Pediatric Fabry Disease

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ABSTRACT. *Background.* Fabry disease is an under-diagnosed, treatable, X-linked, multisystem disorder.

Objectives. To test the hypothesis that quality of life and sweating are decreased among pediatric patients with Fabry disease, compared with control subjects, and to provide quantitative natural history data and novel clinical end points for therapeutic trials.

Design. Prospective, cross-sectional, observational study.
Setting. Referral to the National Institutes of Health.
Participants. Twenty-five male children with Fabry disease (mean age: 12.3 ± 3.5 years) and 21 age-matched control subjects.

Main Outcome Measures. Quality of life (measured with the Child Health Questionnaire) and sweating (assessed with the quantitative sudomotor axon reflex test).

Results. Quality of life scores for pediatric patients <10 years of age with Fabry disease, compared with published normative values, were 55 ± 17 vs 83 ± 19 for bodily pain and 62 ± 19 vs 80 ± 13 for mental health. Bodily pain scores for patients ≥10 years of age were 54 ± 22 vs 74 ± 23. Sweat volume in the Fabry disease group was 0.41 ± 0.46 μL/mm^2, compared with 0.65 ± 0.44 μL/mm^2 in the control group. Renal function, urinary protein excretion, and cardiac function and structure were normal for the majority of patients. The 3 patients with residual α-galactosidase A activity ≥1.5% of normal values were free of cornea verticillata and had normal serum and urinary globotriaosylceramide levels. All other children had glycolipid levels comparable to those of adult patients with Fabry disease. Acroparesthesia and cardiac abnormalities were generally present before anhidrosis and proteinuria. Mapping of the missense mutations on the crystallographic structure of α-galactosidase A revealed that the mutations were partially surface-exposed and distal to the active site among individuals with residual enzyme activity. Mutations associated with left ventricular hypertrophy (defined as left ventricular mass index of >51 g/m$^{2.7}$) were localized near the catalytic site of the enzyme.

Conclusions. Despite the absence of major organ dysfunction, Fabry disease demonstrates significant morbidity already in childhood. We have identified important, potentially correctable or preventable, outcome measures for future therapeutic trials. Prevention of complications involving major organs should be the goal for long-term specific therapy. *Pediatrics* 2005;115:e344–e355. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1678; *adolescence, child, human, Fabry disease, genetics, cornea verticillata, pain, acroparesthesia, diarrhea, heart, cardiomyopathy, echocardiogram, kidney, proteinuria, α-galactosidase A, quantitative sudomotor axon reflex test, sweating, quality of life.*

ABBREVIATIONS. GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; LV, left ventricle; GALA, α-galactosidase A; Gb$_3$, globotriaosylceramide; RWT, relative wall thickness; QSART, quantitative sudomotor axon reflex test; CI, confidence interval; LVM, left ventricular mass.

Fabry disease (OMIM 301500), which was first described in 1898 independently by Johannes Fabry in Germany[1] and William Anderson in the United Kingdom,[2] is a debilitating, chronic, progressive, multisystem, X-linked disorder. It is caused by a deficiency of α-galactosidase A (GALA), which leads to failure to catabolize lipids containing α-D-galactosyl moieties.[3] These lipids include globotriaosylceramide (Gb$_3$), digalactosyl ceramide, and blood group B, B1, and P1 glycolipids, which accumulate in a variety of cell types.[4–10] The gene for GALA (*GLA*) is located on Xq22.1. Although it is known that storage of Gb$_3$ affects a variety of cell types, the precise pathogenic mechanism of the disease remains to be elucidated. Previous studies provided evidence that the morbidity of this phenotypically variable condition increases with age, leading to progressive kidney failure, cardiac dysfunction, and stroke.[11–13]

The diagnosis of Fabry disease is often delayed, especially in the pediatric population. The symptoms appear in a nonspecific pattern in this age group, and it often requires many years to identify the underlying nature of the complaints. Pedigree studies and a careful family history are important. In the absence

of such information, the diagnosis is usually made on the basis of strong clinical suspicion and recognition of the overall coherence of the clinical findings. Diagnosis is often accelerated by an evaluation of a more specific finding, such as angiokeratoma, corneal opacities, or parapelvic kidney cysts.[14,15] The demonstration of deficient GALA enzyme activity or, especially for girls, identification of a pathogenic mutation, is required to confirm the diagnosis.

Enzyme replacement therapy for Fabry disease was shown to be promising for adult hemizygous patients with this disorder.[16,17] It reduced glycolipid storage in various organs and tissues, decreased pain, improved peripheral nerve function and sweating, and appeared to reduce cardiac hypertrophy.[18,19] However, in our experience and others, some patients develop white-matter lesions or strokes despite enzyme replacement therapy or show deterioration of renal and cardiac function.[20,21] Pain control has not been complete.[18,22] It is possible that initiation of therapy at an early age, before significant organ damage and dysfunction occur, could produce better results. However, little is known about the natural history of the disease in childhood, and systematic prospective data on the clinical manifestations of Fabry disease in the pediatric population are not available. Chronic neuropathic pain and subjective hypohidrosis were previously documented among children with Fabry disease[23] but were not analyzed in a quantitative prospective manner.

To characterize fully the disease in childhood and to develop novel clinical outcome measures, we conducted a prospective, single-center, observational study (Table 1). We hypothesized that quality of life and sweating are decreased among hemizygous children with Fabry disease, compared with published normal control subjects validated as a representative sample of the general population or concurrently evaluated, age- and gender-matched, control subjects.

METHODS

Patients

The patients were enrolled in a study approved by the institutional review board of the National Institute of Neurological Disorders and Stroke. For purposes of generalizing our results, we made an effort to include the widest possible range of population groups, including minority groups. Race and ethnicity were therefore classified by the study participants according to the 2-dimensional criteria defined by the US Department of Health and Human Services. Patients were referred to the study by their primary care physicians or were family members of patients enrolled in other Fabry disease studies at the National Institutes of Health. Written informed consent was obtained from the parents. When appropriate for age, patients gave written informed consent or assent. Clinicopathologic laboratory determinations were performed by the Clinical Center laboratory of the National Institutes of Health.

Quality of Life

To estimate the quality of life of the patients, we used the Child Health Questionnaire.[24,25] Patients <10 years of age had a parent complete the CHQ-PF50 questionnaire, and children ≥10 years of age completed the CHQ-CF87 questionnaire themselves. The data were summarized in general scores, each with a range of 0 to 100. These scores included physical functioning, role functioning-emotional, role functioning-physical, bodily pain, behavior, mental health, self-esteem, and general health scales. The CHQ-PF50 questionnaire also included a physical summary score and a psychosocial summary score.

Quantitative Sudomotor Axon Reflex Tests

Computerized quantitative sudomotor axon reflex test (QSART) evaluation (WR Medical Electronics, Stillwater, MN) on the forearm was performed as described previously.[18] Because no normative pediatric data were available, 21 normal male control subjects were recruited through the National Institutes of Health Study Volunteer Program. The ages of the healthy control subjects (mean: 13.2 ± 4.3 years; median: 15 years; range: 5–18 years) were not significantly different from the ages of the 23 patients with Fabry disease (mean: 12.3 ± 3.5 years: median: 12 years; range: 6–18 years) for whom QSART testing results were available ($P = .45$, Mann-Whitney test).

GALA Activity

GALA activity was assayed in isolated white blood cells as described previously.[13] GALA activities <1.5% of control values were considered undetectable because they might represent residual α-galactosidase B activity, which cannot be blocked completely (according to our laboratory experience). Significant residual GALA activity was defined as ≥1.5% of control values.

Gb$_3$ Levels

Gb$_3$ levels in plasma (expressed as nanomoles per milliliter) and urine (expressed as nanomoles per 24 hours and nanomoles per gram of creatinine) were kindly determined by Transkaryotic Therapies (Cambridge, MA), as described previously.[26]

Height, BMI, and Weight

The 2002 length-for age and BMI-for age charts (Centers for Disease Control and Prevention, National Center for Health Statistics, Hyattsville, MD), were used to assess gender-specific height-for-age and BMI-for-age values. BMI was calculated by dividing weight in kilograms by the square of height in meters.

Glomerular Filtration Rate

Glomerular filtration rate (GFR) was calculated with the formula described by Schwartz et al.[27]

Heart Examinations

Electrocardiography

Standard 12-lead electrocardiograms were obtained with a Hewlett Packard Pagewriter XLI 1700A instrument (Hewlett Packard, Palo Alto, CA).

Echocardiography

At baseline presentation, all subjects underwent transthoracic 2-dimensional and Doppler echocardiography with Acuson Sequoia (Siemens, Mountainview, CA) or Sonos 5500 (Philips, Inc, Andover, MA) echocardiography systems. Standard parasternal, apical, and subcostal views were acquired with the patients in the left lateral recumbent position and were stored on videotape for

TABLE 1. Procedures and Assessments Defined in the Study Protocol

History, physical examination, height, and BMI
QSART*
Quality of life questionnaires (CHQ-PF50 and CHQ-CF87)*
Blood tests, including complete blood count, reticulocyte count, and thyrotropin, free thyroxine, and vitamin C concentrations
Estimated GFR and 24-h urinary protein excretion
Electrocardiography and echocardiography
Eye examination, including slit-lamp assessment
GALA enzyme analysis
Gb$_3$ concentrations in serum and 24-h urine samples
Mutational analyses

* Variables for primary hypothesis testing.

analysis. Videotape studies were subsequently digitized, and measurements were performed on digital loops with a Digisonics offline analysis station (version 3.2 software; Digisonics, Houston, TX). Cardiac measurements were performed according to American Society of Echocardiography guidelines.[28] Chamber sizes were indexed to body-surface area and compared with reference values for age-matched normal subjects.[29] Dilation of the aorta and cardiac chambers was defined as a measurement >2 SDs above the mean for body surface area. Fractional shortening of the left ventricle (LV) was determined from the internal dimensions of the LV in diastole and systole and was defined as follows: % fractional shortening = [(LV internal dimension in diastole − LV internal dimension in systole)/LV internal dimension in diastole] × 100.

LV mass (LVM) was calculated with an anatomically validated formula described by Devereux et al,[30] ie, LVM (g) = 0.8(1.04[interventricular septal thickness + posterior wall thickness + LV internal dimension in diastole]^3 − [LV internal dimension in diastole]^3) + 0.6. The LVM index was defined as mass divided by the 2.7 power of height (grams per meter$^{2.7}$) and was used to adjust LVM for the effect of body size.[31] LV hypertrophy (LVH) was defined as a >95th percentile LVM index for children and adults, with a gender-independent partition value of 51 g/m$^{2.7}$.[32] Relative wall thickness (RWT) was defined as (interventricular septal thickness + posterior wall thickness)/LV internal dimension in diastole and was used to assess LV geometry, as described by Ganau et al.[33] Patients with LVH had concentric hypertrophy if their RWT was elevated (>0.41) and eccentric LVH if their RWT was normal (≤0.41). Patients had concentric remodeling if they did not have LVH but their RWT was elevated.

Valves were examined for the presence of focal or diffuse thickening of the leaflets or subvalvular apparatus (for the mitral valve). Color Doppler flow mapping of the mitral and aortic valves was performed in multiple views, to detect the presence or absence of regurgitant flow. In addition, mitral regurgitation was quantitated with color Doppler velocity mapping as the ratio of the area of the color jet divided by the maximal left atrium area, such that a small noneccentric jet with an area of <20% of the left atrium area was considered to represent mild mitral regurgitation.[34] Aortic regurgitation was also quantitated in the parasternal long-axis views as the ratio of the maximal proximal jet width to the LV outflow tract diameter, such that an aortic regurgitation jet with a ratio of <25% was considered to represent mild aortic regurgitation[35]

Eye Examinations

The patients' ophthalmologic status was evaluated with a complete assessment that included a slit-lamp examination.

Genetic Mutation Analyses

DNA was obtained from cultured skin fibroblasts or peripheral blood leukocytes. Mutation analysis was performed with polymerase chain reaction amplification of the 7 exons of the *GLA* gene, followed by single-strand conformational polymorphism analysis and sequencing. If possible, each mutation was confirmed with a second, independent method, eg, restriction enzyme digestion.[36]

Structural Mutation Analyses

Crystallographic mapping of GALA was conducted with the program MolScript[37] and the coordinates of the wild-type human GALA structure, as described.[38] Buried surface areas were calculated with the Crystallography & NMR System computer program.[39]

Statistical Analyses

We applied methods of descriptive statistics. Comparative statistics with the appropriate tests were applied for Fabry disease versus control values. The analyses were 2-tailed, at a significance level of .05. Statistical analyses were performed with SAS version 8.2 for Windows (SAS Institute, Cary, NC) and GraphPad Prism version 4.00 for Macintosh and InStat version 3.0a for Macintosh (GraphPad Software, San Diego, CA). The variable termed burden of disease was the sum of the number of organ systems affected; the presence or absence of acroparesthesia, angiokeratoma, anhidrosis, cornea verticillata, headaches, electrocardiographic ab-

normalities, LVH (with the criteria described by de Simone et al[32]), abdominal pain, diarrhea, and proteinuria was categorically assessed. This assessment did not include central nervous system imaging. Each sign or symptom was equally weighted, and 1 point was attributed for its presence. The sum of all points determined the value of the variable burden, and a linear regression model was used to predict the disease burden as a function of age. Time-to-observation distributions for the sequence of organ manifestation of Fabry disease were estimated with Kaplan-Maier curves. Time was defined as age, because the disease has its onset at birth. To account for recall bias, the observation was defined as the presence of a symptom at the time of assessment if it had not been documented earlier.

RESULTS

Patients

Twenty-five consecutive, hemizygous, pediatric patients with Fabry disease were enrolled in the study. A synopsis of organ manifestations is shown in Table 2. The patients were between 6 and 18 years of age (mean: 12.32 ± 3.5 years; median: 12 years; range: 6-18 years); all were Caucasian, 21 of non-Hispanic ethnicity and 4 of Hispanic ethnicity. Eight patients were siblings from 4 families, whereas 2 patients were maternal cousins. Twenty-two patients (88%) had no detectable GALA activities; 3 patients (12%) had residual GALA activities ≥1.5% of normal control values. The highest activity measured was 2.1% of normal values.

Quality of Life

The results for the group of children <10 years of age (*n* = 9) were compared with previously published values for healthy control boys (*n* = 212). The mean quality of life scores in all aspects were lower for patients, compared with control subjects, but only bodily pain (Fabry disease: 55 ± 17; control: 83 ± 19; *P* = .001, unpaired *t* test) and mental health (Fabry disease: 62 ± 19; control: 80 ± 13; *P* = .02) scores were significantly different. The pain scores were similar to those for a group of children with juvenile rheumatoid arthritis (63 ± 26; *n* = 74).[25] The physical summary score was less than the control value (Fabry disease: 43 ± 13; control: 52 ± 10; *P* = .08). For patients ≥10 years of age (*n* = 15), only the bodily pain score was significantly lower than the control value (Fabry disease: 54 ± 22; control: 74 ± 23; *P* = .003) (Table 3).

QSART

The sweat volume for patients with Fabry disease (mean: 0.41 ± 0.46 μL/mm^2; median: 0.26 μL/mm^2; range: 0.02–1.75 μL/mm^2) was significantly lower than that for age-matched, normal, male, control subjects (mean: 0.65 ± 0.44 μL/mm^2; median: 0.53 μL/mm^2; range: 0.03–1.90 μL/mm^2; *P* = .047, Mann-Whitney test) (Fig 1). There was no difference in sweating between patients with residual GALA activity and those without residual enzyme activity.

Anthropometric Measurements

Four of 25 patients (16%) were obese, defined as gender-specific BMI for age ≥95th percentile[40] (Fig 2A). Five children (25%) were underweight (BMI <5th percentile). Three children (12%) had tall

TABLE 2. Summary of Clinical Findings for 25 Pediatric Patients With Fabry Disease

Patient No.	Age, y	GLA Mutation	Exon	Residual Enzyme, % of Normal Control	24-h Urine Gb₃ Excretion, nmol/g creatine	Plasma Gb₃ Level, nmol/mL	Height, cm	BMI	Angio-keratoma	Cornea Verticillata	Acropares-thesia	Head-aches	Anhidrosis	Enter-opathy	GFR, mL/min per 1.73 m²	Proteinuria, mg/24 h	LVM Index, g/m^2.7	Electrocardiographic Abnormalities
1	6	ΔE358	7	1.4	1886	9.6	126	15.6	0	1	0	1	0	1	173	35	26.8	0
2	6	C172Y	3	0.6	1001	11.6	120	17.1	0	1	0	1	0	0	165	59	55.6*†	0
3	7	G325D	6	0.9	1846	12.8	135	15.1	0	1	1	1	0	0	148	35	45.6†	1
4	9	A97V	2	2.1	32	2.3	144	24.7	0	0	1	1	0	1	198	107	33.4	0
5	9	W162X	3	0.4	1854	9.4	132	18.8	0	ND	1	1	0	1	145	33	36.3	0
6α	9	P259L	5	0.9	ND	ND	126	13.6	0	1	1	0	0	0	139	38	37.4	0
7 (β)	9	R112H	3	2.0	0	1.6	137	14.5	0	0	0	0	0	1	126	68	28.1	0
8 (β)	10	R112H	3	1.6	21	2.1	140	21.8	0	0	1	0	0	1	154	68	28.1	0
9	11	C223Y	5	0.9	932	13.4	158	22.3	1	1	1	1	0	0	144	0	38.0	0
10	12	P205L	4	1.0	2725	7.9	150	29.5	0	1	1	1	ND	1	137	104	40.8†	1
11	12	IVS3–1g>a	3	1.0	2593	9.9	140	28.3	1	1	1	1	ND	0	154	0	35.4	0
12	12	c.59del26	1	0.5	1554	7.3	152	19.2	0	1	1	1	1	1	167	134	34.9	0
13α	12	P259L	5	0.8	ND	ND	146	14.3	0	1	1	0	0	1	160	53	36.9	0
14γ	12	C142X	3	0.2	2525	12.6	158	13.9	0	1	1	0	0	0	124	0	27.6	0
15	14	C172W	3	0.6	3238	9.2	149	17.3	1	1	1	0	0	1	164	127	52.3*†	0
16	14	W226X	5	1.1	2850	11.0	151	38.6	1	1	1	1	1	1	119	120	42.9†	0/1
17	14	R220X	5	1.0	3221	14.6	162	14.7	1	1	1	0	1	1	178	96	32.7	0/1
18δ	15	R227Q	5	0.6	5274	11.5	147	22.1	1	1	1	0	0	1	134	80	28.2	1
19ε	16	I270T	6	0.4	2104	6.3	172	17.9	1	1	1	0	0	1	118	0	38.8	1
20	16	G138E	3	0.5	3151	10.6	158	21.2	0	1	1	0	1	1	144	117	24.5	0/1
21	16	c.1032delTC	7	0.6	1569	16.5	163	19.0	1	1	1	1	0	1	128	213‡	40.4†	0
22γ	16	C142X	3	0.4	863	8.6	180	18.9	1	1	1	0	0	1	110	0	26.4	0
23δ	16	R227Q	5	1.0	5275	7.8	166	18.8	1	1	1	1	1	1	130	122	32.4	0
24	17	R301X	6	0.5	1742	10.2	181	16.3	1	1	1	1	1	1	142	122	40.1†	0
25ε	18	I270T§	6	0.5	1507	8.0	181	20.4	1	1	1	0	0	1	110	111	34.5	0

0 denotes absent or normal; 1, present or abnormal; 0/1, borderline; ND, not done. α, γ, δ, and ε denote siblings, (β) denotes cousins.
* Abnormal LVM index of >95th percentile for children and adults (51 g/m^2.7) according to the criteria described by de Simone et al.[32]
† Abnormal LVM index of >95th percentile (39.36 g/m^2.7) for boys based on the data reported by Daniels.[41]
‡ Proteinuria.
§ Based on the findings for his brother, patient 19.

Parameter	Quality of Life, Mean $\pm$ SD (Range)			
	Age <10 y, CHQ-PF50		Age $\geq$10 y, CHQ-CF87	
	Fabry Disease ($n = 9$)	Control[25] ($n = 212$)	Fabry Disease ($n = 15$)	Control[24] ($n = 232$)
Physical functioning	87 $\pm$ 17 (44–100)	96 $\pm$ 17 (0–100)	81 $\pm$ 22 (37–100)	89 $\pm$ 14
Bodily pain	55 $\pm$ 17 (30–80)*	83 $\pm$ 19 (19–100)*	54 $\pm$ 22 (20–100)*	74 $\pm$ 23*
Behavior	71 $\pm$ 13 (56–92)	74 $\pm$ 16 (25–100)	81.4 $\pm$ 11 (63–98)	77 $\pm$ 15
Mental health	62 $\pm$ 19 (25–85)*	80 $\pm$ 13 (20–100)*	71 $\pm$ 12 (44–89)	73 $\pm$ 16
Self-esteem	62 $\pm$ 33 (8–95)	80 $\pm$ 18 (0–100)	84 $\pm$ 11 (61–98)	82 $\pm$ 16
General health	63 $\pm$ 18 (31–92)	72 $\pm$ 18 (8–100)	62 $\pm$ 17 (34–94)	66 $\pm$ 15
Parent impact-emotional†	62 $\pm$ 26 (8–100)	78 $\pm$ 21 (0–100)	93 $\pm$ 20 (22–100)	86 $\pm$ 21
Physical summary score	43 $\pm$ 13 (16–57)	52 $\pm$ 10 (0.5–64)		
Psychosocial summary score	45 $\pm$ 13 (17–57)	51 $\pm$ 9 (16–64)		

* $P < .05$.
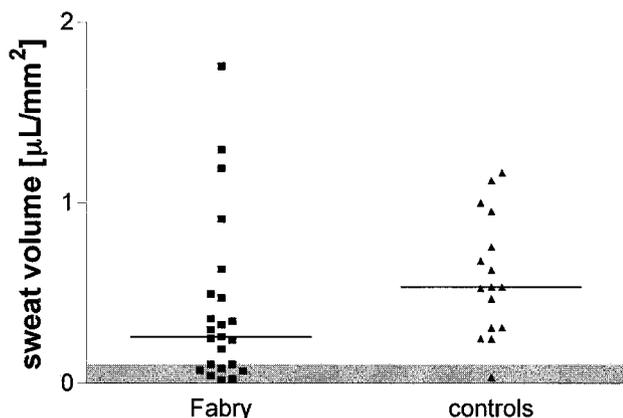† Role functioning-emotional in the CHQ-CF87.

Fig 1. Sweating as assessed with QSART. Patients with Fabry disease ($n = 23$) had significantly lower sweat volumes, compared with control subjects ($n = 21$) ($P = .0473$, Mann-Whitney test). Horizontal lines indicate the medians, and the gray shaded area delineates the range of anhidrosis (sweat volume of <0.1 μL/mm^2)

stature, ie, length >95th percentile for age (Fig 2B), and 3 children had short stature (length <5th percentile for age).

Gb$_3$ Levels

Patients with GALA activity of <1.5% ($n = 20$) had significantly higher mean plasma Gb$_3$ levels, compared with patients with GALA activity of $\geq$1.5% ($n = 3$, $P = .007$, Mann-Whitney test) (Fig 3A). Patients with residual GALA activity <1.5% of control values ($n = 20$) had higher mean urinary Gb$_3$ excretion values, compared with those whose GALA activities were $\geq$1.5% of normal values ($n = 3$, $P = .007$, Mann-Whitney test) (Fig 3B). Plasma and urine Gb$_3$ levels for patients with GALA activity $\geq$1.5% of control values were normal. Urinary Gb$_3$ excretion among patients without residual enzyme activity increased with age ($n = 20$, $r^2 = 0.42$, $P = .0019$). However, after normalization with respect to creatinine excretion, there was no age effect.

Urinary Protein Excretion

The mean 24-hour protein excretion was 92 $\pm$ 45.0 mg/24 hours (median: 100 mg/24 hours; range: 33–213 mg/24 hours). One patient, 15 years of age,

exceeded the critical threshold of 150 mg/24 hours with proteinuria of 213 mg/24 hours. The mean GFR was 144 $\pm$ 22.1 mL/min per 1.73 m^2 (median: 144 mL/min per 1.73 m^2; range: 110–198 mL/min per 1.73 m^2). Nine patients had a GFR of >140 mL/min per 1.73 m^2; 4 patients had a GFR of >165 mL/min per 1.73 m^2.

Electrocardiography

The electrocardiograms of these patients were remarkable for the lack of significant abnormalities; most (18 of 25 [72%]) were within normal limits. Three patients demonstrated borderline abnormalities. Persistence of a juvenile pattern was noted for 2 patients, with 1 of them demonstrating early transition in the precordium. The third borderline finding was a QRS-T angle in the limb leads of 64 degrees. Four patients with abnormal findings manifested LVH ($n = 2$, voltage criteria of SV1 + RV5 > 45 mm), 1-mm diffuse S-T depression ($n = 1$), and left-axis deviation (-6 degrees) with persistence of a juvenile pattern ($n = 1$).

Echocardiography

Among the 25 patients, 2 patients (8%) were found to meet the criteria for LVH in children and adults (LVM index of >51 g/m$^{2.7}$) defined by de Simone et al[32]. Both of these patients had eccentric LVH with normal RWT, whereas 1 patient had concentric remodeling of the LV, on the basis of increased RWT without LVH. One patient with LVH had a dilated aortic root, and the other patient had normal chamber sizes and valves. The LVM index did not correlate with the age of the patients, and there was no difference in the LVM indexes of patients with residual GALA activity of $\geq$1.5%, compared with those with residual activity of <1.5% ($P = .15$). It is noteworthy that the patients who showed high voltage on electrocardiograms, suggesting LVH, exhibited normal LVM on echocardiograms, according to the criteria described by de Simone et al,[32] whereas the 2 patients who exhibited increased LVM had normal voltage (Fig 4).

Application of the pediatric criteria for LVH in boys (LVM index of >39.36 g/m$^{2.7}$) based on data reported by Daniels[41] would increase the incidence of LVH in our population to 28%. In a study of 207
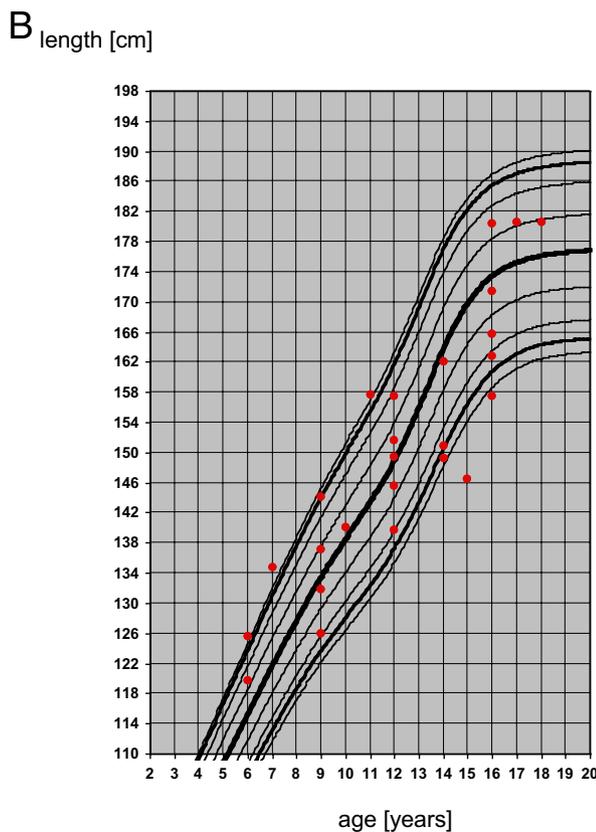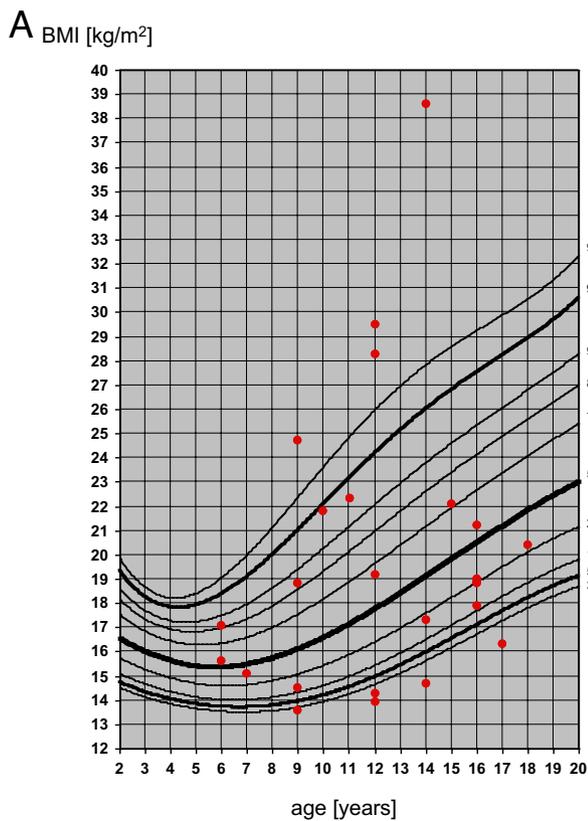
A BMI [kg/m²]

B length [cm]

Fig 2. BMI (A) and length (B) for age for pediatric patients with Fabry disease.

boys that used the same method as used in our study, the 95% confidence interval (CI) for the LVM index ranged from 18 to 33 g/m$^{2.7}$.[42]
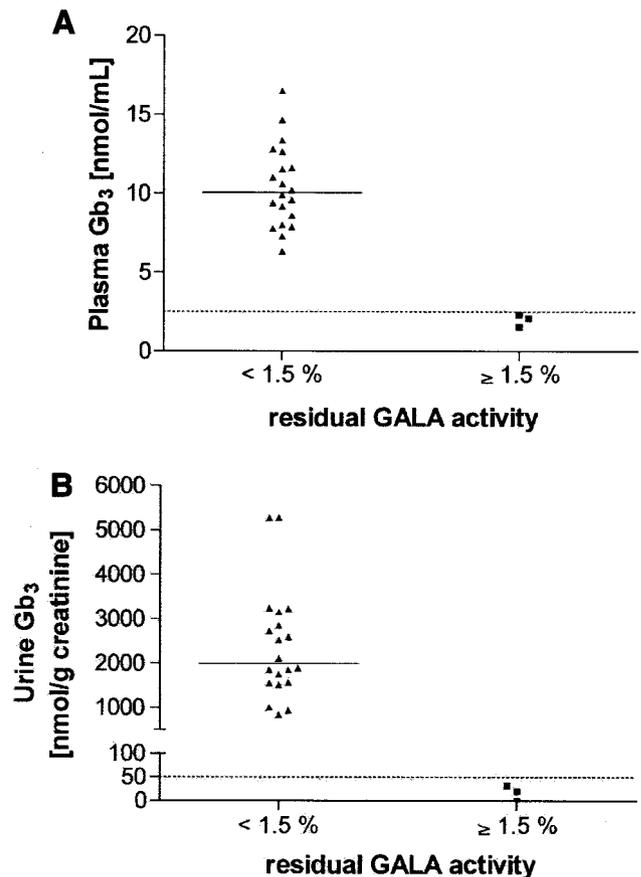
A

B

Fig 3. Glycolipid storage. Patients with Fabry disease with residual GALA activity of ≥1.5% (n = 3) had significantly lower Gb$_3$ concentrations in plasma (A) and urine (B), compared with patients whose residual GALA activity was <1.5% (n = 20). Horizontal lines indicate the medians; dashed lines indicate the upper end of the normal range.

LV systolic function was normal for all patients. One patient had a dilated left atrium, and 3 patients had a dilated aortic root. Valvular abnormalities were infrequent (8% of patients) and included 1 patient with mild mitral valve prolapse and mild mitral regurgitation and 1 patient with a thickened posterior mitral leaflet and a trace of mitral regurgitation. There were a total of 9 patients with mild mitral regurgitation, and all patients had normal aortic valve morphologic features, with trivial aortic regurgitation for 2 patients and no aortic regurgitation for the remaining group.

Gastrointestinal Manifestations

Twenty patients (80%) had symptoms of nonspecific enteropathy, such as recurrent diffuse abdominal pain (n = 18 [72%]) or diarrhea (n = 12 [48%]), often triggered by high-fat foods but also occurring spontaneously.

Pain

Twenty-two patients (88%) reported chronic neuropathic pain. The character of the pain was described as burning and like pins and needles, localized in the hands and feet, radiating proximally, triggered by changes in environmental or body temperature, exercise, or emotional stress, and continu-
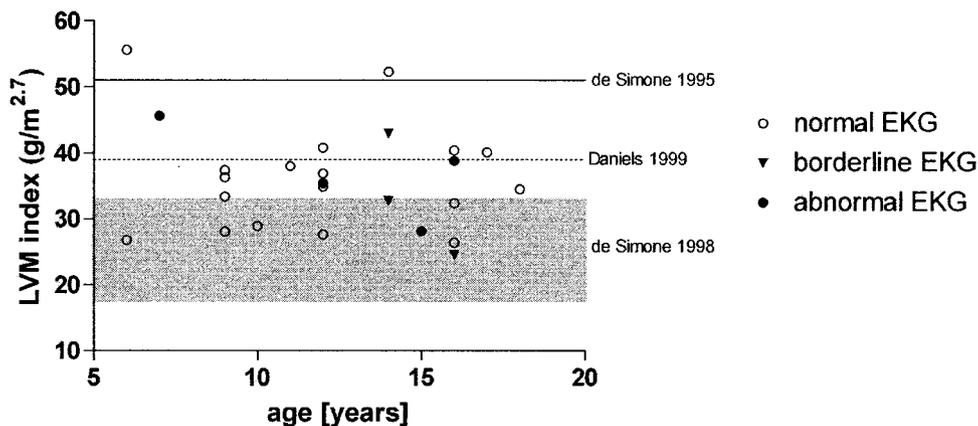
Fig 4. Summary of LVM index and electrocardiographic (EKG) findings as a function of age for 25 children with Fabry disease. The solid line indicates the abnormal LVM index of >95th percentile for children and adults (51 g/m$^{2.7}$) as described by de Simone et al,[32] and the dashed line indicates the abnormal LVM index of >95th percentile (39.36 g/m$^{2.7}$) for boys based on the data reported by Daniels.[41] The shaded area indicates the 95% CI for boys in a different study by de Simone et al.[42]

ous or episodic. The pain was relieved with rest or anticonvulsive medications. Some patients experienced nonspecific febrile episodes. One patient reported chronic itching. For 18 of 22 patients with chronic neuropathic pain, this symptom was reported to be the first manifestation of Fabry disease. The mean onset of neuropathic pain was reported as 7.8 ± 3.2 years of age (median: 8.5 years; range: 2–13 years; $n = 20$). Two patients reported heat intolerance and 1 patient described angiokeratoma as the first manifestation. Two patients did not recall the first symptom.

Thirteen patients (52%) complained about diffuse nonspecific headaches. For some patients, the headaches were localized frontally, possibly related to chronic sinusitis, which is common among these patients. Occasionally there was unilateral or bilateral tinnitus without vertigo.

Skin and Eye Abnormalities

Twelve patients (48%) exhibited angiokeratoma in physical examinations. Mild cornea verticillata was found for 22 patients (88%) and not for the 3 individuals with residual GALA activity ≥1.5% of normal control values. However, only 9 patients (36%) had tortuous retinal vessels.

Laboratory Abnormalities

One patient was anemic, with a hemoglobin level of 11.1 mg/dL. Three patients had decreased reticulocyte levels. Two patients had elevated thyrotropin levels; however, their free thyroxine levels were normal. Five patients had low plasma vitamin C concentrations.

GLA **Mutations and Crystallographic Mapping**

Of the 20 independent *GLA* alleles, all disease-related mutations were identified. The proportions of point mutations (18 of 20 [90%]) versus deletions of 1 to 3 nucleotides were in line with findings in the literature, as was the relative frequency of different types of point mutations (missense, nonsense, and affecting splice consensus sequences). The 3 patients

with residual enzyme activity ≥1.5% of normal control values carried a missense mutation that would be expected to lead to a conservative amino acid exchange (alanine/valine, neutral residues with nonpolar side chains, and arginine/histidine, positively charged basic residues) and affect the folding of the protein.

Most of the mutations in this cohort were detected in exon 3 ($n = 7$) and exon 5 ($n = 5$). Three mutations were found in exon 6 and 2 in exon 7. One mutation could be identified in exon 1, exon 2, and exon 4.

Most of the mutations affected residues located in the first of the 2 domains of the protein, which contains the active site of the enzyme. Mutations with residual enzyme activity of ≥1.5% tended to be closer to the surface of the molecule (median accessible surface area per side chain atom of 1.95 Å^2) (Table 4), compared with mutations with little or no residual enzyme activity (0.2 Å^2). Two different mutations from unrelated patients (C172W and C172Y) (Fig 5) were associated with LVH, according to the stricter criteria described by de Simone et al[32] for pediatric patients. The cysteine at amino acid position 172 forms a disulfide bond in the active site of the enzyme, and mutation of this residue leads to rupture of this highly conserved bond, interfering with the active site of the enzyme.

Sequence of Organ Involvement and Burden of Disease

The sequence of organ involvement distribution, as estimated with Kaplan-Maier curves, is shown in Fig 6A. The use of this figure can guide clinicians regarding what can be expected in evaluations of patients with Fabry disease at a given age. Early symptoms were acroparesthesia and cornea verticillata, for which the time to observation was estimated to be 12 years for 50% of the patients. Approximately one half of the patients were estimated to have enteropathy by 14 years of age, increased LVM index (with the criteria of de Simone et al[32]) or abnormal electrocardiographic findings and angiokeratoma at 15 years of age, and headaches and anhidrosis at 17 years of age. Because the exact time of onset is usu-

TABLE 4. *GLA* Mutations

Fabry Disease Mutation	Importance in GALA Structure	Wild-Type Side Chain Accessible Surface Area, Å²
Point mutations		
G138E	Buried, no room for side chain	0.0
C172W	Required disulfide in active site	11.4
C172Y	Required disulfide in active site	11.4
P205L	Buried, in helix-forming active site	0.0
C223Y	Buried disulfide, no room for tyrosine	0.0
R227Q	Active-site residue	0.4
P259L	Proline forms β turn	11.0
I270T	Buried in hydrophobic core	0.0
G325D	Buried, no room for side chain	0.0
E358del	Ion pairs to Lys-240, H-bonds to Trp-236	6.6
Point mutations with some residual activity		
A97V	Little room for larger side chain	2.0
R112H	Mostly buried, guanidinium group in ion pair	1.9
Stop codons		
C142X	Stop codon	8.8
W162X	Stop codon	2.7
R220X	Stop codon	7.6
W226X	Stop codon	0.0
R301X	Stop codon	3.6
Other mutations		
IVS3–1G>A	Splice defects	
c.57del26	Large deletion in protein	
c.1032 delTC	Frameshift mutation	

The importance to the GALA protein structure of the residues described in this study is indicated. The first column lists the mutations identified among patients in the study, categorized according to type. The second column indicates the effect of the mutation on the protein, on the basis of the crystal structure of wild-type human GALA. The third column lists the average accessible surface area per side chain atom for the wild-type protein. Large values indicate that a residue is exposed to solvent, whereas small values indicate that a residue is buried in the interior of the protein.

ally not known, the event-free time may be underestimated. Of note, no patient <8 years of age had headaches, and there was no patient <11 years of age with anhidrosis. All patients >9 years of age had acroparesthesia, all patients >10 years of age with <1.5% GALA activity had cornea verticillata, and all patients >13 years of age had gastrointestinal problems. The burden of disease, assessed as the sum of the number of organ systems affected, increased with age and could be predicted with a linear regression model (Fig 6B), as follows: number of organ systems affected = $0.5621 + (0.2790 \times age)$, with age being measured in years ($n = 25$; 95% CI for slope: 0.1401–0.4180; $r^2 = 0.4289$; $P = .0004$).

DISCUSSION

In this prospective study, we found that pediatric patients with Fabry disease had a significantly decreased quality of life, compared with their peers. Quantitatively analyzed sweating was decreased, compared with healthy, age-matched, male, control subjects recruited through the National Institutes of Health Study Volunteer Program. Chronic neuropathic pain and gastrointestinal complaints of nonspecific enteropathy were predominant. Major organ dysfunction had not yet occurred for the majority of these patients; however, cardiac involvement in this group was documented with a variety of electrocardiographic abnormalities and morphologic alterations of the myocardium, heart valves, and vessels. One patient exhibited proteinuria. Glomerular function was not compromised, although the GFR values were skewed; 9 patients had values of >140 mL/min

per 1.73 m², which is bordering on hyperfiltration, and 4 patients had GFR values of >165 mL/min per 1.73 m², which suggests hyperfiltration. If these estimated GFR values reflect the true GFR in this population, then this might have negative effects on glomerular function later in life. Determination of GFR among children is methodologically difficult, however, and some authors have expressed concerns regarding the method described by Schwartz et al,[27] although it is used widely in clinical and investigational pediatric settings. Pierrat et al[43] found an overestimation of GFR with the method of Schwartz et al,[27] compared with the inulin clearance method, in their pediatric study population. We did not use the Modification of Diet in Renal Disease study equation[44] because it has not been validated for children. We did not anticipate these results on the basis of previously available information. To avoid radiation exposure, a radioisotopic method was not used for this research protocol. Additional investigation in this population is warranted before any firm conclusions can be drawn from these findings. Renal function assessments in future studies should be conducted with 2 independent methods. Angiokeratoma and cornea verticillata are more specific findings that are helpful for making the diagnosis in a given clinical context. In this report, we document for the first time an estimation of the sequence of organ involvement in a pediatric population of patients with Fabry disease. We could fit a linear regression model to show that the disease is progressive with age.

All except 3 children in this study already had elevated plasma and urine Gb_3 levels, comparable to
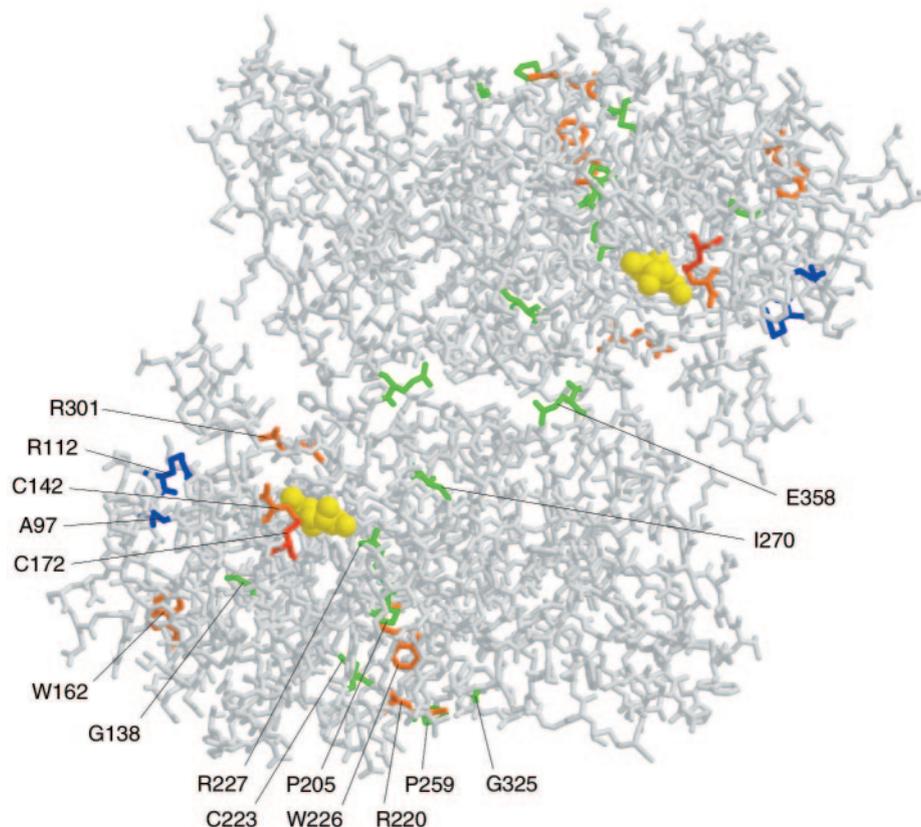
Fig 5. Mapping of *GLA* mutations onto the crystallographic structure. This figure shows the structure of the human GALA dimer. The bonds are colored blue for the missense mutations showing ≥1.5% residual enzyme activity, red for the missense mutations implicated in LVH, and green for other residues with single-amino acid changes examined in this study. Orange residues represent nonsense mutations found among the patients evaluated in this study. The residues in one monomer are identified with their wild-type amino acids. The catalytic product of the enzymatic reaction, galactose, is shown in yellow.

those of adult patients. We were able to provide a linear regression model to predict the increase in daily urinary Gb_3 excretion as a function of age. However, if the overall body development was taken into consideration with normalization of Gb_3 excretion to individual creatinine excretion, then there was no statistically significant age effect. This suggests that glycolipid accumulation in renal tubules is already present at a young age and is not increasing in the age range we studied. We showed previously that residual GALA activity delays the onset of chronic renal insufficiency in Fabry disease.[13] The 3 patients with residual GALA activity ≥1.5% of normal values had no cornea verticillata and normal plasma and urine Gb_3 levels. This finding limits the use of these 2 items for screening for Fabry disease and the use of Gb_3 levels for monitoring patients with significant residual enzyme activity who receive specific therapy such as enzyme replacement therapy. The crystallographic structure analysis of GALA is useful for understanding residual enzyme activity. Mutation analysis identified deletions, nonsense mutations, splice-site mutations, and missense mutations. The mutations were localized in all exons of the gene.[1–7] Missense mutations that were partially surface-exposed and distal to the active site were associated with the presence of residual GALA activity in this cohort. Mutations near the catalytic site of the enzyme resulted in undetectable GALA

activity. Our study, despite the small sample size, suggests that mutations that show some residual enzyme activity tend to involve residues that are more solvent-exposed, compared with mutations that show no residual enzyme activity. This result is consistent with a larger analysis of hundreds of mutations found among patients with Fabry disease.[38]

Secondary systemic disturbances are found among children with Fabry disease. Twenty percent of the patients in this cohort had low vitamin C levels. We showed recently that patients with normal vitamin C intake have significantly reduced blood levels of ascorbate. This is thought to be associated with increased production of reactive oxygen species in Fabry disease. Vitamin C plays an important role in Fabry disease, because reactive oxygen metabolites appear to be involved in the cerebral hyperperfusion in this condition, a phenomenon that is reduced with ascorbate infusions.[45] Four patients had anemia associated with reticulocyte levels in the low-normal range. We identified 2 individuals with subclinical hypothyroidism. Primary hypothyroidism in Fabry disease was described for a 48-year-old patient.[46] The 16% prevalence of excessive body weight in this population was comparable to that in the general US population in 2002, ie, 15.5% among 12- through 19-year-olds and 15.3% among 6- through 11-year-olds.[47] However, we also observed underweight and
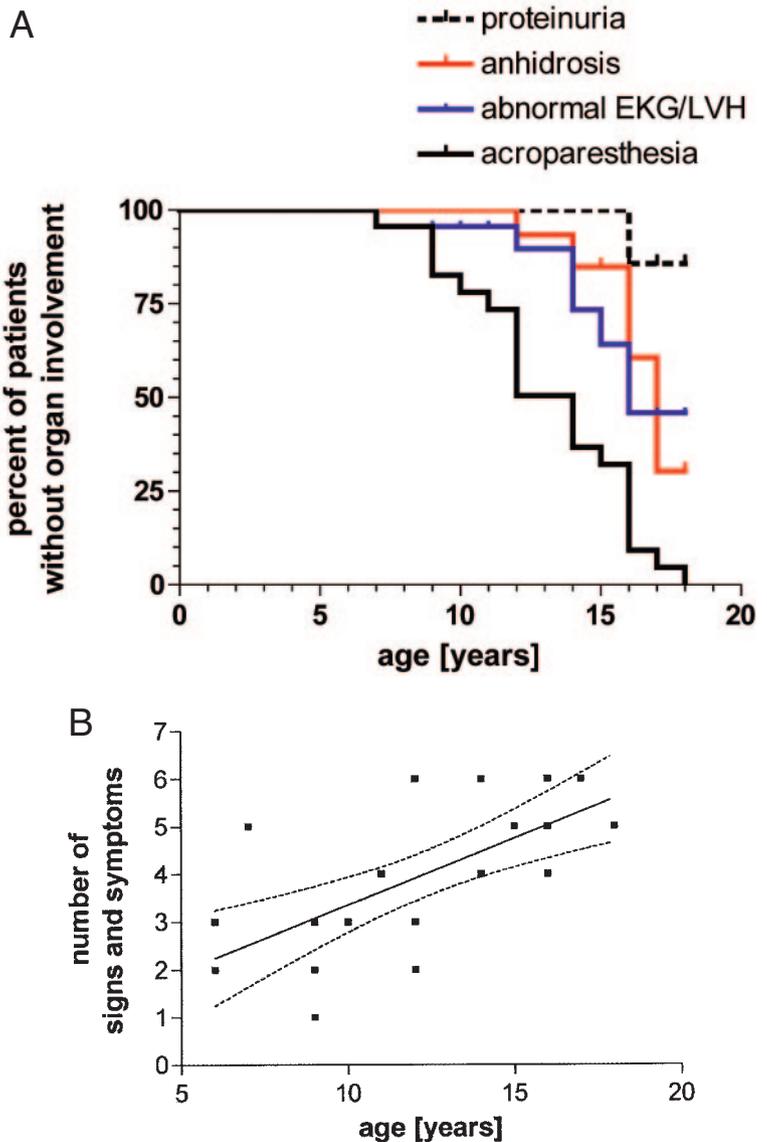
Fig 6. (A) Estimated time-to-observation distribution for the sequence of organ involvement among 25 hemizygous pediatric patients with Fabry disease. (B) Progression of disease. The burden of disease (equally weighted summary scores of categorically rated presence or absence of acroparesthesia, angiokeratoma, anhidrosis, cornea verticillata, headaches, electrocardiographic [EKG] abnormalities, LVH, abdominal pain, diarrhea, and proteinuria) among the pediatric patients with Fabry disease could be predicted with the following linear regression model: number of organ systems affected = $0.5621 + (0.2790 \times age)$, with age being measured in years ($n = 25$; 95% CI for slope: 0.1401–0.4180; $r^2 = 0.4289$; $P = .0004$). The 95% CI is indicated by the dashed lines.

tall and short stature for age, consistent with the diversity in the general population.

This comprehensive study indicates that, despite the absence of major organ involvement or irreversible organ complications (such as stroke or end-stage renal failure), the burden of Fabry disease in childhood is significant. Often pediatric patients with Fabry disease exhibit a subtly evolving disorder that is difficult to diagnose if clinical suspicion is not evident or index patients in the family are unavailable. Children with Fabry disease often appear less active than their peers and are sometimes considered to be malingering. Pain and decreased quality of life may lead to increased numbers of days absent from school and work and may contribute to the underemployment frequently encountered in the adult population. There are, however, numerous examples of successful professionals with Fabry disease in our adult patient population. Recognition of the special needs of these children and an understanding of the pathophysiologic mechanisms is important; the most significant symptomatic treatment is appropriate pain medication. Carbamazepine has been used suc-

cessfully and has been noted anecdotally to be less effective in the extended-release preparations. Patients should be cautioned about coincidental ingestion of grapefruit juice, because grapefruit juice causes increased tegretol levels. Gabapentin is a possible alternative.[48–50] Avoidance of rapid temperature changes can be also beneficial.

This study has several limitations. First, the number of patients in the study was limited. Second, the patients were referred to the National Institutes of Health and may not represent the nonreferred population. Third, the data on the sequence of organ involvement are not based on longitudinal follow-up assessments and therefore are less precise. Fourth, the conclusions with respect to residual enzyme activity are based on data for 3 patients only and should be interpreted cautiously.

We identified important, theoretically corrective, outcome measures, such as QSART and quality of life measurements. Moreover, preventive outcome measures, eg, the absence of major organ involvement for the majority of hemizygous pediatric patients with Fabry disease, can play an essential role

as fundamental clinical end points for future therapeutic trials. Systematic data on enzyme replacement therapy are currently available for adult patients.[16–18] Given the fact that the reversibility of disease progression in adulthood is limited, early enzyme replacement appears reasonable, because the disease progresses with age. It is essential, however, to study the therapeutic and possibly preventive effects of this treatment approach among children in a controlled way. For a selected group of patients with residual enzyme activity, stabilization of the enzyme with a molecular chaperone might represent a novel therapeutic approach.[51]

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Pediatric Fabry Disease

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