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Protocol for Fabry Disease Patients Started on Enzyme Replacement Therapy(ERT)

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Protocol for Fabry disease patients started on ERT:

Background:

Definition: is an X-linked inborn error of glycosphingolipid catabolism. It is multisystem Lysosomal storage disease and it has other names include: Anderson-Fabry Disease or Alpha-Galactosidase A Deficiency.[1,2]

Causes: The disease is caused by a defect in the gene coding for the lysosomal enzyme α-Galactosidase A (*GLA* gene); as a result, the cells of affected individuals are either unable to produce the enzyme or produce it in low amounts. This results in accumulation of glycosphingolipids, mainly globotriaosylceramide (GL-3), in body fluids, in the lysosomes of endothelial, perithelial, and smooth-muscle cells of blood vessels, in ganglion cells, and in many cell types in the heart, kidneys, eyes, and most other tissues.[1,2]

Clinical features:

In classically affected male the following signs should appear as follow:

1. **Acroparesthesias:** onset of symptoms usually occurs in childhood or adolescence with periodic crises of severe pain in the extremities.
2. **Angiokeratomas:** the appearance of vascular cutaneous lesions, dark red to blue-black angiectases in the superficial layers of the skin. The lesions may be flat or slightly raised and do not blanch with pressure. The clusters of lesions are most dense between the umbilicus and the knees; they most commonly involve the hips, back, thighs, buttocks, penis, and scrotum, and tend to be bilaterally symmetric.
3. **Anhydrosis or hypohidrosis**.
4. **Cornea verticillata**:The characteristic corneal and lenticular opacities. Observed only by slit-lamp microscop
5. **Cardiac and/or cerebrovascular disease** is present in most males with the classic phenotype by middle age. Mitral regurgitation may present early in childhood. Left ventricular hypertrophy, valvular involvement, and conduction abnormalities are early findings. ECG changes including ST segment changes, T-wave inversion, and dysrhythmias such as a short PR interval and intermittent supraventricular tachycardias may be caused by infiltration of the conduction system.
6. Cerebrovascular manifestations result primarily from multifocal small vessel involvement and may include thrombosis, transient ischemic attacks (TIA), basilar artery ischemia and aneurysm, seizures, hemiplegia, hemianesthesia, aphasia, labyrinthine disorders, or frank cerebral hemorrhage and stroke.
7. **Renal involvement.** Progressive glycosphingolipid accumulation in the kidney interferes with renal function, resulting in azotemia and renal insufficiency.
8. **Other features:**
    a. **GI involvement:** may cause episodic diarrhea, nausea, vomiting, bloating, cramping abdominal pain, and/or intestinal malabsorption
    b. **Pulmonary:** Several affected individuals have had pulmonary involvement, manifest clinically as chronic bronchitis, wheezing, or dyspnea.
    c. **Vascular.** Pitting edema of the lower extremities may be present in adulthood in the absence of hypoproteinemia, varices, or other clinically significant vascular disease
    d. **Cranial nerve VIII involvement.** High-frequency hearing loss, tinnitus, and dizziness have been reported.
    e. Psychological. Depression, anxiety, severe fatigue, and other psychosocial manifestations lead to decreased quality of life in many affected individuals.

Heterozygous females can be as severely affected as hemizygous males, although the range of symptoms varies widely. A frequent clinical finding in females is the characteristic whorl-like corneal epithetlial dystrophy observed by slit-lamp microscopy (cornea verticillata).[1-3]

Diagnosis: The diagnosis is suspected when there is clinical findings and an increase of plasma (lyso) Gb3. It confirmed by deficiency of the enzyme on dry blood spot or white blood cell or cultured fibroblasts and DNA molecular testing of *GLA* gene. of note, many carrier females have normal α-Gal A enzyme activity and the diagnosis only achieved by molecular testing.

Diagnostic criteria for Fabry disease[4, 5]:

Males	Females
GLA mutation	**GLA mutation**
+	+
AGAL-A deficiency of ≤5% of mean reference value in leukocytes	**Normal or deficient AGAL-A in leukocytes**
+	+
A or B or C	
A	
≥1 characteristic FD sign/symptom (Fabry neuropathic pain, cornea verticillata or clustered angiokeratoma	
B	
Increase of plasma (lyso)Gb3 (within range of males with definite FD diagnosis)	
C	
A family member with a definite FD diagnosis carrying the same GLA mutation	
Uncertain diagnosis of FD (Males/Females	
All patients presenting with a non-specific FD sign (such as LVH, stroke at young age, proteinuria) who do not fulfil the criteria for a definite diagnosis of FD have a GLA variant of unknown significance. Further evaluations are needed, following diagnostic algorithms	
Gold standard for uncertain FD diagnoses	
In subjects with an uncertain FD diagnosis, the demonstration of characteristic storage in the affected organ (e.g. heart, kidney, aside from skin) by electron microscopy analysis, according to the judgment of an expert pathologist, in the absence of medication that can lead to storage, confirms FD	

Treatment: includes symptom-based interventions, enzyme replacement therapy with Replagal® (Agalsidase-alpha) or Fabrazyme®(Agalsidase-beta).[1-3]

Purpose: The purpose of this policy is to dictate the management of patients with Fabry disease who are eligible for enzyme replacement therapy.

Baseline assessments and investigations prior to initiation of enzyme replacement therapy(ERT)[6]:

- **General:**
  - Height, Weight, Head circumference
  - Blood pressure
  - Pain score (Brief Pain Inventory-BPI)
  - Age appropriate Quality of Life score (SF-36 or EQ5D)
  - Severity Score Index – MSSI (Whybra et al 2004)[7]
- **Cardiac:**
  - ECG
  - 24 hours Holter monitor
  - Echocardiogram
- **Renal:**
  - Assess Glomerular filtration rate (GFR) by Tc99m-MAG3 (mercaptoacetyltriglycine) or Tc99m-DTPA (diethylenetriaminepentacetate).
  - Urine analysis
  - 24 Hour urine protein
  - Spot urine Alb/Creatinine ratio
  - Renal biopsy- at the discretion of the renal physician
- **Neurology:**
  - MRI brain examination
  - quantitative sudomotor axon reflex testing (QSART) assessment of sweating (where available)
  - EMG where neuropathy clinically apparent
- **Opthalmology:**
  - Slit-lamp examination (cornea verticillata)
  - Retroillumination (AFD cataract)
  - Retinal examination (vascular abnormalities)
- **Audiology:**
  - Pure tone audiogram

- **Laboratory Investigations:**
  - Full blood count
  - Urea & electrolytes
  - Liver function tests
  - Fasting lipid profile
  - Plasma Gb3(globotriaosylceramide)
  - Enzyme activity level
  - DNA molecular testing for *GLA* gene

- **Urine**
  - Albumin/creatinine ratio
  - Urine Gb3

Consensus criteria for initiation of ERT[5]

	No signs or symptoms	Renal	Cardiac	CNS	Pain	GI
Classical FD, Males	if ≥ 16 years of age	1. Microalbuminuria 2. Proteinuria 3. Renal insufficiency(GFR:45-90)	1. Cardiac hypertrophy (Maximal Wall Thickness > 12 mm(without (or only minimal signs of fibrosis) 2. Signs of cardiac rhythm disturbances	1. White matter lesions 2. Transient ischemic attack /Stroke 3. Hearing loss	Neuropathic pain	GI symptoms
Non-classical FD, Males		Same except Renal insufficiency(GFR:60-90)	Same	Same	Same	Same
Classical FD, Females	Same as classical male					
Non-classical FD, Females	Same as classical male					

Consensus criteria for NOT starting ERT[5]:

1. Advanced cardiac disease with extensive fibrosis
2. End stage renal disease, without an option for renal transplantation, in combination with advanced heart failure
3. End stage FD or other comorbidities with a life expectancy of < 1 year
4. Severe cognitive decline of any cause

Consensus criteria for STOP ERT[5]:

1. Non-compliance > 50% of infusions
2. Failure to attend regularly (according to local guidelines) at FU visits
3. Persistent life threatening or severe infusion reactions that do not respond to prophylaxis, e.g. anaphylaxis
4. Patient request
5. End stage renal disease, without an option for renal transplantation, in combination with advanced heart failure
6. End stage FD or other comorbidities with a life expectancy of < 1 year
7. Severe cognitive decline of any cause
8. Lack of response for 1 year when the sole indication for ERT is neuropathic pain while receiving maximum supportive care

Enzyme replacement therapy(ERT) administration protocol:

Premedication (1 hour prior to ERT infusion) with:

- Acetaminophen (10-15 mg/kg) PO; _____ (mg) PO.
- Diphenhydramine (1mg/kg) IV; _____(mg) IV.
- Methylprednisolone (1mg/kg) IV; _____ (mg) IV.

➢ Replagal™ (Agalsidase alfa)[8]

- **Dose:** 0.2mg/kg IV every 2 weeks.
- **Strength:** 3.5mg/3.5ml, single-use vials.
- Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example if the patient Weight 30 kg give 7 mg instead of 6 mg.

- **Weight:** _____(kg): **calculated dose** _____(mg) IV.

- **Dilution**:
  Dilute the total volume of Replagal® concentrate required in 100 ml normal saline

Infusion rate:[8]

- Infuse over 40 minutes using a dedicated IV line with filter. Do not infuse other agents through same IV line.
- Interrupt infusion in the presence of infusion-related reactions (eg, chills, flushing, dyspnea, rigors, tachycardia, urticaria). Infusion may be restarted after 5-10 minutes if symptoms subside or after administration of analgesics, antipyretics, antihistamines, and/or corticosteroids.

The total volume of the administration should be delivered in approximately 40 minutes.

Or

➢ Fabrazyme® (Agalsidase beta)[9]

- **Dose:** 1 mg/kg IV every 2 weeks.
- **Strength:** 5 mg and 35mg, (5mg/ml), single-use vials.
- Please round the dose up to the nearest whole vial in order not to waste any amount of the enzyme. For example if the patient Weight 32 kg give 35 mg instead of 32 mg.

- **Weight:** _____(kg): **calculated dose** _____(mg) IV.

- **Dilution**:

Recommended Minimum Volumes for Dilution	
Patient weight (kg)	**Minimum total volume (mL)**
< 35	50
35.1 - 70	100
70.1 - 100	250
> 100	500

Special Precautions:

- **Stable only in Normal Saline.**
- The diluted Naglazyme® solution should be filtered through a 0.2 µm, low protein-binding, in-line filter during administration to remove any visible particles.

Infusion rate:[9]

- IV: Initial infusion not to exceed 15 mg/hour (0.25 mg/minute); after patient tolerance to initial infusion rate is established, the infusion rate may be increased in increments of 3 to 5 mg/hour (0.05- to 0.08 mg/minute) with subsequent infusions.

- Per the manufacturer's recommendation:

- For patients weighing <30 kg, the maximum infusion rate should remain at 0.25 mg/min.
- For patients weighing >30 kg, the administration duration should not be less than 1.5 hours (based upon individual tolerability).
- An initial maximum infusion rate of 0.01 mg/minute should be used for rechallenge in patients with IgE antibodies; may increase infusion rate (doubling the infusion rate every 30 minutes) to a maximum rate of 0.25 mg/minute as tolerated.

Nurses: Monitor vital signs during (prior to each rate increase) and up to 1 hour following infusion. If abnormal, contact the physician to decrease the rate or temporarily hold the infusion.

Undesirable effects: anaphylaxis and allergic reactions, infusion reactions, and immune mediated reactions, Very common adverse reactions included chills, pyrexia, feeling cold, nausea, vomiting, headache and paraesthesia.

Note:

- If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of Replagal® or Fabrazyme ® and initiate appropriate medical treatment.
- If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, or administering additional antipyretics and/or antihistamines may ameliorate the symptoms.

Monitoring the response to enzyme replacement therapy:[5,6]

	Every 3 months	Every 12 months
General		
Medical history **Physical examination** **General appearance**	**X**	
Pain score	**X**	
Quality of Life score (SF-36 or EQ5D)	**X**	
Mainz Severity Score Index	**X**	
Lab test		
CBC, diff **Electrolytes** **Liver enzymes** **CPK level** **Bone profile and vitamin D levels** **Fasting lipid profile**	**X**	
Urine test		
Urine analysis	**X**	
Albumin/Creatinine ratio	**X**	
Plasma and urine Gb3		**X**
GFR and 24 hour urinary protein		**X**
IgG and IgEantibody testing		**X**
Neurology		
MRI of brain		**X**
ENT evaluation (audiometry and ABR test)		**X**
Ophthalmology evaluation(visual acuity, retinal examination, corneal examination)		**X**
Cardiology evaluation (ECG, 24 hour holter monitor, Echocardiogram)		**X**

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