Original Article

DOI: 10.5582/irdr.2025.01070

Multidisciplinary approach to the assessment and management of children with Fabry disease: Insights from the Chinese Children Genetic Kidney Disease Database

Jing Wang[1,§], Jialu Liu[2,§], Jing Chen[2], Aihua Zhang[3], Jianhua Mao[4], Tong Shen[5], Xiaoyun Jiang[6], Mo Wang[7], Yuhong Tao[8], Bo Zhao[9], Xiaowen Wang[10], Zhihui Li[11], Ai Chen[12], Chaoying Chen[13], Bili Zhang[14], Dongfeng Zhang[15], Lijun Zhao[16], Yuhua Zhao[17], Ying Bao[18], Ling Bai[19], Cuihua Liu[20], Feiyan Wang[21], Fangqi Hu[22], Meili Chen[23], Xueyun Lv[24], Shuzhen Sun[1,*], Qian Shen[2,*], Hong Xu[2,*]

[1] Department of Pediatric Nephrology and Rheumatism and Immunology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China;
[2] Department of Nephrology, Children's Hospital of Fudan University; National Children's Medical Center; Shanghai Kidney Development and Pediatric Kidney Disease Research Center; National Key Laboratory of Kidney Diseases, Shanghai, China;
[3] Children's Hospital of Nanjing Medical University, Nanjing, China;
[4] Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China;
[5] Xiamen Maternal and Child Health Care Hospital, Xiamen, China;
[6] The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China;
[7] Children's Hospital of Chongqing Medical University, Chongqing, China;
[8] West China Second University Hospital, Sichuan University, Chengdu, China;
[9] Kunming Children's Hospital, Kunming, China;
[10] Wuhan Children's Hospital, Wuhan, China;
[11] Hunan Children's Hospital, Changsha, China;
[12] Department of Paediatrics, West China School of Medicine, Sichuan University; Sichuan University affiliated Chengdu Second People's Hospital, Chengdu, China;
[13] Affiliated Children's Hospital of Capital Institute of Pediatrics, Beijing, China;
[14] Tianjin Children's Hospital, Tianjin, China;
[15] Hebei Children's Hospital, Shijiazhuang, China;
[16] Shanxi Children's Hospital, Xi'an, China;
[17] Inner Mongolia Maternal and Child Health Hospital, Hohhot, China;
[18] Xi'an Children's Hospital, Xi'an, China;
[19] Xinjiang Uygur Autonomous Region Children's Hospital, Urumqi, China;
[20] Henan Children's Hospital, Zhengzhou, China;
[21] Urumqi First People's Hospital Children's Hospital, Urumqi, China;
[22] Anqing Municipal Hospital, Anqing, China;
[23] The First Affiliated Hospital of Anhui Medical University, Anqing, China;
[24] Department of Pediatrics, Liaocheng People's Hospital, Liaocheng, China.

SUMMARY: Fabry disease (FD) is a rare multisystemic lysosomal storage disorder with diverse pediatric manifestations. This multicenter study analyzed 64 children with FD from the Chinese Children Genetic Kidney Disease Database following establishment of the first national pediatric FD multidisciplinary team (MDT) in April 2020, which expanded to 15 centers by January 2022. Median diagnostic age was 11.4 years in males and 9.4 years in females, with diagnostic delays of 4.4 and 4.0 years, respectively. Family screening accounted for most female diagnoses (72.2%), while 6.5% of males were incidentally detected during genetic testing for other diseases. Missense variants predominated (65.2% males, 66.7% females). Biochemically, males had markedly reduced α-Gal A activity (0.6 ± 0.4 μmol/L/h), and most patients showed elevated globotriaosylsphingosine (Lyso-GL-3), including 87.0% of males and 83.3% of females. Neuropathic pain was the most common initial symptom (52.2% males, 27.8% females; median onset 8 years), primarily acroparesthesia (92.1% and 85.7%, respectively). Other frequent features included anhidrosis/hypohidrosis (58.7% males, 11.1% females). Multisystem involvement included cardiac (arrhythmia n = 11, left ventricular hypertrophy n = 3), pulmonary (obstructive airway disease in 24.2% of males), skeletal (low bone mineral density in 4/7 tested males), and renal manifestations (reduced glomerular filtration rate (GFR) in 3). Thirty-seven patients received enzyme replacement therapy at median ages of 12.9 years (males) and 11.7 years (females). This first nationwide pediatric FD cohort highlights substantial diagnostic delays and underscores the importance of MDT collaboration, family screening, and early recognition to improve outcomes in affected children.

Keywords: Fabry disease, children, multidisciplinary team

1. Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder characterized by reduced or complete absence of the enzyme α-galactosidase A (α-Gal A) due to mutations in the GLA gene. In 2018, FD was included in the first official list of 121 rare diseases in China (No. 27). Clinical symptoms frequently emerge in childhood or adolescence (*1-5*). With the accumulation of the substrate globotriaosylceramides (GL-3) and its derivative deacetyl GL-3 (globotriaosylsphingosine, Lyso-GL-3), early symptoms can develop into life-threatening complications, leading to serious clinical events including renal, cardiac, cerebrovascular complications or death. However, the initial symptoms of FD are atypical, the clinical manifestations are diverse, and there is a significant delay from the onset of symptoms to diagnosis, which can be as long as 14-16 years (*6*).

The approval of enzyme replacement therapy (ERT) in China in 2019 positioned FD as one of the few genetic metabolic diseases amenable to targeted therapy. With advances in enzymatic assays and genetic testing, early diagnosis provides a crucial opportunity for timely intervention before irreversible organ damage occurs. To address diagnostic challenges, the Children's Hospital of Fudan University established the first pediatric multidisciplinary diagnosis and treatment (MDT) team for FD in April 2020. A tertiary referral framework was introduced, incorporating risk-based symptom and family screening, dried blood spot (DBS) triple testing (α-Gal A activity, lyso-GL-3 levels, and GLA sequencing), and targeted newborn genetic testing for high-risk metabolic disorders (*7*).

The Fabry Aim Children Early (ACE) Project, jointly initiated by the Chinese Association for Improving Birth Outcome and Child Development and the Children's Hospital of Fudan University, expanded MDT implementation to 21 institutions between July 2021 and January 2022 (Supplementary Table S1 and Supplementary Figure S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=281*). These teams were established in tertiary hospitals across China to improve early detection and provide effective interventions for children and families with FD.

A clearer understanding of pediatric FD phenotypes in China is essential for guiding both diagnosis and long-term management. This study summarizes the clinical characteristics and treatment status of children diagnosed through the MDT network.

2. Patients and Methods

2.1. Study design and data sources

This retrospective multicenter study enrolled pediatric patients (≤ 18 years) diagnosed with FD before March 2025 from the Chinese Children's Genetic Kidney Disease Database (CCGKDD, *www.ccgkdd.com.cn*) – a national multicenter registry systematically documenting genotypic and phenotypic data of children with inherited kidney diseases in China (*8*).

Inclusion criteria: *i*) Age ≤ 18 years at diagnosis; *ii*) Confirmed FD diagnosis meeting one of the following criteria (*9*):

Identification of a pathogenic or likely pathogenic (P/LP) GLA gene variant according to the American College of Medical Genetics and Genomics (ACMG) guidelines (*10*);

For males: Presence of a GLA gene variant of uncertain significance (VUS) combined with deficient α-Gal A activity (< 2.4 μmol/L/h);

For females: Presence of a GLA VUS with elevated plasma Lyso-GL-3 (≥ 1.11 ng/mL) and/or deficient α-Gal A activity.

Exclusion criteria: *i*) Absence of essential biochemical data—specifically, α-Gal A activity or Lyso-GL-3 levels—required for diagnostic confirmation; *ii*) Initiation of ERT before collection of baseline clinical data.

Clinical information was collected using a standardized questionnaire to ensure uniform data acquisition across centers. Collected data included demographics, presenting symptoms, organ involvement, genetic test results, and treatment status.

2.2. Data collection and management

A standardized, web-based electronic case report form (e-CRF) was specifically designed for this study to ensure uniform and comprehensive data collection across all participating centers. The e-CRF captured the following domains:

i) Demographics: Age, sex, family history.

ii) Diagnostic data: Age at first symptom onset, age at diagnosis, reason for diagnostic testing (symptoms *vs.* family screening), diagnostic delay.

iii) Genetic data: GLA gene variant (nucleotide and protein change), zygosity, ACMG classification, segregation analysis within the family.

iv) Biochemical data: α-Gal A enzyme activity (reference: > 2.4 μmol/L/h), plasma Lyso-GL-3 level (reference: < 1.11 ng/mL).

v) Clinical manifestations: A comprehensive review of systems was conducted to document involvement across neurological (pain characteristics: acroparesthesia, Fabry crises, burning sensation, tingling, numbness), dermatological (angiokeratoma), ophthalmological (cornea verticillata, cataracts), gastrointestinal (abdominal pain, diarrhea, constipation), renal (microalbuminuria, proteinuria, estimated glomerular filtration rate - eGFR), cardiac (arrhythmias, left ventricular hypertrophy, valvular abnormalities), respiratory (pulmonary function tests), auditory (hearing loss), and skeletal (bone mineral density) systems.

Severe clinical events were defined as: cardiac events

(atrial fibrillation, admission for any rhythm disturbance or congestive heart failure), stroke, and the need for dialysis and transplantation.

vi) Treatment data: Use of ERT (agalsidase alfa or beta), age at ERT initiation, duration of ERT, adjunctive therapies (analgesics, RAAS inhibitors, *etc*.), and reported adverse events.

All data extracted for analysis were collected prior to the initiation of ERT to accurately represent the natural history of the disease.

2.3. Statistical analysis

Descriptive statistics were used to summarize the patient characteristics. Categorical variables were presented as numbers and percentages (*n*, %). Continuous variables were expressed as mean ± standard deviation (SD) and median with range (min-max). Data visualization was conducted using GraphPad Prism (version 9.0, GraphPad Software, San Diego, CA, USA).

2.4. Ethical approval

The study was approved by the Institutional Review Board of Children's Hospital of Fudan University (No. 2021241) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all legal guardians and from patients aged ≥ 8 years. All personal identifiers were anonymized to protect participant privacy.

3. Results

A total of 64 pediatric patients with FD from the Chinese Children Genetic Kidney Disease Database were included in this study (Supplementary Table S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=281*), comprising 46 males (71.9%) and 18 females (28.1%).

3.1. Baseline demographic and diagnostic characteristics

The baseline demographic and diagnostic characteristics, stratified by sex, are presented in Table 1.

The median age at diagnosis was 11.4 years (range: 0.1–18.2) for males and 9.4 years (range: 1.7–16.7) for females. Family screening accounted for 72.2% of female and 34.8% of male diagnoses, highlighting a marked sex difference in diagnostic pathway. In three males (6.5%), GLA variants were identified incidentally during genetic testing for unrelated conditions.

The median age at symptom onset was slightly earlier in males (6.4 years) than in females (7.0 years), with corresponding diagnostic delays of 4.4 years and 4.0 years, respectively.

Neuropathic pain was the most frequent presenting symptom, observed in 52.2% of males and 27.8% of females, with a median onset age of 8 years.

3.2. Genetic and biochemical characteristics

Genetic and biochemical features are summarized in Table 1.

Missense variants were the predominant mutation type in both sexes (males: 65.2%; females: 66.7%). Male patients exhibited markedly reduced α-Gal A enzyme activity (0.6 ± 0.4 μmol/L/h), while females showed variable but generally normal enzyme levels (2.3 ± 0.9 μmol/L/h).

Despite this, elevated plasma Lyso-GL-3 levels were detected in the majority of both sexes (males: 87.0%; females: 83.3%), indicating significant substrate accumulation even among females with normal enzymatic activity.

3.3. Clinical manifestations and multisystem involvement

The spectrum and frequency of organ system involvement are detailed in Table 2, with further visualization provided in Figure 1 and Figure 2. Key systemic manifestations are summarized below:

i) Neurological involvement: During follow-up, 90.5% of symptomatic males and 38.9% of females experienced neuropathic pain. Acroparesthesia was predominant (males: 92.1%; females: 85.7%) and manifested as burning (52.6% *vs.* 14.3%), tingling (31.6% *vs.* 57.1%), or numbness (10.5% *vs.* 14.3%). Fabry crises were reported in 63.2% of males and 28.6% of females.

ii) Renal involvement: Although overt kidney disease was uncommon, early renal abnormalities were evident. Among 41 males with evaluable data, 14.6% had renal abnormalities, most commonly microalbuminuria (12.2%) and reduced estimated GFR (7.3%). One patient presented with renal tubular dysfunction, suggesting early tubular involvement.

iii) Cardiac manifestations: Cardiac abnormalities were observed in both sexes. Arrhythmias occurred in 27.5% of males and 44.4% of females. Left ventricular hypertrophy (LVH) was noted in 7.5% of males, while valvular dysfunction and conduction disturbances were reported across both groups.

iv) Additional organ system involvement: Notable involvement was also found in other organ systems. Ophthalmological examination revealed cornea verticillata in a substantial proportion of both males and females (48.7% and 53.8%, respectively). Respiratory function testing identified obstructive airway disease in 24.2% of the male patients. Furthermore, sensorineural hearing loss was detected in 10.8% of males. Involvement of other systems included: skeletal, with low bone mineral density found in 4 out of 7 (57.1%) tested males.

3.4. Treatment status

Table 1. Summary of demographic and disease characteristics by sex

Characteristic	Male (*n* = 46)	Female (*n* = 18)
Age at Fabry diagnosis (years)		
Mean ± SD	10.6 ± 4.6	9.8 ± 4.0
Median age (range)	11.4 (0.1–18.2)	9.4 (1.7–16.7)
Diagnostic Data		
Age at first onset of symptom (years)		
Patients with symptoms, *n* (Percentage)	42 (91.3%)	9 (55.0%)
Mean ± SD	5.5 ± 4.5	5.5 ± 4.8
Median age (range)	6.4 (0–16.0)	7.0 (0–13.0)
Diagnostic delay (years)		
Mean ± SD	5.6 ± 5.1	4.5 ± 5.5
Median age (range)	4.4 (0–17.5)	4 (-4.8–13.5)
Reason for testing, *n* (%)		
Symptoms	27 (58.7%)	5 (27.8%)
Family screening	16 (34.8%)	13 (72.2%)
Patients at risk of genetic metabolic disorders	3 (6.5%)	0
Family members diagnosed with Fabry, *n* (%)		
Yes	41 (89.1%)	11 (100%)
No	3 (6.5%)	0
Unknown/not reported	2 (4.3%)	0
Genetic Data		
GLA variants Type, *n* (%)		
Missense	30 (65.2%)	12 (66.7%)
Truncating	6 (13.0%)	3 (16.7%)
Deletion	6 (13.0%)	1 (5.6%)
Splicing	2 (4.3%)	1 (5.6%)
Intron	2 (4.3%)	1 (5.6%)
Biochemical Data		
GLA activity, Mean ± SD (μmol/L/h)	0.6 ± 0.4	2.3 ± 0.9
Elevated plasma lyso-GL-3, *n* (%)	40 (87.0%)	15 (83.3%)

Treatment details are summarized in Table 3.

A total of 37 patients (31 males, 6 females) received ERT, initiated at median ages of 12.9 years in males and 11.7 years in females. The median interval from symptom onset to ERT initiation was 7.3 years in males and 4.0 years in females.

Most patients received agalsidase beta (Fabrazyme®). ERT was generally well tolerated; only two males (6.5%) experienced grade 3 adverse events, with no grade ≥ 4 reactions reported.

Adjunctive medications included analgesics (41.3% of males) and renin–angiotensin–aldosterone system (RAAS) inhibitors (13.0%), reflecting proactive nephroprotective management within multidisciplinary care frameworks.

3.5. Severe clinical events

During the study observation period, severe clinical events were rare. Only one male patient (2.2%) experienced a significant renal event requiring transplantation. There were no reported deaths, cardiac, or cerebrovascular events.

4. Discussion

This nationwide study, conducted through China's first MDT network dedicated to pediatric FD, provides the first comprehensive overview of its clinical spectrum, diagnostic patterns, and management practices in Chinese children. The key findings include diagnostic delays, early multisystem involvement, sex-related clinical differences, and the increasing adoption of early enzyme replacement therapy within MDT care frameworks.

4.1. Diagnostic delay and the critical role of family screening

Diagnostic delay remains a key challenge in FD, particularly in pediatric populations. International registries have documented prolonged intervals between symptom onset and diagnosis—reaching 13.7 years in males and 16.3 years in females (*11*). Against this global background, our study demonstrates meaningful progress within China's emerging MDT framework: the median diagnostic delay in our pediatric cohort was 4.4 years for males and 4.0 years for females.

This substantial reduction reflects the early success of the national pediatric FD MDT network, underscoring the benefits of systematic family screening, cascade genetic testing, and improved clinician awareness. Notably, 72.2% of female patients in our cohort were diagnosed through family screening, highlighting the decisive role of this strategy in shortening the diagnostic odyssey. This approach aligns with both Chinese expert consensus (*12*) and international recommendations from European (*13,14*) and the United States (*15*) guidelines, which emphasize cascade testing as the most effective

Table 2. Prevalence of organ system involvement and clinical manifestations

Parameter	Male	Female
Total number	46	18
Organ system, *n* (%)	42 (91.3%)	9 (50.0%)
Neuropathic pain symptoms	38 (82.6%)	7 (38.9%)
Age at acroparaesthesia onset, Mean ± SD (years)	8.4 ± 3.0	9.0 ± 2.1
Age at acroparaesthesia onset, (years)	8	8
Median age (range)	(0–16)	(7–13)
Acroparaesthesia in hands	27 (58.7%)	4 (22.2%)
Acroparaesthesia in feet	36 (73.5%)	7 (38.9%)
Fabry crises	24 (52.2%)	2 (11.1%)
Burning pain	24 (52.2%)	1 (5.6%)
Tingling	12 (26.1%)	4 (22.2%)
Numbness	4 (8.7%)	1 (5.6%)
Headache/migraine	3 (6.5%)	1 (5.6%)
Anhidrosis or hypohidrosis	27 (58.7%)	2 (11.1%)
Angiokeratoma	21 (45.7%)	2 (11.1%)
Gastroenterological	9 (19.6%)	3 (16.7%)
Abdominal pain	6 (13.0%)	2 (11.1%)
Constipation/Diarrhea	5 (10.9%)	1 (5.6%)
Nausea/Vomiting	2 (4.3%)	1 (9.1%)
Ophthalmology (*NA = 7/5)	23 (59.0%)	7 (53.8%)
Cornea verticillata	19 (48.7%)	7 (53.8%)
Posterior subcapsular cataract	3 (7.7%)	0
Visual impairment	1 (2.6%)	0
Retinal vascular tortuosity	1 (2.6%)	0
Sensorineural hearing loss (*NA = 9/7)	4 (10.8%)	0
Depression (*NA = 37/16)	1 (1.1%)	0
Respiratory (*NA = 13/7)	8 (24.2%)	0
Obstructive respiratory diseases	8 (24.2%)	0
Restrictive respiratory diseases	1 (3.0%)	0
Renal (*NA = 5/6)	6 (14.6%)	0
Microalbuminuria	5 (12.2%)	0
Low glomerular filtration rate	3 (7.3%)	0
Renal tubular dysfunction	1 (2.4%)	0
Cardiovascular (*NA = 6/7)	23 (57.5%)	4 (44.4%)
Arrythmias	11 (27.5%)	4 (44.4%)
Valvular dysfunction	3 (7.5%)	0
Conduction abnormalities	3 (7.5%)	0
Left ventricular hypertrophy	3 (7.5%)	0
T-wave inversion on electrocardiogram	2 (5.0%)	0
Congenital heart disease	2 (5.0%)	0
Low bone mineral density (*NA = 39/17)	4 (57.1%)	0

*NA = number of patients with no data available in groups of male and female.

means of early identification.

To further narrow this gap, the integration of systematic family-based cascade screening with expanded newborn and high-risk population screening programs is critical. Such coordinated efforts within the MDT framework will be pivotal in realizing true early detection and timely intervention for children with FD in China.

4.2. Sex differences and clinical relevance in females

As expected, given FD's X-linked inheritance, male patients in our cohort presented with earlier symptom onset and more severe clinical manifestations, notably neuropathic pain and anhidrosis/hypohidrosis. However, a significant proportion of female children (nearly half) were symptomatic, some exhibiting severe features like Fabry crises and cardiac arrhythmias.

The recent consensus review by Hopkin *et al.* (*16*) demonstrated that over two-thirds of female patients develop multisystem involvement, and more than one-third experience severe clinical features in adults. The clinical heterogeneity observed in females primarily arises from random X-chromosome inactivation and the lack of effective cross-correction of the enzymatic defect between cells. These pathophysiological mechanisms explain the potential for significant tissue and organ damage even with normal plasma α-Gal A activity (*16*). Therefore, female children with confirmed GLA variants or relevant clinical symptoms should receive equally rigorous monitoring and longitudinal assessment as males, independent of their enzyme activity levels.

4.3. Early organ involvement and expanding the monitoring paradigm

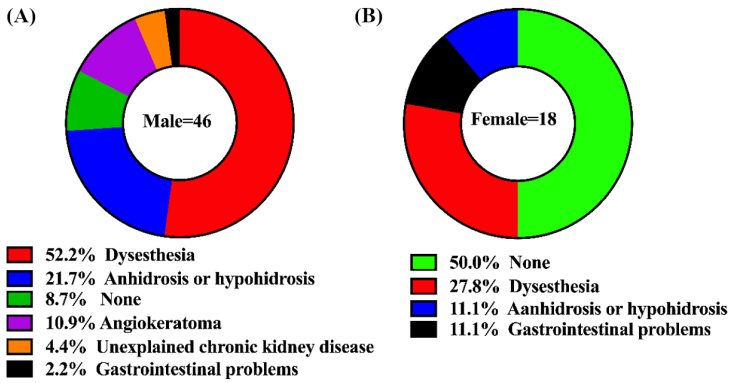

Figure 1. The first symptoms in male and female patients diagnosed with Fabry disease. (A) Proportion and type of first symptoms reported in male patients (n = 46); **(B)** Proportion and type of first symptoms reported in female patients (n = 18). Symptom categories include: Angiokeratoma, Unexplained chronic kidney disease, Anhidrosis or hypohidrosis, Dysesthesia, Gastrointestinal problems and none. Data are presented as percentage of patients reporting each symptom as their first manifestation.

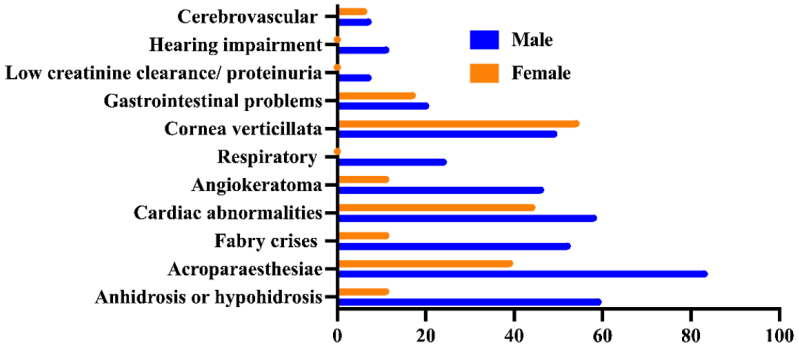

Figure 2. Proportion of male and female patients with Fabry disease showing different clinical manifestations at diagnosis. Bar chart comparing the prevalence of various clinical manifestations at the time of diagnosis between male (n = 46) and female (n = 18) patients. Manifestations shown: Cerebrovascular, Hearing impairment, Low creatinine clearance/proteinuria, Gastrointestinal problems, Cornea verticillata, Respiratory, Respiratory, Angiokeratoma, Cardiac abnormalities, Fabry crises, Acroparaesthesia, Anhidrosis or hypohidrosis. Data are derived from the same cohort as in Figure 1.

Table 3. Treatment patterns and details of enzyme replacement therapy

Parameter	Male	Female
Total number	46	18
Medication, *n* (%)	31 (67.4%)	7 (38.9%)
ERT, *n* (%)	31 (67.4%)	6 (33.3%)
Fabrazyme®, agalsidase beta 1 mg/kg/14 days (*n*)	24	6
Replagal®, agalsidase alfa 0.2 mg/kg/14 days (*n*)	7	0
Switch between therapies (*n*)	2	1
Age at first ERT (years), Mean ± SD	12.92 ± 2.88	11.73 ± 2.78
Age at first ERT (years), Median age (range)	12.9 (7.7–18.6)	12.9 (7.2–14.1)
Symptom onset to first ERT (years), Mean ± SD	7.40 ± 4.85	5.11 ± 4.91
Symptom onset to first ERT (years), Median age (range)	7.25 (0.8-17.8)	3.95 (0.3–13.7)
Duration of ERT (years), Mean ± SD	2.90 ± 1.37	2.55 ± 1.16
Patients with grade 3 adverse event, *n* (%)	2 (6.5%)	0
Patients with grade 4-5 adverse event, *n* (%)	0	0
Analgesics	19 (41.3%)	1
RAAS blockers	6 (13.0%)	0
Potassium citrate	1 (2.2%)	0

Abbreviations: ERT, enzyme replacement therapy; RAAS, Renin-angiotensin-aldosterone system.

Consistent with previous studies (*1,3,15,17*), our findings reaffirm that FD is a multisystem disorder from early childhood, with neuropathic pain as the earliest and most prevalent symptom. In our cohort, 90.5% of symptomatic males and 38.9% of females reported pain. This manifestation, primarily in the form of acroparesthesia (affecting 92.1% of symptomatic males and 85.7% of females), often exhibits gender-specific characteristics, with a predominant burning sensation in males (52.6%) and tingling in females (57.1%). Notably, Fabry crises occurred in 63.2% of males and 28.6% of females, underscoring the severe and episodic nature of this neuropathic phenotype. These results echo previous pediatric reports (*3,18*) and highlight the need for proactive surveillance rather than reactive symptom management.

Neuropathy in FD often coexists with subclinical injury in other organ systems, progressing silently during childhood. Renal involvement—manifested as microalbuminuria or early GFR reduction—can precede overt nephropathy, supporting the use of sensitive biomarkers (*e.g.*, urinary podocyte markers, advanced imaging) to detect preclinical injury (*17,19*). Cardiac abnormalities, including arrhythmias and LVH, were also observed, aligning with data that identify cardiac disease as the leading cause of mortality in FD (*20*). Therefore, annual ECG and echocardiographic monitoring from diagnosis are warranted.

This study identifies additional features contributing to the pediatric phenotype, beyond neurologic, renal, cardiac, ophthalmologic, and angiokeratoma presentations. Low bone mineral density in over half of tested males and obstructive pulmonary dysfunction in nearly one-quarter indicate previously underappreciated skeletal and respiratory involvement. These findings, consistent with emerging evidence (*21,22*), suggest Fabry pathology may extend to mesenchymal and connective tissues, warranting integration of skeletal and pulmonary assessments into routine follow-up. Sensorineural hearing loss, detected in 10.8% of males compared with 6.4% in prior reports (*23*), further supports inclusion of audiologic evaluation in comprehensive care. Gastrointestinal symptoms, though less frequently reported here, are likely underrecognized due to nonspecific presentations (*24,25*); structured and targeted assessment should thus be part of pediatric evaluation.

Collectively, these findings emphasize that multisystem involvement—including renal, cardiac, skeletal, respiratory, auditory, and gastrointestinal systems—can emerge in early childhood, even before overt decline. We therefore advocate an expanded, integrated monitoring paradigm that addresses neuropathic pain as a sentinel feature while systematically screening for subclinical organ injury. Such a holistic, anticipatory approach is essential to delay disease progression and optimize long-term outcomes in pediatric FD.

4.4. Timing of therapy and indications for early intervention

The rationale for early treatment is firmly supported by pathological and clinical evidence. Gb3 accumulation and podocyte injury begin in early childhood, preceding overt albuminuria or renal function decline (*26*). A recent study (*27*) further suggests that early diagnostic kidney biopsies should be considered irrespective of biochemical findings, to facilitate timely ERT initiation in pediatric FD.

The median age of ERT initiation in our cohort (12.9 years in males, 11.7 years in females) was slightly higher than the recommended early-intervention window. Current disease-specific therapies include agalsidase beta—approved in Europe for patients aged ≥ 8 years and in the U.S. for those aged ≥ 2 years; agalsidase alfa—approved in Europe from age ≥ 7 years; and pegunigalsidase alfa—approved in both Europe and the US in 2023 for adults. Migalastat was additionally approved in Europe in 2021 for patients aged ≥ 12 years (*28*).

International and national guidelines consistently advocate early intervention once Fabry-related symptoms or biomarkers appear. In the United States, the 2016 Fabry Pediatric Expert Panel recommends ERT for any symptomatic boy or girl, regardless of age, with neuropathic pain, renal or cardiac disease, or gastrointestinal involvement. For asymptomatic boys with classical mutations, treatment is discussed by 8–10 years, while asymptomatic girls are followed longitudinally (*15*). The French 2019 consensus recommends initiating ERT in symptomatic patients with neuropathic pain, albuminuria ≥ 3 mg/mmol, or cardiac/gastrointestinal involvement, and considering earlier therapy in asymptomatic boys with classic GLA variants and Lyso-Gb3 > 20 nmol/L (*29*). Similarly, a Portuguese review advises treatment for classic males from 8–10 years and for females or late-onset males once organ involvement is evident (*30*).

The 2021 Chinese Expert Consensus on the Diagnosis and Treatment of Fabry Disease (2nd edition) aligns with these recommendations, suggesting ERT initiation in boys and girls presenting with Fabry-related symptoms, though without a defined age threshold (*12*). This symptom-based, individualized approach reflects a growing national emphasis on early recognition and timely management of pediatric FD.

Collectively, these perspectives underscore that early ERT initiation, guided by genotype, biomarkers, and subclinical organ involvement, is essential to prevent irreversible progression. The modest delay in treatment initiation in our cohort highlights the ongoing need to improve early diagnosis and therapy access within China's developing pediatric FD network.

4.5. Study limitations

This study has limitations inherent to its retrospective design. The modest sample size, recruited from specialized centers, may limit generalizability. The analysis focused exclusively on pre-ERT data, which, while informative of the natural history, does not allow for assessment of treatment response. Future prospective, longitudinal studies are needed to evaluate the impact of early ERT initiation on long-term outcomes.

5. Conclusion

In summary, this study—based on the Chinese Children Genetic Kidney Disease Database—confirms that pediatric FD in China manifests as a multisystem disorder with significant renal, cardiac, skeletal, respiratory, and auditory involvement from an early age. Findings from this Chinese cohort underscore the importance of MDT-driven strategies, family screening, and early therapeutic intervention to improve long-term outcomes in Chinese children with FD.

Acknowledgements

We thank all the families who participated in this study for their invaluable contributions.

Funding: This work was supported by grants from the Basic Research Program of the Shanghai Science and Technology Innovation Action Plan (No. 23JC1401200), the Key Development Program of Children's Hospital of Fudan University (No. EK2022ZX01), and the Excellence Visiting Scholars Program of Children's Hospital of Fudan University (No. EKJY2025040202).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Laney DA, Peck DS, Atherton AM, Manwaring LP, Christensen KM, Shankar SP, Grange DK, Wilcox WR, Hopkin RJ. Fabry disease in infancy and early childhood: A systematic literature review. Genet Med. 2015; 17:323-330.
2. Ramaswami U, Parini R, Pintos-Morell G, Kalkum G, Kampmann C, Beck M, FOS Investigators. Fabry disease in children and response to enzyme replacement therapy: Results from the Fabry outcome survey. Clin Genet. 2012; 81:485-490.
3. Hopkin RJ, Bissler J, Banikazemi M, Clarke L, Eng CM, Germain DP, Lemay R, Tylki-Szymanska A, Wilcox WR. Characterization of Fabry disease in 352 pediatric patients in the Fabry registry. Pediatr Res. 2008; 64:550-555.
4. Li Q, Wang J, Tian M, Yang Z, Yu L, Liu S, Wang C, Wang X, Sun S. Clinical features and enzyme replacement therapy in 10 children with Fabry disease. Front Pediatr. 2023; 11:1084336.
5. Hwu WL, Chien YH, Lee NC, Chiang SC, Dobrovolny R, Huang AC, Yeh HY, Chao MC, Lin SJ, Kitagawa T, Desnick RJ, Hsu LW. Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A (IVS4+919G>A). Hum Mutat. 2009; 30:1397-1405.
6. Wilcox WR, Oliveira JP, Hopkin RJ, *et al*. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry registry. Mol Genet Metab. 2008; 93:112-128.
7. Shen Q, Liu J, Chen J, *et al*. Multidisciplinary approach to screening and management of children with Fabry disease: Practice at a tertiary children's hospital in China. Orphanet J Rare Dis. 2021; 16:509.
8. Rao J, Liu X, Mao J, *et al*. Genetic spectrum of renal disease for 1001 Chinese children based on a multicenter registration system. Clin Genet. 2019; 96:402-410.
9. Stiles AR, Zhang H, Dai J, McCaw P, Beasley J, Rehder C, Koeberl DD, McDonald M, Bali DS, Young SP. A comprehensive testing algorithm for the diagnosis of Fabry disease in males and females. Mol Genet Metab. 2020; 130:209-214.
10. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, Committee ALQA. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. Genet Med. 2015; 17:405-424.
11. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: Baseline clinical manifestations of 366 patients in the Fabry outcome survey. Eur J Clin Invest. 2004; 34:236-242.
12. Chinese Fabry Disease Expert Panel. [Expert consensus for diagnosis and treatment of Fabry disease in China (2021)]. Zhonghua Nei Ke Za Zhi. 2021; 60:321-330.
13. Biegstraaten M, Arngrímsson R, Barbey F, *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. 2015; 10:36.
14. Germain DP, Altarescu G, Barriales-Villa R, Mignani R, Pawlaczyk K, Pieruzzi F, Terryn W, Vujkovac B, Ortiz A. An expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease. Mol Genet Metab. 2022; 137:49-61.
15. Hopkin RJ, Jefferies JL, Laney DA, Lawson VH, Mauer M, Taylor MR, Wilcox WR, Fabry Pediatric Expert Panel. The management and treatment of children with Fabry disease: A United States-based perspective. Mol Genet Metab. 2016; 117:104-113.
16. Hopkin RJ, Laney D, Kazemi S, Walter A. Fabry disease in females: Organ involvement and clinical outcomes compared with the general population (103/150 characters). Orphanet J Rare Dis. 2025; 20:433.
17. Chimenz R, Chirico V, Cuppari C, Ceravolo G, Concolino D, Monardo P, Lacquaniti A. Fabry disease and kidney involvement: Starting from childhood to understand the future. Pediatr Nephrol. 2022; 37:95-103.
18. Rajan JN, Ireland K, Johnson R, Stepien KM. Review of mechanisms, pharmacological management, psychosocial implications, and holistic treatment of pain in Fabry disease. J Clin Med. 2021; 10:4168.
19. Ezgu F, Alpsoy E, Bicik Bahcebasi Z, Kasapcopur O, Palamar M, Onay H, Ozdemir BH, Topcuoglu MA, Tufekcioglu O. Expert opinion on the recognition,

diagnosis and management of children and adults with Fabry disease: A multidisciplinary Turkey perspective. Orphanet J Rare Dis. 2022; 17:90.
20. Pieroni M, Namdar M, Olivotto I, Desnick RJ. Anderson-Fabry disease management: Role of the cardiologist. Eur Heart J. 2024; 45:1395-1409.
21. Lu Z, Huang G, Yu L, Wang Y, Gao L, Lin L, Hu L, Mao J. Low skeletal muscle mass as an early sign in children with Fabry disease. Orphanet J Rare Dis. 2023; 18:199.
22. Ahmed H, Backer V, Effraimidis G, Rasmussen ÅK, Kistorp CM, Feldt-Rasmussen U. Respiratory impairments in patients suffering from Fabry disease - A cross-sectional study. Chron Respir Dis. 2024; 21:14799731231221821.
23. Suntjens E, Dreschler WA, Hess-Erga J, Skrunes R, Wijburg FA, Linthorst GE, Tondel C, Biegstraaten M. Hearing loss in children with Fabry disease. J Inherit Metab Dis. 2017; 40:725-731.
24. Dargenio VN, Natale M, Castellaneta SP, Grasta G, Paulucci L, Dargenio C, Francavilla R, Cristofori F. Unraveling the hidden burden of gastrointestinal and nutritional challenges in children with Fabry disease: A systematic review with meta-analysis. Nutrients. 2025; 17:1194.
25. Lenders M, Brand E. Fabry disease - a multisystemic disease with gastrointestinal manifestations. Gut Microbes. 2022; 14:2027852.
26. Mignani R, Biagini E, Cianci V, Pieruzzi F, Pisani A, Tuttolomondo A, Pieroni M. Effects of current therapies on disease progression in Fabry disease: A narrative review for better patient management in clinical practice. Adv Ther. 2025; 42:597-635.
27. Najafian B, Svarstad E, Bostad L, Gubler MC, Tøndel C, Whitley C, Mauer M. Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease. Kidney Int. 2011; 79:663-670.
28. Avarappattu J, Gaspert A, Spartà G, Rohrbach M. Impact of kidney biopsy on deciding when to initiate enzyme replacement therapy in children with Fabry disease. Pediatr Nephrol. 2024; 39:131-140.
29. Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P, Fila M, Rivera S, Deschênes G, Lacombe D. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clin Genet. 2019; 96:107-117.
30. Azevedo O, Gago MF, Miltenberger-Miltenyi G, Sousa N, Cunha D. Fabry disease therapy: State-of-the-art and current challenges. Int J Mol Sci. 2020; 22:206.

Received October 22, 2025; Revised December 9, 2025; Accepted December 22, 2025.

[§]These authors contributed equally to this work.

**Address correspondence to:*
Shuzhen Sun, Department of Pediatric Nephrology and Rheumatism and Immunology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 324 Jingwu Road, Huaiyin District, Ji'nan, Shandong 250021, China.
E-mail: ssztml@163.com

Qian Shen and Hong Xu, Department of Nephrology, Children's Hospital of Fudan University; National Children's Medical Center; Shanghai Kidney Development and Pediatric Kidney Disease Research Center; National Key Laboratory of Kidney Diseases, 399 Wanyuan Road, Minhang District, Shanghai 201102, China.
E-mail: shenqian@shmu.edu.cn (QS), hxu@shmu.edu.cn (HX)

Released online in J-STAGE as advance publication December 27, 2025.