Fabry Disease: Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy in Canada

Lorne A. Clarke[1], Joe T.R.Clarke[2], Sandra Sirrs[3], Michael L West[4], R. Mark Iwanochko[5], John R. Wherrett[5], Cheryl R. Greenberg[6], Alicia K.J. Chan[7], Robin Casey[8].

1. Department of Medical Genetics, University of British Columbia, Vancouver, B.C.

2. Department of Pediatrics, University of Toronto and Hospital for Sick Children, Toronto, Ont.

3. Department Medicine, Division of Endocrinology, University of British Columbia, Vancouver, B.C.

4. Department of Medicine, Division of Nephrology, Dalhousie University, Halifax, N.S.

5. Department of Medicine, University of Toronto, Toronto, Ont.

6. Departments of Pediatrics and Medical Genetics University of Manitoba, Winnipeg, MB.

7. Department of Medical Genetics, Stollery Children's Hospital; Edmonton, Alb.

8. Departments of Pediatrics and Medical Genetics University of Calgary, Calgary, Alb.

Corresponding author: Dr. Lorne A. Clarke, Medical Director Provincial Medical Genetics Program, Children's and Women's Hospital, University of British Columbia, 4500 Oak Street, Room C234, Vancouver, B.C. Fax: 604-875-2376, E-Mail: lclarke@cw.bc.ca.

Abstract:

Recent advances in direct enzyme replacement therapy for Fabry disease requires the establishment of diagnostic and management guidelines for this rare genetic disease. The heterogeneity and complexity of this disorder and the expense of enzyme replacement regimes call for national guidelines for management of this devastating disease. Individual Canadian centers and physicians will have limited experience with diagnosis, management and clinical follow up of Fabry patients thus Canadian consensus recommendations are needed to ensure the highest standard of care for Canadian patients and their families. In addition, these recommendations will provide guidance for provincial health care programs in the planning for provision of care for these patients. These guidelines were established by a working group, led by Dr. Lorne Clarke, consisting of physicians from across Canada who are involved in direct care of Fabry individuals and/or provide diagnostic and counseling to Fabry families. Previous clinical studies, published material, and recently established American Fabry treatment guidelines were reviewed by the group and discussed at a panel meeting, which took place in Toronto on May 24, 2003. Support for the panel meeting was provided by Genzyme Canada as an unrestricted grant. Genzyme Corporation had no role in the formation of the guidelines nor the approach or recommendations provided by the panel.

Introduction:

Fabry disease is an X-linked recessive lysosomal storage disorder caused by deficient activity of α-galactosidase A (α-Gal A, also known as ceramide trihexosidase),[1,2] with the resultant accumulation of globotriaosylceramide and other glycosphingolipids.[3-6] The classic Fabry disease phenotype, includes cutaneous, renal, cardiac and cerebrovascular manifestations that

lead to early death. Severely affected patients have either no or very small amounts of detectable enzyme activity. Milder variant phenotypes have been described in which detectable though markedly decreased enzyme activity is present.[7-9] Recent reports indicate that patients may present with isolated end stage renal disease (ESRD) or late onset hypertrophic cardiomyopathy as their initial manifestation. Fabry disease has been reported in 1.2% (6/514) of Japanese males with ESRD [10] and in 6.3 % (5/79) of males with late onset hypertrophic cardiomyopathy. [11]

The disease is pan ethnic, with estimates of incidence ranging from about one in 40,000 to 60,000 males.[5,12] A founder effect exists in Nova Scotia in which an extended kindred has been described. In this region, the frequency of disease is estimated to be as high as 1/15,000.[13] Fabry disease predominantly affects males, although carrier females are also often affected.[5]

Clinical onset of the disease in affected males often occurs in childhood and the initial presenting features of disease may be subtle, thus many cases of Fabry disease are not diagnosed until adulthood (average age 29 years),[5] when the pathology may already be advanced and possibly irreversible. A comprehensive review of Fabry disease management and diagnosis by Desnick et. al. in 2002,[6] has highlighted the importance of the development of guidelines for the medical management of Fabry disease tailored to the Canadian medical community and health care system.

Prior to enzyme replacement therapy, patients have been managed with non-specific treatment for pain, end-stage renal disease, cardiac and cerebrovascular complications. The results of recent clinical trials of α-Gal A replacement have demonstrated that enzyme replacement can prevent further deterioration and in some instances can reverse some of the major pathological consequences of the disease.[14-17]

Enzyme replacement therapy for lysosomal storage disorders is a rapidly progressing area of clinical research and holds much promise for the alleviation of the devastating effects of these rare genetic diseases. This group of genetic diseases is unique in that direct replacement of the gene-based product effectively replaces the missing intracellular enzyme and alters the clinical course. In no other class of single gene disorders is this approach applicable. This form of therapy has been utilized in Canada for Gaucher disease for approximately 14 years and is soon to be available for other lysosomal disorders; including Mucopolysaccharidosis I (MPS I), Pompe disease, and MPS VI.

The establishment of Canadian guidelines for the diagnosis and management of Fabry disease will serve as an initial model for the establishment of a national process for guideline development for other lysosomal storage diseases as well as other rare genetic diseases. The European Agency for Evaluation of Medical Products (EMEA) and the United States Food and Drug Administration (FDA) has approved the use of recombinant alpha galactosidase for the treatment of Fabry disease. The Therapeutic Products Directorate of Health Canada has also recently approved its use with the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) recommendations currently pending common drug review.

Recommendations for Diagnosis and Treatment

Children: Symptoms in childhood are usually subtle and commonly attributed to other causes including functional complaints. Children may experience acute, unexplained episodes of pain, which are often accompanied by fever. In addition, chronic pain or discomfort in the extremities; heat, cold, and exercise intolerance and unexplained gastrointestinal disturbances are reported

commonly in children with Fabry disease. Cutaneous symptoms and signs consisting of angiokeratomas and hypohidrosis may also be noted. Proteinuria if present is generally mild.

Adults: Adults often present with worsening of symptoms, which began in childhood but may also present with isolated end stage renal failure, hypertrophic cardiomyopathy, hearing loss, and stroke. Even in classic Fabry disease, presentation can vary markedly. The frequency of painful episodes may subside during adulthood. In addition the characteristic angiokeratomas may be present only over the genital area.

Criteria for Testing for Fabry Disease:

The availability of therapy, that is more likely to be effective in altering disease progression than disease reversibility, has now brought to light the importance of early diagnosis. In addition, being an X-linked disorder, detection of the proband leads to identification of many other family members at risk and thus complete family pedigree determination is critical in providing early diagnosis and counseling.

Criteria for the consideration of a diagnosis of Fabry disease are highlighted in table I. These are characterized as either major or minor criteria. Adults with one major and one minor or with three minor criteria should be investigated further for Fabry disease. In children less than 16 years of age one major criterion or three minor criteria are sufficient indications for evaluation for Fabry disease. Early in the disease course patients are often misdiagnosed as having the disorders listed in table II.

Diagnostic testing for Fabry disease:

All persons being evaluated for Fabry disease should be assessed in a multidisciplinary setting by individuals with expertise in Fabry disease. Ideally, the team should consist of individuals with expertise in the areas of: nephrology, neurology, metabolic genetics, genetic counseling, molecular genetics, cardiology, and social work.

Laboratory diagnosis of Fabry disease involves the demonstration of markedly deficient or absent α-Gal A activity in plasma or peripheral blood leukocytes. [18] This test can be performed or organized through most genetic centers in Canada.

Confirmation of the diagnosis of Fabry disease in women is more difficult. Carrier detection by enzyme analysis is not reliable since obligate heterozygotes have α-Gal A activities that overlap the normal range. If the index of suspicion is high the demonstration of substrate accumulation in tissues (plasma, urine, renal tissue, cardiac tissue) is diagnostic of Fabry disease. Any woman being evaluated for Fabry disease (according to the criteria in Table 1) should undergo molecular testing for the identification of disease-causing mutations in the GLA gene or haplotype analysis.

With the advent of enzyme replacement and the realization that early symptoms of the disease may be subtle, testing of asymptomatic children is indicated provided that the family has received appropriate genetic counseling and will be provided with appropriate medical follow up.

Prenatal diagnosis of Fabry disease can be performed with cultured amniocytes or chorionic villus samples by showing a deficiency of α-Gal A enzyme activity or by direct mutation testing.

Genetic Counseling:

Identification of an index case can lead to the identification of multiple individuals who are at risk of having the disease or passing the disease to their offspring. Genetic counseling should be available to all individuals and their families.

Medical Follow-up of Fabry disease:

All patients with Fabry disease or found to have α-gal deficiency, should be followed regularly, with comprehensive medical evaluations at least once per year. Suggested schedules of monitoring are shown in Tables III and IV. All females known to carry Fabry disease, or at significant risk of carrying Fabry disease, should be considered at risk for developing complications of the disease, and should be evaluated by a physician with expertise in Fabry disease. Symptomatic carriers should be followed annually according to the monitoring protocol shown in Table III and asymptomatic females should be re-evaluated less frequently but at least every two years with particular emphasis on cardiovascular and cerebrovascular complications of the disease.

Treatment guidelines:

Risk Factor Management:

Specific attention should be paid to risk factors for coronary artery disease and stroke and treated appropriately. Patients identified with Fabry disease or carriers of Fabry disease should be considered a very high risk for vascular events and therefore, other risk factors for vascular events such as hypertension, dyslipidemia and diabetes should be appropriately and aggressively addressed [19]. Hypertension should be promptly and effectively treated in order to minimize renal, cardiovascular, and cerebrovascular disease. An angiotensin converting enzyme (ACE) inhibitor

or an angiotensin receptor blocker (ARB, in patients intolerant of ACE inhibitors) should be considered in the treatment of hypertension associated with Fabry disease. There is currently no evidence that the use of ACE inhibitors in the context of Fabry disease will significantly benefit the proteinuria or impact renal function. Prophylaxis of vascular events with ASA should be considered for all patients provided they do not have contraindications for ASA use. Failure of ASA prophylaxis may be an indication for additional antithrombotic agents. In addition, patients with Fabry disease should not smoke and thus smoking cessation counseling should be offered.

Pain and painful episodes: Lifestyle modifications (in particular, avoidance of stimuli that precipitate Fabry pain i.e. fatigue, lack of sleep) and certain prophylactic medications can be useful for symptom management. Diphenylhydantoin (Dilantin), [20] carbamazepine (Tegretol), [21] and gabapentin (Neurontin) [22] have been found to be effective in some patients. Nonsteriodal anti-inflammatory drugs, serotonin re - uptake inhibitors or tricyclic antidepressants may be used for intermittent pain. Chronic, debilitating pain is managed best by an expert in pain management.

Abdominal complaints (e.g. pain, diarrhea): Pancrelipase or metoclopramide can improve gastrointestinal symptoms.[23]

Advanced renal disease: Dialysis and/or transplantation often prolongs life but does not alter the course of disease in other organ systems.[24]

Cardiac disease: These patients often require care of a cardiologist for progressive heart disease, recognizing that some patients may even require cardiac transplantation.

Psychosocial Support: Due to the chronic debilitating nature of Fabry disease the psychosocial needs of this group are considerable.

Enzyme replacement therapy:

The guidelines for enzyme replacement therapy are evolving, as the experience with this form of therapy is limited. Although Fabry disease may not present clinically until adulthood, it is clear that the pathological changes begin early in childhood. Thus it is expected that the best long-term outcome will be seen with early commencement of therapy. As the published studies have been performed on patients who have in many cases, had advanced disease, the application of this information to specific guidelines is complex. Thus, data from current clinical trials are not helpful in determining when and which patients should be treated, nor allow conclusions as to the ultimate effect of early therapy on disease course. We conclude that enzyme replacement therapy should be considered in patients, of any age who meet any of the following criteria.

1) Renal function:

Declining renal function (baseline age adjusted creatinine clearance is less than 80 ml/min) or persistent decline of 10% of renal function is an indication for enzyme replacement therapy. Proteinuria alone is not considered an indication for enzyme replacement therapy at present.

2) Cardiac:

Any patient with Fabry disease and cardiac disease as defined in the criteria (Table I) for cardiac diagnosis should be considered a candidate for enzyme replacement if they have:

1. Two major cardiac criteria.
2. One major and one minor cardiac criterion.

3. Three minor cardiac criteria.

3) Neurological:

Transient ischemic attacks documented by a neurologist or early onset CNS infarction or unexplained, progressive white matter changes identifiable as microvascular changes on magnetic resonance imaging.

4) Gastrointestinal:

Severe GI symptoms: intractable abdominal pain and diarrhea, refractory to other therapies.

5) Pain:

Intractable neuropathic pain refractory to other therapies

Further recommendations and comments:

Further outcome studies in patients who have had therapy commenced early in their disease will be needed to refine these guidelines. Although it is hoped that early initiation of therapy i.e. prior to significant disease manifestations or complications, may result in improved outcomes for patients, this has yet to be systematically studied. In addition, further studies are necessary to establish the optimum dose of recombinant enzyme that will lead to prevention of storage or reversal of specific disease manifestations. The role of enzyme replacement therapy for Fabry disease in childhood also requires systematic investigation. For all of these reasons, we urge that Canadian patients with Fabry disease be entered into a confidential registry that will capture demographic and treatment status to direct future research and refinement of treatment.

References

1. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N Engl J Med 1967; 276:1163-7

2. Kint JA. Fabry's disease: alpha-galactosidase deficiency. Science 1970; 167(922):1268-9.

3. Sweeley CC, Klionsky B. Fabry's disease: classification as sphingolipidosis and partial characterization of a novel glycolipid. J Biol Chem 1963; 238:3148-50.

4. Brady RO, Schiffman RS. Clinical features of and recent advances in therapy for Fabry disease. JAMA 2000; 284:2771-5.

5. Desnick RJ, Ioannou YA, Eng CM. α Galactosidase A deficiency: Fabry disease. In: The Metabolic Bases of Inherited Disease. New York: McGraw Hill, 2001; 3733-74.

6. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, Grabowski G, Packman S, Wilcox, WR. Fabry Disease, an under-recognized multisysyemic disorder: expert recommendations for diagnosis, management and enzyme replacement therapy. An Intern Med. 2003;138:338-46.

7.von Scheidt W, Eng CM, Fitzmaurice TF, Erdmann E, Hübner G, Olsen EGJ, Christomanou H, Kandolf R, Bishop D, Desnick RJ. An atypical variant of Fabry's disease with manifestations confined to the myocardium. N Engl J Med 1991; 324:395-9.

8. Nakao S, Takenaka T, Maeda M, Kodama C, Takana A, Tahara M, Yoshida A, Kuriyama M, Hayashibe H, Sakuraba H, Tanaka H. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med 1995; 333:288-93.

9. Yoshitama T, Nakao S, Takenaka T, Teraguchi H, Sasaki T, Kodama C, Tanaka A, Kisanuki A, Tei C. Molecular genetic, biochemical, and clinical studies in three families with cardiac Fabry's disease. Am J Cardiol 2001; 87: 71-5.

10. Nakao S, Kodama C, Takenaka T, Tanaka A, Yasumoto Y, Yoshida A, Kanzaki T, Enriquez AL, Eng CM, Tanaka H, Tei C, Desnick RJ. Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. Kidney Int. 2003 Sep;64(3):801-7.

11. Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, Elliott PM. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation 2002;105:1407-11.

12. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999a; 281:249-54.

13. West M, Dyack S, Riddell C, LeMoine,K, Camfield C, Camfield, P. A Nova Scotia kindred with Fabry disease. Acta Paed 2002, 91:439S:116.

14. Schiffmann R, Murray GJ, Treco D, Daniel P, Sellos-Moura M, Myers M, Quirk JM, Zirzow C, Borowski M, Loveday K, Anderson T, Gillespie F, Oliver KL, Jeffries NO, Doo E, Liang TJ, Kreps C, Gunter K, Frei K, Crutchfield K, Selden RF, Brady RO. Infusion of alpha-galactosidase A reduces tissue globotriaosylceramide storage in patients with Fabry disease. Proc Natl Acad Sci U S A 2000; 97:365-70.

15. Eng CM, Banikazemi M, Gordon RE, Goldman M, Phelps R, Kim L, Gass A, Winston J, Dikman S, Fallon JF, Brodie S, Stacy CB, Mehta D, Parsons R, Norton K, O'Callaghan M, Desnick RJ. A Phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetic, substrate clearance, and safety studies. Am J Hum Genet 2001a; 68:711-22.

16. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Lidthorst GE, Desnick RJ. A multicenter randomized, double-blind, placebo-controlled study of the safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry disease. N Engl J Med 2001b; 345: 9-16.

17. Schiffmann R, Kopp JE, Austin HA, Sabnis S, Moore DF, Weibel T, Balow JE, Brady RO. Enzyme replacement therapy in Fabry disease. A randomized controlled trial. JAMA 2001; 285: 2743-9.

18. Desnick RJ, Allen KY, Desnick SJ, Raman MK, Bernlohr RW, Krivit W. Fabry's disease: enzymatic diagnosis of hemizygotes and heterozygotes. Alpha-galactosidase activities in plasma, serum, urine, and leukocytes. J Lab Clin Med 1973;81:157-71.

19. Genest J, Frohlich J, Fodor G, McPherson R; Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. CMAJ. 2003 Oct 28;169(9):921-4.

20. Lockman LA, Hunninghake DB, Krivit W, Desnick RJ. Relief of pain of Fabry's disease by diphenylhydantoin. Neurology 1973, 23:871-5.

21. Lenoir G, Rivron M, Gubler MC, Dufier JL, Tome FS, Guivarch M. La maladie de Fabry. Traitement du syndrome acrodyniforme par la carbamazepine. Arch Fr Pediatr 1977; 34:704-16.

22. Germain DP. Fabry disease (α-galactosidase A deficiency): new therapeutic perspectives. J Soc Biol 2002; 196 (2):183-90.

23. Argoff CE, Barton NW, Brady RO, Ziessman HA. Gastrointestinal symptoms and delayed gastric emptying in Fabry's disease: response to metoclopramide. Nucl Med Commun 1998; 19:887-91.

24. Kramer W, Thormann J, Mueller K, Frenzel H. Progressive cardiac involvement by Fabry's disease despite successful renal allotransplantation. Internat J Cardiol 1985; 7:72-5.

Table I: Diagnostic Criteria for Fabry disease

Diagnostic Feature	Details
Major Criteria	
Family history of Fabry disease	
Angiokeratoma	
Renal disease	Renal insufficiency or isolated proteinuria
Corneal whorls	
Acroparesthesias	Hands and feet
Hypertrophic cardiomyopathy	LV wall thickness (either posterior wall or septum) greater than 13mm. Measurement to be obtained by either MRI, or 2D echocardiography. LVH by ECG using Estes-Rohmhilt criteria. ECG score must be 5 or greater. LV mass index, either by 2D echo or MRI, must be above normal limit for gender by at least 20%.

Other cardiac criteria (major)	Diastolic filling abnormalities: Must be measured using 2D echocardiography. The E/A ratio must be greater than 2, and the deceleration time (DT) should be 140 msec or less.

Premature TIA and single or multiple small cerebral infarcts documented by a neurologist	Not diabetic, not hypertensive
Minor Criteria	
Chronic gastrointestinal disturbance	Diarrhea, abdominal pain/cramps[not vomiting, nausea]
Hypohidrosis	
Heat intolerance	
Lymphedema	
Hearing impairment, tinnitus	
Postural hypotension	
Cardiac criteria (minor)	Increased left atrial size on 2D echocardiography. In the parasternal long axis view (PLAX) the LA size should be > 33mm, and in the four chamber view it should be > 42mm Conduction abnormalities: AV block, short PR interval (in the absence of known Wolf-Parkinson-White Syndrome), Left bundle branch block. Moderate mitral or aortic insufficiency in the absence of other known valvular abnormalities.

Unexplained MRI white matter changes	
Vertigo	
Monocular blindness (ischemic optic neuropathy)	
Joint pain (arthralgias/arthritis)	Often indistinguishable from arthritis

Table II: Potential Misdiagnoses

Multiple sclerosis
Rhematoid arthritis
Rheumatic fever
Celiac disease, Irritable bowel syndrome, “lactose intolerance”
Neurosis
Porphyria
Ankylosing spondylitis
Raynaud’s phenomenon
Fibromyalgia
Hypertensive nephrosclerosis
Idiopathic hypertrophic cardiomyopathy
Diabetic complications (nephropathy, retinopathy, neuropathy)
Cerebral vasculitis

Table III: Monitoring of adults with confirmed diagnosis of Fabry disease.

Parameter	Baseline	Annually
24 hour urine for protein (or urine protein/creatinine ratio)	✔	✔
Creatinine clearance (24-hour)	✔	✔
Electrolytes	✔	
Urinalysis	✔	
Cardiovascular risk factor analysis as per Canadian guidelines (e.g., lipids)[37]	✔	✔
Homocysteine	✔	
Brain MRI	✔	
Echocardiogram	✔	✔
EKG	✔	✔
Eye exam	✔	
Audiogram	✔	

Table IV: Monitoring of children with confirmed diagnosis of Fabry disease.

Parameter	Baseline	Annually
Urinalysis	✔	✔
EKG (over aged 10)	✔	
Echocardiocram	✔	Biannual
Eye exam	✔	
Audiogram	✔	