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PROFESSIONAL ISSUES

Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counselors

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Abstract Identification and comprehensive care of individuals who have Fabry disease (FD) requires a multidisciplinary approach inclusive of genetic testing, test interpretation, genetic counseling, long term disease symptom monitoring, treatment recommendations, and coordination of therapy. The purpose of this document is to provide health care professionals with guidelines for testing, care coordination, identification of psychosocial issues, and to facilitate a better understanding of disease treatment expert recommendations for patients with Fabry disease. These recommendations are the opinions of a multicenter working group of genetic counselors, medical geneticists, and other health professionals with expertise in Fabry disease counseling, as well as representatives/founders of the two United States based Fabry disease patient advocacy groups who are themselves affected by Fabry disease. The recommendations are U.S. Preventive Task Force Class III, and they are based on clinical experience, a review of pertinent English-language articles, and reports of expert committees. This document reviews the genetics of Fabry disease, the indications for genetic testing, interpretation of results, psychosocial considerations, and references to professional and patient resources.

Keywords Fabry disease · Enzyme replacement therapy · Genetic counseling · Newborn screening · Lysosomal storage diseases

Introduction

Knowledge of Fabry disease natural history and treatment is continuously changing, accordingly the recommended testing, monitoring, and treatment practices for Fabry disease

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must be updated frequently. A Pubmed search of the literature from January 2005 to April 26, 2013, reveals over 2,985 articles about Fabry disease with several updated guidelines and management articles from within and outside the United States. In order to appropriately diagnose and coordinate care for potential and confirmed patients with Fabry disease, this document reviews important topics and recommends practical genetic counseling tips for patient management. The working group hopes that this guidance will improve the care of patients with Fabry disease by establishing a comprehensive and detailed set of recommendations for the genetic counseling and management of this population.

Methods and Process

Treatment recommendations for Fabry disease have become more directive for men affected by Fabry disease, but are still less focused for women and children. Accordingly, our intent is to provide informed recommendations based on current clinical care and research. We will draw upon the clinical experience of the expert panel and published peer reviewed articles. (Bennett et al. 2002; Eng et al. 2006; Ortiz et al. 2008b; Wang et al. 2011) We expect that these recommendations will help a cross section of medical practitioners including nurses, genetic counselors, other allied health professionals, medical geneticists, and physicians specializing in nephrology, neurology, ophthalmology, audiology, cardiology, and other involved areas. Genetic counseling specific recommendations are provided in a table format with informative summaries and references supporting each recommendation.

Background

Fabry disease (Online Mendelian Inheritance in Man, Catalogue #301500) is an X-linked inherited lysosomal storage disorder of glycosphingolipid catabolism resulting from deficient or absent activity of the lysosomal enzyme α-galactosidase A (α-gal A). This enzyme breaks down glycolipids (complex sugar–fat substances). The enzymatic defect leads to progressive accumulation of the glycolipid globotriaosylceramide (GB3 or GL3) in the lysosomes in the cells of most organs. This abnormal storage leads to selective damage of the renal glomerular and tubular epithelial cells, the myocardial cells and valvular fibrocytes, neurons of the dorsal root ganglia and autonomic nervous system, as well as the endothelial, perithelial, and smooth muscle cells of the vascular system. Fabry disease is a panethnic condition with no racial or ethnic predilection.

The incidence of Fabry disease is currently under scrutiny as variant forms of Fabry disease and newborn screening numbers challenge the traditional 1 in 40,000 classically affected males. (Desnick and Ioannou 2006; Meikle 1999) Incidence ranges from the high prevalence of a presumed cardiac Fabry mutation (IVS4+919G) at 1 in 1,600 males in Taiwan to the 1 in 3,000 reported by the early newborn screening data from Illinois and 1 in 10,000 (males and females) in Washington state. (Lin et al. 2009; Brower et al. 2011; Scott et al. 2011) Studies have also found an increased incidence of Fabry disease in patients with cryptogenic strokes, hypertrophic cardiomyopathy, and dialysis patients with numbers ranging from 1:20 to 1:1000. (Chimenti et al. 2004; Germain 2010)

Fabry disease is a chronic progressive condition with symptoms such as chronic neuropathic pain, acute pain crises, heat and cold intolerance, and fatigue often beginning in childhood. The average presentation age in males is 6–8 years of age and 9 years of age in females, although age of symptom onset varies from individual to individual even within the same family. (Hopkin et al. 2008; Ries et al. 2005; Ramaswami et al. 2006) Over time the storage of globotriaosylceramide (GB3 or GL3) results in a variety of multisystemic disease symptoms which may include: angiokeratoma, tinnitus, hearing loss, corneal whorls, vertigo, transient ischemic attacks, strokes, cardiomyopathy, left ventricular hypertrophy, cardiac arrhythmias including atrial fibullation, cardiac valve insufficiency, gastrointestinal issues including chronic alternating diarrhea and constipation, obstructive pulmonary disease, proteinuria, progressive renal disease, panic attacks, depression, and adaptive function disorders. (Albano et al. 2010; Banikazemi et al. 2007; Bennett et al. 2002; Brady and Schiffmann 2000; Desnick 2004; Desnick and Ioannou 2006; Elstein et al. 2010; Germain 2010; Hopkin et al. 2008; Laney et al. 2010; MacDermot et al. 2001a,b; Mehta 2004; Mehta et al. 2006; Ries et al. 2005; Sims et al. 2009; Stryker and Kreps 2001; Wang et al. 2007; Zarate and Hopkin 2008; Hershberger et al. 2009) Progressive renal insufficiency, cardiovascular, and peripheral and central nervous system disease are causes of significant morbidity and mortality in Fabry disease, but virtually any organ may be affected. (Desnick et al. 2003; MacDermot et al. 2001a,b)

In the past, females were considered asymptomatic; however, the majority of females heterozygous for a Fabry disease mutation exhibit disease manifestations that may be as severe as the phenotype in males affected by Fabry disease. (Wang et al. 2007; Desnick and Ioannou 2006; MacDermot et al. 2001b; Ortiz et al. 2008a) Prior to the dialysis and kidney transplant era, the average age of death in males was 41 years. (Colombi et al. 1967; Wise et al. 1962) A more recent report analyzing Fabry Registry data found the life expectancy of males with Fabry disease was 58.2 years, compared with 74.7 years in the general population of the United States. The life expectancy of females with Fabry disease was 75.4 years, compared with 80.0 years in the United States general population. (Waldek et al. 2009) However, a detailed analysis of survival after treatment with

enzyme replacement therapy (ERT) has not yet been performed. As ERT has been shown to stabilize kidney function and improve cardiac structure, it would be expected to increase life expectancy for females and males, particularly in individuals who begin ERT early in the disease course, prior to irreversible damage. Over the past 10 years, Fabry disease has expanded beyond the classic form to include forms such as "cardiac variants" and the presence of Fabry disease in women and children. As the condition is progressive, any discussion of Fabry disease symptoms must be considered a snapshot of the disease at a particular time and that other symptoms will likely emerge over time.

Treatment

The information on treatment below is not meant to guide genetic counselors in the treatment of Fabry disease and NSGC is not engaged in the practice of medicine. It is solely for informational purposes. Genetic counselors do not prescribe medications or set treatment plans. Such activities should be conducted by the appropriate medical professionals.

Intravenous enzyme replacement therapy (ERT) using agalsidase beta (Fabrazyme®, Genzyme, Inc.) is currently approved in the United States for the treatment of Fabry disease. Clinical trials have found ERT with agalsidase beta to be effective in reducing plasma and tissue GL3 levels in the vascular endothelium of the kidney, skin, and heart as surrogate markers of clinical benefit. (Banikazemi et al. 2007; Desnick et al. 2003; Eng et al. 2001a, b) There are also indications of decreased pain and improvement in quality of life. (Watt et al. 2010; Street et al. 2006) The earlier treatment with ERT is begun, the greater the potential for benefit. This improved response with early treatment is supported by a study indicating that long-term ERT in young patients can result in complete GL3 clearance of the mesangial and glomerular endothelial cells of the kidney with dose dependent clearance of the renal podocyte inclusions. (Tøndel et al. 2013) However, ERT is not a "cure" for Fabry disease and does not remove the need for concomitant medications or monitoring. End organ damage is largely irreversible and may progress despite ERT. Adjunctive therapies, managed by the appropriate medical professionals, are still required during treatment with ERT for medical issues such as proteinuria and depression.

Another ERT pharmacologic agent for Fabry disease is available in Europe and Canada: agalsidase alfa (Replagal®, Shire Human Genetic Therapies, Inc.). The function of the medication is essentially similar in all studies available to agalsidase beta (Lee et al. 2003; Lidov et al. 2010; Schiffmann 2000, 2001). No formal dosing trials have been done, and only one study has been done comparing the 2 drugs. (Vedder et al. 2007) One small scale study of long-term ERT in young patients did find that a dose–response effect on the clearance of GL3 was seen only in the kidney podocyte cells, but not other examined renal cells (glomerular endothelial or mesangial cells). (Tøndel et al. 2013) The best dosing for enzyme infusions remains to be proven through outcome data and continues to be a subject of controversy. Given the relatively slow progression of Fabry disease and the lack of reliable biomarkers of disease activity, it is unlikely that this will be resolved in the near future. Studies examining the impact of switching from agalsidase beta to agalsidase alfa and agalsidase alfa and agalsidase beta are underway and results should be reported in 2013.

Other genetic therapies are being considered for the treatment of Fabry disease, such as substrate reduction therapy, residual enzyme activators, chemical chaperone therapy, *GLA* promoter activation, protein homeostasis regulation, next generation ERT, and gene therapy. The safety and efficacy of one form of chaperone therapy (Amicus, AT1001) is being studied in phase III clinical trials. This therapy is designed to stabilize the naturally occurring enzyme in some Fabry patients. Other therapeutics options are still early in research development. (Abe et al. 2000; Desnick et al. 2003; Motabar et al. 2010; Gahl 2001).

Diagnostic Testing

Biochemical Analysis

Biochemical testing diagnostic for the presence or absence of Fabry disease usually includes the measurement of α-galactosidase A (α-gal A) enzyme levels. Males affected by Fabry disease have reduced levels of α-gal A in leukocytes and plasma. Females affected by Fabry disease have α-gal A levels that can range from deficient to normal levels and do not correlate with disease severity. Biomarkers used in Fabry disease that may assist with treatment monitoring include globotriaosylceramide (GB3 or GL3) and Lysoglobotriaosylceramide (LysoGL3) measured in plasma, fibroblasts, and/or urine. However, GL3 and LysoGL3 levels can be difficult to correlate with organ involvement or long term disease progression in females and individuals not affected by the classic form of Fabry disease. (Wang et al. 2011 and Germain 2010)

Molecular Analysis

Fabry disease is caused by pathogenic mutations in the *GLA* gene located on Xq22.1. More than 431 mutations have been identified in the *α-gal A* gene (Human Gene Mutation Database, http://www.hgmd.cf.ac.uk/ac/index.php); most of the mutations are unique ("private mutations") in each novel

proband. (Germain 2010; Desnick and Ioannou 2006; Ashton-Prolla et al. 2000) Therefore it is necessary to sequence the entire *GLA* gene and flanking regions to identify the Fabry disease mutation in a family. Several familial mutations where conventional genomic sequencing did not identify a mutation in the coding/flanking region of the gene have been identified by microarray based duplication/deletion testing of the *GLA* gene. The limitations of gene sequencing and duplication/deletion testing include limited clinical availability from CLIA-approved laboratories, labor intensity, the possibility that not all mutations will be identified, and the possible identification of sequence variations of uncertain significance.

Testing and Diagnosis Recommendations

A suspicion that a patient is affected by Fabry disease is usually based on a targeted patient medical history and a detailed family history. High yield clinical and family history features are summarized in Table 1. Although Fabry disease is considered highly penetrant in males and females, it can be variable in its expression.

Diagnosis of Fabry disease is confirmed using a combination of biochemical and molecular testing. (see Fig. 1)

1. Fabry disease can be confirmed in males with deficiency of α-gal A, most commonly measured in blood (leukocytes), and the presence of a disease causing mutation in the *GLA* gene located on Xq22.1. Although in the past low α-gal A activity has been considered sufficient for diagnosis in males, the presence of a common pseudodeficiency allele, D313Y, that results in low plasma alpha-gal A activity and slightly reduced leukocyte enzyme activity suggests that a diagnosis of Fabry disease should not be finalized until a disease causing GLA mutation is identified. (Yasuda et al. 2003)
2. Measurement of α-gal A enzyme activity is not reliable for diagnosis of Fabry in females because obligate heterozygotes have variable levels of α-gal A that can overlap with enzyme levels found in healthy controls. In females confirmation of Fabry is via identification of a Fabry disease causing mutation in the *GLA* gene.
3. Biopsies of heart or kidney are not required for diagnosis in this condition, although storage patterns on biopsies may suggest a Fabry disease diagnosis in an affected individual.

Prenatal diagnosis of Fabry disease is possible using amniocytes and chorionic villi for enzymatic & molecular testing, although only molecular testing is routinely performed in the United States. Preimplantation genetic diagnosis for families with a known familial mutation is also available via assisted reproduction centers.

Newborn screening for Fabry disease is now technically possible and programs have begun in Taiwan, Missouri, Washington State, and Illinois. Other states such as New Mexico and New Jersey also have legislated beginning newborn screening for Fabry and will begin testing in the near future. The methods utilized are designed to limit false positive and negatives, but most are based on enzyme measurement which will predominantly diagnose males and a subset of affected females with low enzyme. Although not currently on the recommended panel of conditions to screen, several state legislatures have mandated screening for Fabry disease. The goals of newborn screening for Fabry disease are to diagnosis patients earlier, avoid the "diagnostic odyssey", monitor and treat patients prior to irreversible damage, and identify family members at-risk to be affected by Fabry disease. Issues surrounding the testing also relate to identification of other affected family members. Newborn screening has begun in selected states, so the issue of pediatric management and timing of initiation of ERT has expanded.

Clinical Follow-Up and Intervention by Appropriate Medical Professionals

The progressive nature of Fabry disease requires at least annual evaluation and revision of management based on

Table 1 When to consider Fabry disease as a diagnosis

Test ANY patient who has:
1. A family history of Fabry Disease OR
2. Corneal verticillata ("whorls") on slit lamp exam
In the absence of these two factors, test patients with at least two of the features below.
1. Decreased sweating (anhidrosis or hypohidrosis)
2. Reddish-purple skin rash in the bathing trunk area (angiokeratomas)
3. Personal and/or family history of kidney failure
4. Personal or family history of "burning" or "hot" pain in the hands and feet, particularly during fevers (acroparesthesias)
5. Personal or family history of exercise, heat, or cold intolerance.
6. Patients with sporadic or non-autosomal dominant (no male-to-male) transmission of unexplained cardiac hypertrophy

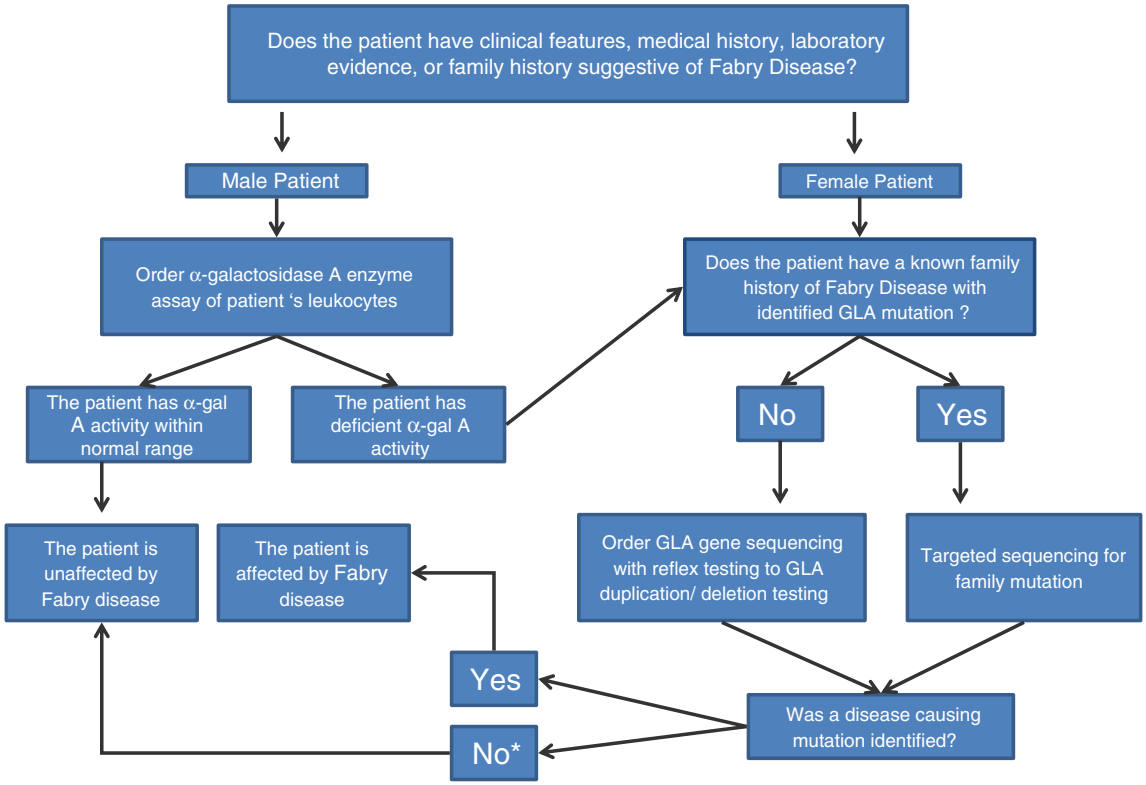

Fig. 1 Fabry Testing Roadmap. *Standard sequencing of GLA will not detect large deletions, large duplications, some intronic mutations, and mutations in the promoter or other regulatory regions. Results must be interpreted in the context of an individual's clinical and/or biochemical profile

clinical and lab assessments by the appropriate medical professionals. Guidelines for multidisciplinary management and ERT treatment have been published for both pediatric and adult patients. (Bennett et al. 2002; Eng et al. 2006 and Desnick 2004; Ortiz et al. 2008b; Wang et al. 2011) In short, the following steps are recommended for any individual once a diagnosis of Fabry disease is made:

1. Referrals by appropriate medical professionals to a metabolic specialist and genetic counselor for discussion of diagnosis, recurrence risk, construction of a detailed family history, identification of other at risk family members, and development of a comprehensive monitoring and treatment plan. Contact information for medical professionals experienced in treating Fabry disease patients can be found by contacting the National Fabry Disease Foundation.
2. Baseline evaluations to be ordered by and under the supervision of appropriate medical professionals as recommended for age group include (Eng et al. 2006):
   - CBC, platelet count, serum creatinine and BUN, GL3, thyroid studies, common thrombophilic blood coagulation disorders, and a basic metabolic chemistry panel
   - Routine urinalysis
   - 24 h urine with creatinine, glomerular filtration rate, and protein clearance
   - First morning urine measuring total protein and creatinine levels.
   - EKG
   - 24 h Holter monitor
   - Echocardiogram and/or Cardiac Magnetic Resonance Imaging
   - Brain Magnetic Resonance Imaging or Head CT
   - Hearing examination
   - Ophthalmologic examination
   - Pulmonary function testing
   - Depression/Anxiety assessment
3. Discussion with appropriate medical professionals of treatment with enzyme replacement therapy (ERT) treatment practices vary widely in recommended timing of beginning ERT, the decision to initiate therapy should be determined based on the clinical judgment of the managing metabolic specialist after reviewing baseline evaluations in conjunction with the patient or patient's family in affected minors.

Genetic Counseling Recommendations

Genetic counseling specific recommendations related to issues in Fabry disease encompass a wide range of topics (Table 2). (Bennett et al. 1995; Bennett et al. 2002; Bennett et al. 2008; Bennett 2010a,b; Clarke & Flinter 1996; Clarke 1998; Davis 1997; Dink 2000; Gibas et al. 2008; Grewal 1993; Holmes et al 2001; Hopkin et al. 2008; Laney and Fernhoff 2008; Laney et al. 2010; McConkie-Rosell et al. 2000; Michie 1996; National Society of Genetic Counselors 1995; Resta 2000; Sorensen & Hasholt 1983; Uhlmann et al. 2009; Wang et al. 2011; Weil 2000; Wertz et al. 1994; Wilcox et al. 2008; Williams et al. 2000).

Specific points to examine further during sessions include:

1. Ascertaining patients' needs and concerns relating to a Fabry disease diagnosis
2. Identifying at-risk family members through construction of a detailed pedigree and diagnostic testing,
3. Explaining the natural history and inheritance pattern of Fabry disease,
4. Provision of pre- and post- counseling regarding genetic testing including the issue of non-paternity,
5. Navigation of personal and family testing (enzyme, sequencing, duplication/deletion testing),
6. Discussions related to prenatal testing and decision making, assessing the subjects' psychosocial issues,
7. Identifying appropriate support resources.

Key Fabry-specific points to address during these discussion topics include:

1. The X-linked pattern of inheritance for Fabry disease and testing at-risk family members. On average, there are five family members diagnosed with Fabry disease for every proband. Discussion should include issues of misattributed paternity which could arise from testing. This disease should be referred to as an X-linked disorder not an "X-linked recessive disorder."
2. Clinical manifestations of Fabry disease occur in men and women. Women are not "just carriers".
3. Fabry disease is progressive and often becomes symptomatic in childhood. The average presentation age in males is 6–8 years of age and 9 years of age in females, although age of symptom onset varies from individual to individual even within the same family. Nevertheless life threatening complications are rare in pediatric patients.
4. Types of genetic testing available and test limitations (e.g., enzyme assay can be normal in heterozygous females; the percentage of residual α-gal-A enzyme activity does not correlate with clinical severity; and mutations frequently cannot predict disease severity)
5. Issues related to genetic testing for Fabry disease such as testing "healthy" minors and insurance implications
6. Testing kidney donors, particularly family members, prior to transplant for Fabry disease.
7. Reproductive options including gamete donation, prenatal diagnosis and preimplantation diagnosis.
8. Teratogenic risk of frequently used medications in Fabry disease such as Dilantin, Carbamazepine (Tegretol), and ACE Inhibitors in pregnancy.
9. Issues related to treatment compliance on a life-long infusion therapy including: transition from parent to patient directed medical care as the patient becomes an adult, insurance issues, realistic expectations of treatment efficacy, continued need for concomitant treatments and monitoring, and possible weight gain.
10. Identify potential substance abuse; pain can be one of the most debilitating features of Fabry disease, and there can be problems with substance abuse as a form of self-medication.
11. Identify issues of sexuality. Men and women with Fabry disease may have concerns about body image, intimacy, and sexuality. For example, affected individuals may be embarrassed by angiokeratomas in their genital region. Chronic pain and fatigue and erectile dysfunction may also contribute to difficulties and problems with intimacy.
12. Review of management options and prevention, and referral to specialists as appropriate
13. Due to years of misdiagnosis, there can be an inherent mistrust of health professionals.
14. Discussion of the increased rate of depression, anxiety, and adaptive function disorders (ability to function in daily life and maintain relationships) seen in Fabry disease.
15. Discussion of the unique psychosocial issues in relation to Fabry disease. Overall the psychosocial issues in relation to a diagnosis of Fabry disease are similar to those associated with a diagnosis of other chronic genetic disorders (e.g., anxiety, anger, grief, denial, blame, hopelessness, and influence on self-esteem and self-identify, changed relationships with family of origin). The chronic nature of this condition can stress relationships. There is a higher rate of unemployment and suicide.

Conclusion

Significant morbidity and mortality are associated with Fabry disease. Given the potential benefits of early medical and psychological interventions, genetic counselors need to have increased awareness about genetic testing, evaluation, and

Table 2 Fabry disease features and management in genetic counseling. (Albano et al. 2010; Banikazemi et al. 2007; Bennett et al. 2002; Brady and Schiffmann 2000; Desnick et al. 2003; Desnick 2004; Elstein et al. 2010; Germain 2010; Hopkin et al. 2008; Laney et al. 2010; MacDermot et al. 2001a, b; Mehta et al. 2006; Ries et al. 2005; Sims et al. 2009; Stryker and Kreps 2001; Wang et al. 2007; Zarate and Hopkin 2008)

	Recommended assessments	Clinical features	Typical age of onset and estimated incidence	Management
Psychosocial	Symptom review focused on changes over time	Depression	May manifest at any time Depression reported in 46–58 % of males and females	Optimized pain management.
	Every 6–12 months in pediatric and adult patients	Anxiety/Panic attacks	Anxiety reported in 39 % of males and females	Referral for supportive counseling and medication, as appropriate
		Attention deficit hyperactivity (ADHD)	ADHD reported in 24 % of males and females	
		Adaptive function disorders	May become manifest at any time usually evident in adolescence or adulthood Reported in 15 % of males and 33 % of females	Referral for supportive counseling and medication, as appropriate
	Symptom review focused on changes over time using Quality of Life assessment tools (SF-36)	Decreased quality of life	May become manifest at any time; usually evident in adolescence or Adulthood	Quality of life measurement tools
	Every 6–12 months in pediatric and adult patients		Reported in the majority of males and females	Supportive counseling and medication, as appropriate
				Pediatric patients: work closely with school to ensure understanding of the disease (pain, fatigue, gastrointestinal, symptoms, physical abilities, limitations and school absences) as well as treatment
Prenatal/ Preconcep-tion	Preconceptional assessment of Fabry symptoms by appropriate medical professionals	Pre-existing Fabry symptoms which could progress during the course of the pregnancy or at delivery	Any female of child-bearing ability	Discuss options such as donor gametes and adoption as well as preconception/prenatal options including: preimplantation genetic testing, chorionic villus sampling, and amniocentesis for known genetic mutations in GLA.
				Prenatal enzyme analysis for deficient alpha-galactosidase A levels is not offered clinically by laboratories in the United States.
				Review medication list and discuss any potentially teratogenic medications.
				Suggest that appropriate medical professional work with the patient's OB/Gyn to monitor proteinuria, wean patient off any teratogenic medications, review patient health status, and decide if Maternal Fetal Medicine consult warranted.
				Suggest that appropriate medical profession discuss continuing or discontinuing ERT during all or part of the pregnancy.

management of Fabry disease. Genetic counselors play a critical role in not only identifying individuals and at-risk relatives with Fabry disease, but in providing genetic testing services, disease management, and counseling. Through on-going education and

support, genetic counselors encourage families to enroll in Fabry disease registries, Quality of Life studies, and clinical trials so that more can be learned about the clinical manifestations of Fabry disease, appropriate modes of evaluation and therapy, and strategies for psychological support of these families.

Resources

Table 3 Advocacy groups for individuals and their families with Fabry disease

Organization	Address	Phone, Fax, Website
Fabry Support and Information Group	FSIG P. O. Box 510, Concordia, MO 64020, USA	Phone: 1-866-30-FABRY (866-303-2279) Phone: (660) 463-1355 Fax: (660) 463-1356 Email: info@fabry.org Website: http://www.fabry.org
National Fabry Disease Foundation	NFDF 4301 Connecticut Ave. N.W. Suite 404 Washington, DC 20008-2369	Phone: 1-800-651-9131 FAX: 1-800-651-9135 Email: info@fabrydisease.org Website: http://www.fabrydisease.org/
NORD—National Organization for Rare Disorders	P. O. Box 8923, New Fairfield, CT 06812-8923, USA	Phone: (203) 746-6518 Fax: (203) 746-6481 Website: http://www.rarediseases.org

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The practice guidelines of the National Society of Genetic Counselors (NSGC) are developed by members of the NSGC to assist genetic counselors and other health care providers in making decisions about appropriate management of genetic concerns; including access to and/or delivery of services. Each practice guideline focuses on a clinical or practice-based issue, and is the result of a review and analysis of current professional literature believed to be reliable. As such, information and recommendations within the NSGC practice guidelines reflect the current scientific and clinical knowledge at the time of publication, are only current as of their publication date, and are subject to change without notice as advances emerge.

In addition, variations in practice, which take into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments and/or procedures that differ from the recommendations outlined in this guideline. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does the use of such recommendations guarantee a particular outcome. Genetic counseling practice guidelines are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient or patient population. Practice guidelines are published by NSGC for educational and informational purposes only, and NSGC does not "approve" or "endorse" any specific methods, practices, or sources of information.

References

Abe, A., Gregory, S., Lee, L., Killen, P. D., Brady, R. O., Kulkarni, A., et al. (2000). Reduction of globotriaosylceramide in Fabry disease mice by substrate deprivation. *The Journal of Clinical Investigation, 105*, 1563–1571.

Albano, L. M., Rivitti, C., Bertola, D. R., Honjo, R. S., Kelmann, S. V., Giugliana, R., et al. (2010). Angiokeratoma: a cutaneous marker of Fabry's disease. *Clinical and Experimental Dermatology, 35*(5), 505–508.

Ashton-Prolla, P., Tong, B., Shabeer, J., Eng, C. M., & Desnick, R. J. (2000). 22 novel mutations in the alpha-galactosidase A gene and genotype/phenotype correlations including mild hemizygotes and severely affected heterozygotes. *Journal of Investigative Medicine, 48*, 227.

Banikazemi, M., Bultas, J., Waldek, S., Wilcox, W. R., Whitley, C. B., McDonald, M., et al. (2007). Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Annals of Internal Medicine, 146*(2), 77–86.

Bennett, R. L. (2010a). *The practical guide to the genetic family history* (2nd ed.). Hoboken: Blackwell.

Bennett, R. L. (2010b). Genetic counseling and psychosocial issues for individuals and their families with Fabry disease. In Elstein D, Altarescu G, Beck M (Eds.), *Fabry disease*. New York: Springer.

Bennett, R. L., Steinhaus, K. A., Uhrich, S. B., O'Sullivan, C. K., Resta, R. G., Lochner-Doyle, D., et al. (1995). Recommendations for standardized pedigree nomenclature. *American Journal of Human Genetics, 56*, 745–752.

Bennett, R. L., Hart, K. A., O'Rourke, E. O., et al. (2002). Fabry disease in genetic counseling practice: recommendations of the National Society of Genetic Counselors. *Journal of Genetic Counseling, 11*(2), 121–146.

Bennett, R. L., Steinhaus, K. A., Resta, R. G., & Doyle, D. L. (2008). Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. *Journal of Genetic Counseling, 7*(5), 424–433.

Brady, R. O., & Schiffmann, R. (2000). Clinical features of and recent advances in therapy for Fabry disease. *Journal of the American Medical Association, 284*, 2771–2775.

Brower, A., Hoffman, A. J., Thompson, B. H, & Watson, M. S. (2011). Utilization of the newborn screening translational research network to advance research and clinical applications in lysosomal storage disorders. 7th WORLD symposium 2011.

Chimenti, C., Pieroni, M., Morgante, E., et al. (2004). Prevalaence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circulation, 110*(9), 1047–1053. Epub 2004 Aug 16.

Clarke, A. (Ed.). (1998). *The genetic testing of children*. Oxford: BIOS Scientific.

Clarke, A., & Flinter, F. (1996). The genetic testing of children: A clinical perspective. In T. Marteau & M. Richards (Eds.), *The troubled helix: Social and psychological implications of the new human genetics* (pp. 164–176). New York: Cambridge University Press.

Colombi, A., Kostyal, A., Bracher, R., Gloor, F., Mazzi, R., & Tholen, H. (1967). Angiokeratoma corporis diffusum: Fabry's disease. *Helvetica Medica Acta, 34*, 67–83.

Davis, D. S. (1997). Genetic dilemmas and the child's right to an open future. *The Hastings Center Report, 27*, 7–15.

Desnick, R. J. (2004). Enzyme replacement therapy for Fabry disease: lessons from two alpha-galactosidase A orphan products and one FDA approval. *Expert Opinion on Biological Therapy, 4*, 1167–1176.

Desnick, R., & Ioannou, Y., (2006). Eng C. α-Galactosidase A deficiency: Fabry disease. In: Valle D, Baudette A, Vogelstein KC, (Eds.), *The online metabolic & molecular bases of inherited disease*. McGraw-Hill Companies Inc. www.ommbid.com, accessed Mar 2011.

Desnick, R. J., Brady, R., Barranger, J., et al. (2003). Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Annals of Internal Medicine, 138*, 338–346.

Dink, A., Sims, I., Pay, S., Calgary, K., & Can, C. (2000). Fabry's disease mimicking familial Mediterranean fever. *Clinical and Experimental Rheumatic, 18*, 787–788.

Elstein, D., Altars, G., & Beck, M. (ends) (2010). *Fabry disease*, Springer.

Eng, C. M., Banikazemi, M., Gordon, R. E., Goldman, M., Phelps, R., Kim, L., et al. (2001a). A phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetic, substrate clearance, and safety studies. *American Journal of Human Genetics, 68*, 711–722.

Eng, C. M., Guffon, N., Wilcox, W. R., Germain, D. P., Lee, P., Waldek, S., et al. (2001b). Safety and efficacy of recombinant human ®-galactosidase A replacement therapy in Fairy's disease. *The New England Journal of Medicine, 345*, 9–16.

Eng, C. M., Germain, D. P., Banikazemi, M., Warnock, D. G., Wanner, C., Hopkin, R. J., et al. (2006). Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genetics in Medicine, 8*(9), 539–548.

Gahl, W. A. (2001). New therapies for Fabry's disease. *The New England Journal of Medicine, 345*, 55–57.

Germain, D. P. (2010). Fabry disease. *Orphanet Journal of Rare Diseases, 5*, 30. Review.

Gibas, A. L., Klatt, R., Johnson, J., Clarket, J. T. R., & Katz, J. (2008). Disease rarity, carrier status, and genera: a triple disadvantage for women with Fabry disease. *Journal of Genetic Counseling, 17*, 528–537.

Grewal, R. P. (1993). Psychiatric disorders in patients with Fabry's disease. *International Journal of Psychiatry in Medicine, 23*, 307–312.

Hershberger, R. E., Lindenfeld, J., Mestroni, L., Seidman, C. E., Taylor, M. R. G., & Towbin, J. A. (2009). *Journal of Cardiac Failure, 15*(2), 83–97.

Holmes, L. B., Harvey, E. A., Coull, B. A., Huntington, K. B., Khoshbin, S., Hayes, A. M., et al. (2001). The teratogenicity of anticonvulsant drugs. *The New England Journal of Medicine, 344*, 1132–1138.

Hopkin, R. J., Bissler, J., Banikazemi, M., Clarke, L., Eng, C. M., Germain, D. P., et al. (2008). Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. *Pediatric Research, 64*, 550–555.

Laney, D. A., & Fernhoff, P. M. (2008). Diagnosis of Fabry disease via analysis of family history. *Journal of Genetic Counseling, 17*(1), 79–83.

Laney, D.A., Gruskin, D.J., Fernhoff, P.M., Cubells, J.F., Ousley, O.Y., Hipp, H., et al. (2010). Social-adaptive and psychological functioning of patients affected by fabry disease. *Journal of Inherited Metabolic Disease*. Online.

Lee, K., Jin, X., Zhang, K., Copertino, L., Andrews, L., Baker-Malcolm, J., et al. (2003). A biochemical and pharmacological comparison of enzyme replacement therapies for the glycolipid storage disorder Fabry disease. *Glycobiology, 13*, 305–313.

Lidov, O., West, M., Pintos-Morell, G., et al. (2010). Effects of enzyme replacement therapy in Fabry disease—A comprehensive review of the medical literature. *Genetics in Medicine, 12*(11).

Lin, H. Y., Chong, K. W., Hsu, J. H., et al. (2009). High incidence of the cardiac variant of Fabry disease revealed by newborn screening in the Taiwan Chinese population. *Circulation. Cardiovascular Genetics, 2*, 450–456.

MacDermot, K. D., Holmes, A., & Miners, A. H. (2001a). Anderson Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *Journal of Medical Genetics, 38*, 750–760.

MacDermot, K. D., Holmes, A., & Miners, A. H. (2001b). Anderson Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *Journal of Medical Genetics, 38*, 769–775.

McConkie-Rosell, A., & DeVellis, B. M. (2000). Threat to parental role: a possible mechanism of altered self-concept related to carrier knowledge. *Journal of Genetic Counseling, 9*, 285–302.

Mehta, A., Ricci, R., Widmer, U., et al. (2004). Fabry disease defined, baseline clinical manifestations of 366 patients in the Fabry outcome survey. *European Journal of Clinical Investigation, 34*(3), 235–242.

Mehta, A., Beck, M., & Sunder-Plassmann, G. (Eds.). (2006). *Fabry disease: Perspectives from 5 years of FOS*. Oxford: Oxford PharmaGenesis.

Meikle, P. J., Hopwood, J. J., Clague, A. E., & Carey, W. F. (1999). Prevalence of lysosomal storage disorders. *Journal of the American Medical Association, 281*, 249–254.

Michie, S. (1996). Predictive genetic testing in children: Paternalism or empiricisms? In T. Marteau & M. Richards (Eds.), *The troubled helix: Social and psychological implications of the new human genetics* (pp. 177–183). New York: Cambridge University Press.

Motabar, O., Sidransky, E., Goldin, E., & Zheng, W. (2010). Fabry disease- current treatment and new drug development. *Current Chemical Genomics, 4*, 50–56.

National Society of Genetic Counselors. (1995). National Society of Genetic Counselors, Position statement on prenatal and childhood testing for adult-onset disorders. *Perspectives Genetic Counseling, 17*, 5.

Ortiz, A., Oliveira, J. P., Waldek, S., Warnock, D. G., Cianciaruso, B., Wanner, C., et al. (2008a). Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. *Nephrology, Dialysis, Transplantation, 23*, 1600–1607.

Ortiz, A., Oliveira, J. P., Wanner, C., Brenner, B. M., Waldek, S., & Warnock, D. G. (2008b). Recommendations and guidelines for the diagnosis and treatment of Fabry nephropathy in adults. *Nature Clinical Practice Nephrology, 4*(6), 327–336.

Ramaswami, U., Whybra, C., Parini, R., et al. (2006). Clinical manifestations of Fabry disease in children: data from the Fabry Outcome Survey. *Acta Paediatrica, 95*, 86–92.

Resta, R. G. (Ed.). (2000). *Psyche and helix, Psychological aspects of genetic counseling. Essays by Seymour Kessler, PhD*. New York: Wiley-Liss.

Ries, M., Gupta, S., Moore, D. F., Sachdev, V., Quirk, J. M., Murray, G. J., et al. (2005). Pediatric Fabry disease. *Pediatrics, 115*(3), e344–e355. Resta RG (ed) (2000).

Schiffmann, R., Murray, G. J., Treco, D., Daniel, P., Sellos-Moura, M., Myers, M., et al. (2000). Infusion of α-galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease. *PNAS, 97*, 365–370.

Schiffmann, R., Kopp, J. B., Austin, H. A., Sabnis, S., Moore, D. F., Weibel, T., et al. (2001). Enzyme replacement therapy in Fabry disease. A randomized controlled trial. *Journal of the American Medical Association, 285*, 2743–2749.

Scott, C. R., Elliot, S., Glass, M., Buroker, N., Thomas, L., Keutzer, J., et al. (2011). Gelb MH (2011) Application of a triplex assay by MS/MS for the detection of Fabry, Pompe, and MPS-I within a newborn screening laboratory. 7th WORLD symposium

Sims, K., Politei, J., Banikazemi, M., & Lee, P. (2009). Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: Natural history data from the Fabry registry. *Stroke, 40*, 788–794.

Sørensen, S. A., & Hasholt, L. (1983). Attitudes of persons at risk for Fabry's disease towards predictive tests and genetic counseling. *Journal of Biosocial Science, 15*, 89–94.

Street, N. J., Yi, M. S., Bailey, L. A., & Hopkin, R. J. (2006). Comparison of health-related quality of life between heterozygous women with Fabry disease, a healthy control population, and patients with other chronic disease. *Genetics in Medicine, 8*(6), 346–353.

Stryker, V. L., & Kreps, C. (2001). Fabry disease. *The American Journal of Nursing, 101*, 39–44.

Tøndel, C., Bostad, L., Larsen, K., et al. (2013). Agalsidase benefits renal hisotology in young patients with Fabry disease. *Journal of the American Society of Nephrology, 24*, 137–148.

Uhlmann, W. R., Schuette, J. L., & Yashar, B. (2009). *A guide to genetic counseling* (2nd ed.). Hoboken: Wiley Blackwell.

Vedder, A. C., Linthorst, G. E., Houge, G., Groener, J. E., Ormel, E. E., Bouma, B. J., et al. (2007). Treatment of Fabry disease: outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2mg/kg. *PLoS One, 2*(7), e598.

Waldek, S., Patel, M. R., Banikazemi, M., Lemay, R., & Lee, P. (2009). Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry registry. *Genetics in Medicine, 11*(11), 790–796.

Wang, R. Y., Lelis, A., Mirocha, J., & Wilcox, W. R. (2007). Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genetics in Medicine, 9*(1), 34–45.

Wang, R. Y., Bodamer, O. A., Watson, M. S., Wilcox, W. R., & on behalf of the ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. (2011). Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. *Genetics in Medicine, 13*(5), 457–484.

Watt, T., Burlina, A. P., Cazzorla, C., Schönfeld, D., Banikazemi, M., Hopkin, R. J., et al. (2010). Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry. *Genetics in Medicine, 12*(11), 703–712.

Weil, J. (2000). *Psychosocial genetic counseling*. Oxford: Oxford University Press.

Wertz, D., Fanos, J. H., & Reilly, P. R. (1994). Genetic testing for children and adolescents: who decides? *Journal of the American Medical Association, 272*, 875–881.

Wilcox, W. R., Oliveira, J. P., Hopkin, R. J., Ortiz, A., Banikazemi, M., Feldt-Rasmussen, U., et al. (2008). Females with Fabry disease frequently have major organ involvement: lessons from the Fabry registry. *Molecular Genetics and Metabolism, 93*(2), 112–128.

Williams, J. K., Schutte, D. L., Evers, C., & Holkup, P. A. (2000). Redefinition: coping with normal results from predictive gene testing for neurodegenerative disorders. *Research in Nursing & Health, 23*, 260–269.

Wise, D., Wallace, H. F., & Jellinek, E. H. (1962). Angiokeratoma corporis diffusum. *Oxford Journals Medicine New Series, XXXI*(122), 177–212.

Yasuda, M., Shabbeer, J., Benson, S. D., Maire, I., Burnett, R. M., & Desnick, R. J. (2003). Fabry disease: characterization of alpha-galactosidase A double mutations and the D313Y plasma enzyme pseudodeficiency allele. *Human Mutation, 22*, 486–492.

Zarate, Y. A., & Hopkin, R. J. (2008). Fabry's disease. *Lancet, 372*(9647), 1427–1435.