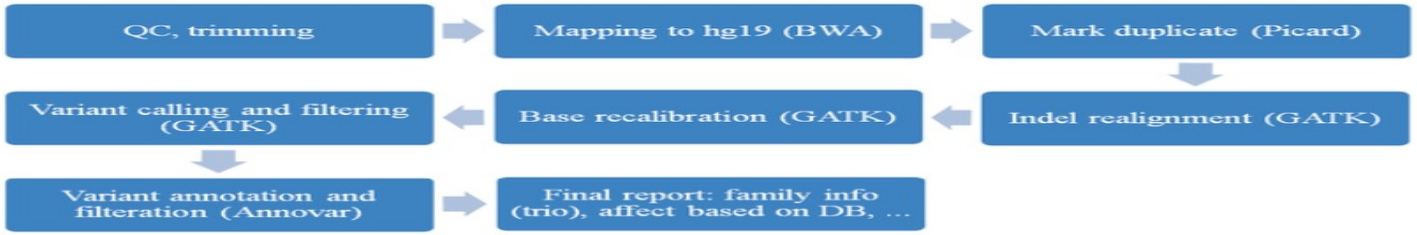
Recommendations توصیه ها:

Clinical correlation of the patient's phenotype with this result by physicians is recommended. Genetic counseling of the family is recommended to discuss the implications of this report. Further validation of SNP by Sanger sequencing in healthy relatives is recommended.

Type of Experiment and Analysis Workflow نوع آزمایشات و خلاصه گردش کار:

Sequencing process: Whole Exome Sequencing **Platform:** NovaSeq6000 **Read Length (bp):** 150bp PE

Library Type: SureSelect V7-Post **Coverage:** 100X **Single/paired-end sequencing:** Paired-end sequencing

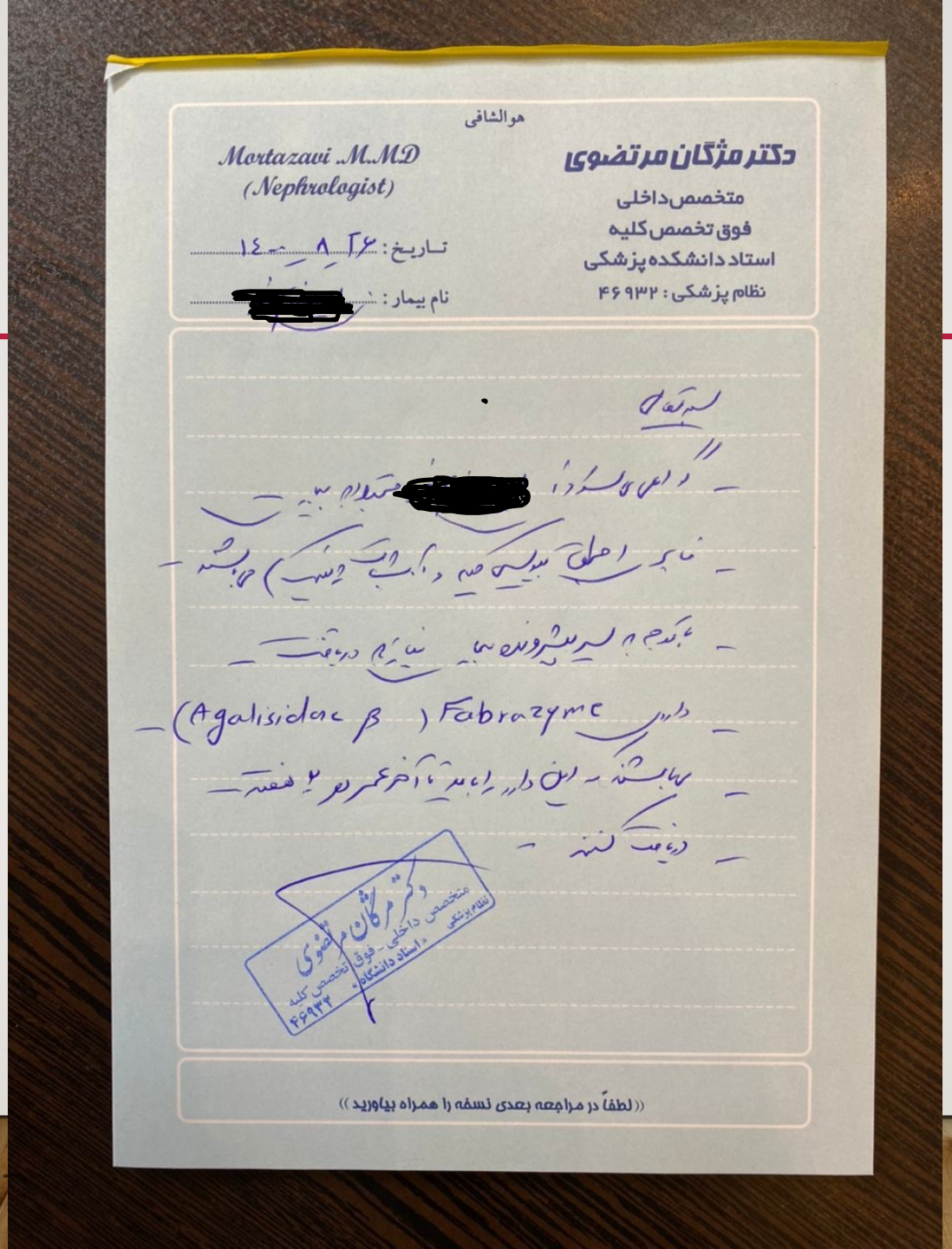


Methods and Limitation روش انجام آزمایش و محدودیتهای آن:

The Whole Exome Sequencing test is a highly complex test that is newly developed for the identification of changes in a patient's DNA that are causative or related to their medical concerns. In contrast to current sequencing tests that analyze one gene or small groups of related genes at a time, the Whole Exome Sequencing test will analyze the exons or coding regions of thousands of genes simultaneously using next-generation sequencing techniques. The principle of the test is to sequence nucleotide by nucleotide, the human exome of an individual to a depth of coverage necessary to build a consensus sequence with high accuracy. This consensus sequence is then compared to standards and references and the parental WES data and the result is interpreted by board-certified laboratory directors and clinicians. By sequencing the exome of a patient and their parents and then comparing it to normal reference sequence, variations in an individual's DNA sequence can be identified and related back to the individual's medical concerns in an effort to discover the cause of the medical disorder.

Although whole Exome Sequencing (WES) is a technique for sequencing all the protein-coding genes (exome) of a genome, however, certain genes may not be covered completely therefor some mutations could be missed. In in this method first only the subset of DNA that encodes proteins (exons) will be selected, and then they will be sequenced using Illumine high throughput DNA sequencing technology. There are 180,000 exons, which constitute about 1% of the human genome, or approximately 30 million base pairs, but mutations in these sequences are much more likely to have severe consequences than in the remaining 99%. The goal of this approach is to identify genetic variation that is responsible for both Mendelian and common diseases. The segregation of candidate pathogenic variation(s) are advised to be tested by Sanger sequencing. This exome sequence test is designed to evaluate single nucleotide variants within the human exome.

Certain types of sequence variation include large deletions, insertions, duplications, copy number variations, long repeat sequences, triplet repeat expansions, structural chromosomal rearrangements, polyploidy, repetitive regions such as mono-, di- and tri-nucleotide repeats, GC rich regions, intronic variants outside of the splice-site, and epigenetic effects are difficult to identify and have not been validated to be reliably detected for current clinical use. The test is limited in its ability to detect mosaicism. This technology is limited in its ability to accurately identify variants occurring in regions with high sequence identity to other regions of the genome (e.g paralogous genes and pseudogenes).Normal findings do not rule out the diagnosis of genetic abnormalities. If specific clinical disorders are suspected, specific evaluation of known genes by alternate test methods should be considered. Variants that interfere with DNA sequencing and medical procedures such as bone marrow transplantation and blood transfusion may result in misleading results. The clinical implications of certain variants may be unknown at the time of analysis.



هوالشافی

دکتر مژگان مرتضوی

متخصص داخلی
فوق تخصص کلیه
استاد دانشکده پزشکی
نظام پزشکی: ۴۶۹۳۲

Mortazavi .M.MD
(Nephrologist)

تاریخ: ۱۴۰۰/۸/۲۶

نام بیمار: [redacted]

نسخه

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

دکتر مژگان مرتضوی
متخصص داخلی - فوق تخصص کلیه
استاد دانشگاه
نظام پزشکی ۴۶۹۳۲

«لطفاً در مراجعه بعدی نسخه را همراه بیاورید»

KULLANMA TALİMATI

FABRAZYME® 35 mg

İnfüzyonluk çözeltİ için konsantre toz
Damar yoluyla kullanılır.
Steril

SANOFI

Etkin madde: 35 mg agalsidaz beta
Yardımcı maddeler: Mannitol, Sodyum Fosfat Monobazik monohidrat, Sodyum Fosfat Dibazik heptahidrat

Bu ilacı kullanmaya başlamadan önce bu KULLANMA TALİMATINI dikkatlice okuyunuz, çünkü sizin için önemli bilgiler içermektedir.
- *Bu kullanma talimatını saklayınız. Daha sonra tekrar okumaya ihtiyaç duyabilirsiniz.*
- *Eğer ilave sorularınız olursa, lütfen doktorunuza veya eczacınıza danışınız.*
- *Bu ilaç kişisel olarak size reçete edilmiştir, başkalarına vermeyiniz.*
- *Başkalarının belirtileri sizinkilerle aynı dahi olsa, ilaç o kişilere zarar verebilir.*
- *Bu ilacın kullanımı sırasında, doktora veya hastaneye gittiğinizde doktorunuza bu ilacı kullandığınızı söyleyiniz.*
- *Bu talimatta yazılanlara aynen uyunuz. İlaç hakkında size önerilen dozun dışında **yüksek veya düşük** doz kullanmayınız.*

Bu Kullanma Talimatında:

Başlıkları yer almaktadır.

1. FABRAZYME nedir ve ne için kullanılır?

FABRAZYME, beyaz ila beyazımsı liyofilize kütle veya toz halindedir. 35 mg agalsidaz beta içerir. Sindirim sistemi ve metabolizma ürünleri altındaki enzimler grubuna dahildir.
FABRAZYME etkin madde olarak agalsidaz beta içerir ve alfa galaktosidaz enzim aktivitesinin olmadığı veya normalden düşük olduğu Fabry hastalığında enzim yerine koyma tedavisi olarak kullanılır. Fabry hastası iseniz, globotriaosilseramid (GL-3) denilen yağlı madde organlarınızdaki hücrelerden atılamaz ve organlarınızdaki damarların duvarlarında birikmeye başlar.
FABRAZYME, Fabry hastalığı teşhisi konmuş hastalarda uzun süreli enzim yerine koyma tedavisinde kullanılır.
Fabrazyme, yetişkinler, 8 yaş ve üzeri çocuk ve ergenlerde kullanılır.

2. FABRAZYME'ı kullanmadan önce dikkat edilmesi gerekenler

FABRAZYME'ı aşağıdaki durumlarda KULLANMAYINIZ
Eğer agalsidaz beta veya FABRAZYME'ın diğer bileşenlerine karşı alerjiniz (aşırı duyarlılığınız) varsa kullanmayınız.

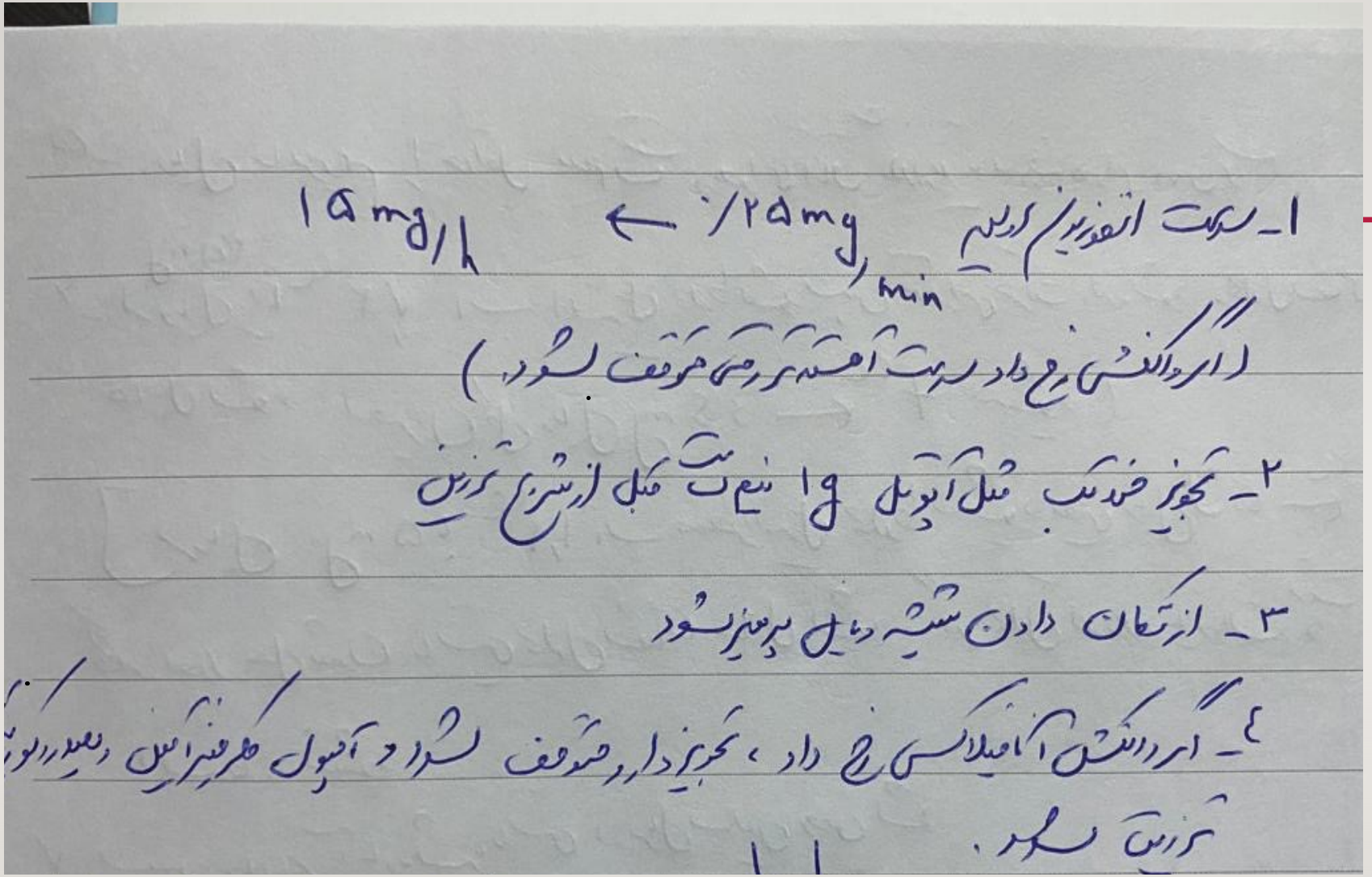
FABRAZYME'ı aşağıdaki durumlarda DİKKATLİ KULLANINIZ

FABRAZYME'ı kullanmadan önce doktorunuza danışınız.

Eğer FABRAZYME ile tedavi görüyorsanız, infüzyona bağlı reaksiyonlar gelişebilir. İnfüzyona bağlı reaksiyon, infüzyon sırasında veya infüzyon uygulanan günün sonuna kadar oluşan herhangi bir istenmeyen etkidir (Bkz. Bölüm 4. Olası Yan etkiler). Böyle bir reaksiyon ile karşılaşmanız durumunda hemen doktorunuza haber vermelisiniz. Bu reaksiyonların oluşumunu önlemek için ilave ilaç uygulamasına ihtiyaç duyabilirsiniz.

Bu uyarılar, geçmişteki herhangi bir dönemde dahi olsa sizin için geçerliyse lütfen doktorunuza danışınız.

FABRAZYME'ın yiyecek ve içecek ile kullanılması
FABRAZYME damar yolu ile kullanıldığından yiyecek ve içeceklerle herhangi bir etkileşim söz konusu değildir ve birlikte kullanabilirsiniz.



۱- سرعت انفوزیون کردیم ۰/۲۵mg/min ← ۱۵mg/h

(اگر واکنش رخ داد سرعت آهسته‌تر یا متوقف شود.)

۲- تجویز خودتنب مثل آتروپین ۱g نیم ساعت قبل از شروع تزریق

۳- از تکان دادن شیشه دایل پرهیز شود

۴- اگر واکنش آنافیلاکسی رخ داد، تجویز دارو متوقف شود و اصول طرفیت‌آمین و اپی‌نفرین و اکسیژن

۵- ویال خانزیم را حداقل نیم ساعت در هوای اتاق بگذارید تا به درجه هوای اتاق برسد

۶- هر ویال ۳۵ mg را با ۷/۲ cc آب استریل مخلوط شود سپس به آرامی حرکت داده شود و محلول شفافی حاصل شود (میزان کل ویال 35 mg ← 7 cc میشود)

[هر ویال ۵ mg با ۱/۱ cc آب مقطر استریل مخلوط میشود یعنی ویال ۵ mg ← ۱ cc]

نکته: بعد از حل شدن باید محلول شفافی حاصل شود. اگر محلول کدر بود یا ذرات داشت استفاده نشود.

۷- سپس ویال‌های آماده شده باید در نرمال سالین رقیق شود

۸- طبق جدول چون شما حدود ۷۰kg هستید حداقل حجم محلول انفوزیون ۱۰۰cc باید باشد.

patien dose (in mg) ÷ 5mg/ml

۷۰ ÷ ۵ = ۱۴ ml of fabrazyme

هر ویالی که حل کردیم ۷cc شد یعنی ۲ ویال که میشود ۱۴cc.

(۳۵mg)

۹- مستقیم محلول حل برداریم آماده شده در ۲تا ۷cc است را به داخل سرم نرمال سالین تزریق کنید

۱۰- سپس به آرامی سرم را برگردانید

[redacted]

100 F.C. Tablets

(نوبت اول حداقل طول زمان تزریق ۵ ساعت است)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fabrazyme® is indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- The recommended dosage of Fabrazyme is 1 mg/kg body weight infused every two weeks as an intravenous infusion.
- Infusion rate:
  - The initial intravenous infusion rate is 0.25 mg/min (15 mg/hour). Slow the infusion rate in the event of infusion-associated reactions *[see Warnings and Precautions (5.2)]*.
  - For patients >30 kg, after patient tolerance to the infusion is well established, increase the infusion rate in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hour) with each subsequent infusion. The minimum infusion duration is 1.5 hours (based on individual patient tolerability).
  - For patients weighing <30 kg, the maximum infusion rate is 0.25 mg/minute (15 mg/hour).
- Because of the potential for severe infusion-associated reactions, appropriate medical support measures should be readily available when Fabrazyme is administered *[see Warnings and Precautions (5.2)]*.
- Administer antipyretics prior to infusion of Fabrazyme *[see Warnings and Precautions (5.2)]*.
- Rechallenge: Patients who have had a positive skin test to Fabrazyme or who have tested positive for anti-Fabrazyme IgE may be successfully rechallenged with Fabrazyme. The initial rechallenge administration should be a low dose at a lower infusion rate, e.g., one-half the therapeutic dose (0.5 mg/kg) at 1/25th of the initial standard recommended rate (0.01 mg/min). Once a patient tolerates the infusion, the dose may be increased to reach the approved dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/minute), as tolerated *[see Adverse Reactions (6.2)]*.

2.2 Preparation and Administration Instructions

Fabrazyme does not contain any preservatives. Vials are for single use only. Discard any unused product.

Avoid shaking or agitating this product. Do not use filter needles during the preparation of the infusion.

Reconstitution and Dilution (using Aseptic Technique)

1. Allow Fabrazyme vials and diluent to reach room temperature prior to reconstitution (approximately 30 minutes). The number of 35 mg and 5 mg vials needed is based on the patient's body weight (kg) and the recommended dose of 1 mg/kg.
   Select a combination of 35 mg and 5 mg vials so that the total number of mg is equal to or greater than the patient's number of kg of body weight.
2. Reconstitute each 35 mg vial of Fabrazyme by slowly injecting 7.2 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 35 mg, 7 mL).
   Reconstitute each 5 mg vial of Fabrazyme by slowly injecting 1.1 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 5 mg, 1 mL).
3. Visually inspect the reconstituted vials for particulate matter and discoloration. Do not use the reconstituted solution if there is particulate matter or if it is discolored.
4. The reconstituted solution should be further diluted with 0.9% Sodium Chloride Injection, USP to a total volume based on patient weight specified in Table 1 below. Prior to adding the volume of reconstituted Fabrazyme required for the patient dose, remove an equal volume of 0.9% Sodium Chloride Injection, USP from the infusion bag.

Table 1: Total Infusion Volume Based on Patient Weight

Patient Weight (kg)	Minimum Total Volume (mL)
≤35	50
35.1 to 70	100
70.1 to 100	250
>100	500

Patient dose (in mg) ÷ 5 mg/mL = Number of mL of reconstituted Fabrazyme required for patient dose

Example: Patient dose = 80 mg

80 mg ÷ 5 mg/mL = 16 mL of Fabrazyme

Slowly withdraw the reconstituted solution from each vial up to the total volume required for the patient dose. Inject the reconstituted Fabrazyme solution directly into the Sodium Chloride solution. Do not inject in the airspace within the infusion bag. Discard any vial with unused reconstituted solution.

5. Gently invert infusion bag to mix the solution, avoiding vigorous shaking and agitation.
6. Do not infuse Fabrazyme in the same intravenous line with other products.
7. Administer Fabrazyme using an in-line low protein binding 0.2 µm filter.

Storage of Reconstituted Solution

Use reconstituted and diluted solutions of Fabrazyme immediately. If immediate use is not possible, the reconstituted and diluted solution may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F).

3 DOSAGE FORMS AND STRENGTHS

For injection: 5 mg or 35 mg of agalsidase beta as a white to off-white, lyophilized cake or powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

The data described below reflect exposure of 80 patients, ages 10 to 61 years, to 1 mg/kg Fabrazyme every two weeks in two separate double-blind, placebo-controlled clinical trials, for periods ranging from 1 to 35 months (mean 15.5 months). All 58 patients enrolled in one of the two studies continued into an open-label extension study of Fabrazyme treatment for up to 54 additional months. Patients were treated with antipyretics and antihistamines prior to the infusions.

Most Common Adverse Reactions

Table 2 enumerates adverse reactions that occurred during the double-blind treatment periods of the two placebo-controlled trials (Study 1 and Study 2) *[see Clinical Studies (14)]*. The most common adverse reactions reported with Fabrazyme were infusion-associated reactions, (Fabrazyme 59% vs placebo 27%) some of which were severe (Fabrazyme 5.0% vs placebo 1.7%). Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion.

Common adverse reactions which occurred in ≥20% of patients treated with Fabrazyme and >2.5% compared to placebo are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness and rash. Table 2 lists the common adverse reactions (≥5%).

Summary and Recommendation

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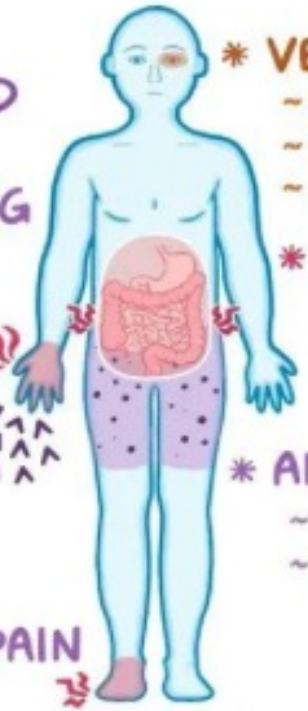
FABRY DISEASE ♂ ♀

CLASSIC
└ STARTS in CHILDHOOD

* ↓ SWEATING
* BURNING
* TINGLING & PRICKLING
* NEUROPATHIC PAIN
  ~ HANDS & FEET



* VERTICILLATA
  ~ CORNEA
  ~ SPLIT LAMP EYE EXAM
  ~ ✕ AFFECT VISION
* GASTROINTESTINAL
  ~ CRAMPS
  ~ FREQUENT BOWEL MOVEMENT
  ~ CONSTIPATION
  ~ DIARRHEA

* ANGIOKERATOMAS
  ~ LOWER ABDOMEN
  ~ BATHING TRUNK

w/o TREATMENT
* KIDNEY DISEASE
* ABNORMAL HEART RHYTHMS
* HEART ENLARGEMENT
* ↑ STROKE RISK

Osmosis

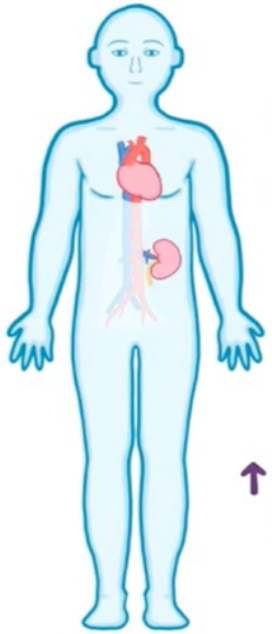
Also appears in

FABRY DISEASE ♂ ♀

NONCLASSIC (LATE-ONSET)

CHILDHOOD

✗ SYMPTOMS of PAIN & GASTROINTESTINAL ISSUES



ADULTS

✓ MULTIPLE SYMPTOMS as YOUNG ADULTS

OTHERS:

* HEART
* KIDNEYS

↑ RISK of FABRY-ASSOCIATED COMPLICATIONS

SUMMARY AND RECOMMENDATION

- Fabry disease (FD) is a multisystem lysosomal storage disorder induced by a mutation in the alpha-galactosidase A (GLA) gene located on the X chromosome.
- Reduced activity or deficiency of alpha-galactosidase A (AGAL) is leading to escalating storage of intracellular globotriaosylceramide (GL-3) in numerous organs, including the nervous system, kidneys and heart.
- Typical manifestations include peripheral neuropathic pain, gastrointestinal symptoms, angiokeratoma, anhidrosis, left ventricular (LV) hypertrophy, cornea verticillate, renal failure or cryptogenic stroke.

SUMMARY AND RECOMMENDATION

- measurement of AGAL activity is highly recommended.
- In males, reduced AGAL activity (<1% of the mean normal) is extremely suggestive of classic FD.
- In females and in patients with late-onset mutations, the enzyme activity may be residual or even in a normal range; thus, in such cases, genetic testing for Fabry mutations is essential .
- The supplementary measurement of globotriaosylsphingosine (Lyso-Gb3) is advocated. Lyso-Gb3 levels ≥2.7 ng/mL are pathological and in general the level of Lyso-Gb3 is related to disease activity and to the severity of mutation .

SUMMARY AND RECOMMENDATION

- In addition, Lyso-Gb3 can be used to monitor therapy effects during specific treatment such as chaperone therapy.
- For assessment of important cardiac involvement, measurements of highly sensitive Troponin (hsTnT) and B-type natriuretic peptide (NT-proBNP), as biomarkers, are recommended .
- Whereas hsTnT indicates mainly myocardial fibrosis in hypertrophic left ventricles, NT-proBNP is elevated in end-stage Fabry cardiomyopathy.
- Both blood biomarkers are part of the important diagnostic tools to initiate and to monitor chaperone therapy.

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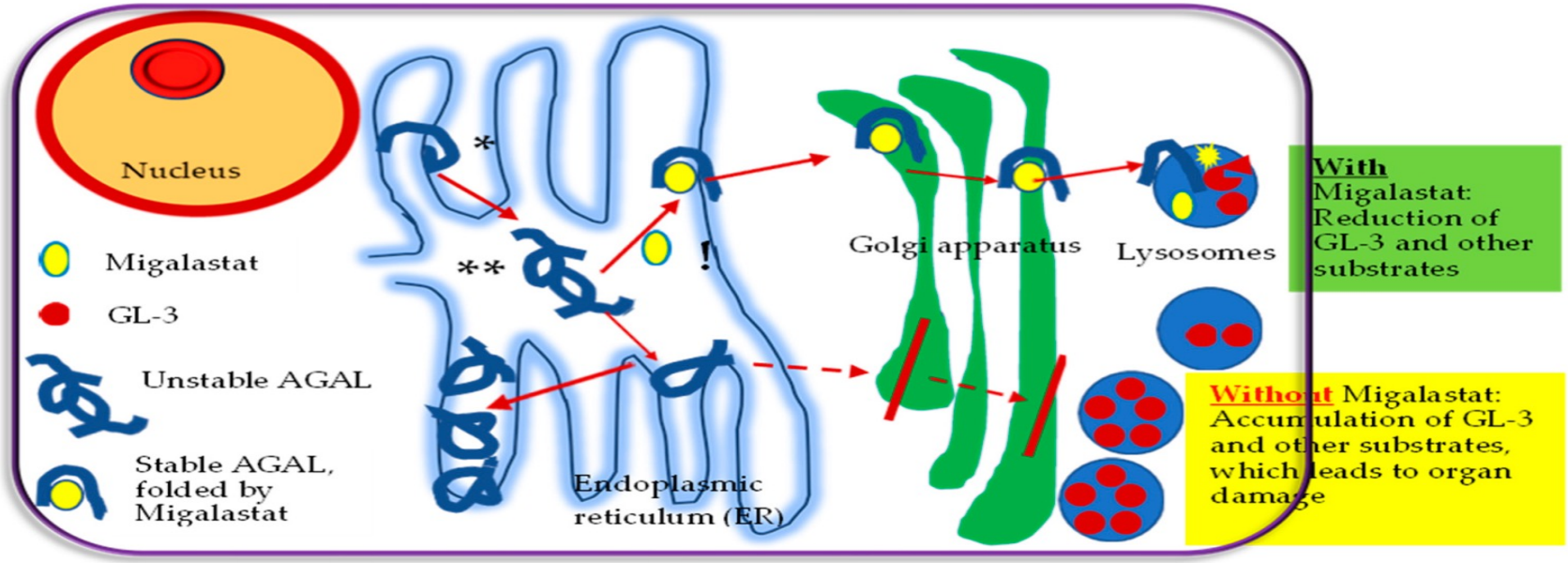

Figure 1. Overview of action of Migalastat. AGAL, alpha-galactosidase A. GL-3, Globotriaosylceramide. (*) Synthesis of misfolded AGAL. (**) Accumulation of misfolded AGAL.

Migalastat is also a strong competitive inhibitor of AGAL [10]; however, at lower doses, it increases enzymatic activity for amenable AGAL mutations [25], as described in Figure 1.

3.1. Migalastat

Currently, Migalastat is the only small molecule oral treatment for FD, administered 123 mg once every other day. Migalastat was approved by the European Medicines


Thank You
For Your
Attention