Diagnosis and Management of Gaucher Disease in India – Consensus Guidelines of the Gaucher Disease Task Force of the Society for Indian Academy of Medical Genetics and the Indian Academy of Pediatrics

RATNA DUA PURI[1], SEEMA KAPOOR[2], PRIYA S KISHNANI[3], ASHWIN DALAL[4], NEERJA GUPTA[5], MAMTA MURANJAN[6], SHUBHA R PHADKE[7], ANUPAM SACHDEVA[8], ISHWAR C VERMA[1] AND PRAMOD K MISTRY[9]; FOR THE GAUCHER DISEASE TASK FORCE

From [1]Institute of Medical Genetics and Genomics, and [8]Pediatric Hematology Oncology and Bone Marrow Transplantation unit, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India; [2]Department of Pediatrics, Maulana Azad Medical College, New Delhi, India; [3]Pediatrics Medical Genetics, Duke University Medical Center, USA; [4]Diagnostics Division, Centre for DNA Fingerprinting and Diagnostics, Hyderabad, Andhra Pradesh, India; [5]Division of Genetics, All India Institute of Medical Education and Research, New Delhi, India; [6]Department of Clinical Genetics, Seth GS Medical College and KEM Hospital,Mumbai, India; PD Hinduja National Hospital and Medical Research Centre, Mumbai, India; [7]Department of Genetic Medicine, Sanjay Gandhi Postgraduate Institute, Lucknow, India; [9]Metabolic Liver and Lysosomal Disease Program, Yale University School of Medicine, New Haven, USA.

Correspondence to: Dr Ratna Dua Puri, Professor, Institute of Medical Genetics and Genomics, Room Number 027, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi 110 060, India.

Justification: Gaucher disease (GD) is amongst the most frequently occurring lysosomal storage disorder in all ethnicities. The clinical manifestations and natural history of GD is highly heterogeneous with extreme geographic and ethnic variations. The literature on GD has paucity of information and optimal management guidelines for Indian patients.

Process: Gaucher Disease Task Force was formed under the auspices of the Society for Indian Academy of Medical Genetics. Invited experts from various specialties formulated guidelines for the management of patients with GD. A writing committee was formed and the draft guidelines were circulated by email to all members for comments and inputs. The guidelines were finalized in December 2016 at the annual meeting of the Indian Academy of Medical Genetics.

Objectives: These guidelines are intended to serve as a standard framework for treating physicians and the health care systems for optimal management of Gaucher disease in India and to define unique needs of this patient population.

Recommendations: Manifestations of GD are protean and a high index of suspicion is essential for timely diagnosis. Patients frequently experience diagnostic delays during which severe irreversible complications occur. Leucocyte acid β-glucosidase activity is mandatory for establishing the diagnosis of Gaucher disease; molecular testing can help identify patients at risk of neuronopathic disease. Enzyme replacement therapy for type 1 and type 3 Gaucher disease is the standard of care. Best outcomes are achieved by early initiation of therapy before onset of irreversible complications. However, in setting of progressive neurological symptoms such as seizures and or/ neuroregression, ERT is not recommended, as it cannot cross the blood brain barrier. The recommendations herein are for diagnosis, for initiation of therapy, therapeutic goals, monitoring and follow up of patients. We highlight that prevention of recurrence of the disease through genetic counseling and prenatal diagnosis is essential in India, due to uniformly severe phenotypes encountered in our population.

Keywords: *Enzyme replacement therapy, Genetic counselling, Lysosomal storage disorder, Treatment*.

Gaucher disease (GD) is the commonest lysosomal storage disorder (LSD) with an estimated global incidence of 1: 40,000 to 1:60,000 live births [1]. The metabolic defect is a deficiency of acid β-glucosidase (lysosomal glucocerebrosidase) due to biallelic mutations in *GBA* gene that results in the accumulation of glucocerebroside in lysosomes, classically in tissue macrophages; other cell types involved in disease pathophysiology include immune cells, osteoblasts and hepatocytes [2]. Glucocerebroside-laden macrophages (Gaucher cells) accumulate throughout the body and this is the hallmark of multi-systemic disease manifestations. The severity and pattern of organ involvement is highly heterogeneous and only partly explained by *GBA* mutations.

Gaucher disease represents a prototype of rare lysosomal diseases for development of diagnostic and management algorithms based on regional characteristics

as well as transformative therapies, including Enzyme replacement therapy (ERT) and recently approved, oral Substrate reduction therapy (SRT). In case of diagnostic delay, patients suffer from disabling and potentially life-threatening complications. Hence, it is important to diagnose and manage Gaucher disease in a timely and optimal manner. We herein provide guidelines and recommendations for an optimal approach to diagnosis and management of Gaucher disease in Indian patients.

GAUCHER DISEASE IN INDIA

Gaucher disease is a pan-ethnic disorder; although, most published literature is almost entirely focused on Caucasian patients [4]. Due to the tradition of consanguineous marriages in parts of the country, it seems likely that the frequency of Gaucher disease may be higher in India. Of more than 300 mutations catalogued in Gaucher disease, L444P appears to be the most prevalent in India [5]. This mutation occurs normally in the pseudogene sequence; vulnerability of *GBA* locus to gene conversion events underlies relatively high prevalence of this mutation world-wide. We have found that homozygosity for L444P mutation is most common genotype in most parts of the country while in the northern region, in addition to L444P, there is a relatively higher rate of rare private mutations [5,6]. Homozygosity for L444P mutation typically results in neuronopathic disease but within this group there is extreme variation, which can range from lethal collodion skin baby phenotype at birth to a less severe type III phenotype with minimal oculomotor apraxia as the sole neurologic abnormality [7]. Knowledge of *GBA* genotype of individual patients is helpful to guiding optimal monitoring, estimating prognosis, timing of enzyme therapy and genetic counseling.

Traditionally, Gaucher disease patients are classified into three broad phenotypes based on the presence or absence of neurological manifestations and their severity (***Table* I**). However there is a continuum of phenotypes, ranging from mildly affected adults to the severe, life-threatening manifestations of type 2 patients presenting with non-immune hydrops fetalis and neurodegenerative disease [8]. Patients with type 1 Gaucher disease in India present from as early as infancy to late childhood with a median age of 3.6 years [9]. This highly aggressive phenotype with spleno-hepatomegaly, cytopenia, irritability, bone involvement and failure to thrive is associated with early mortality without treatment [10]. The common differential diagnosis of the most prevalent presenting phenotype of splenohepatomegaly in Gaucher disease include hemolytic anemias typically hemoglobinopathies, non-cirrhotic portal hypertension, tropical splenomegaly, lymphoreticular malignancies and

TABLE I CLINICAL FEATURES OF GAUCHER DISEASE

	Type 1 *Non-neuronopathic*	*Type 2 (acute/infantile)*	*Type 3 (sub-acute/chronic/juvenile)* *Neuronopathic*		
			Type 3a	Type 3b	Type 3c
Incidence (live births)	~ 1:40,000 - 1: 60,000	<1: 100,000	<1: 50,000 - <1: 100,000		
Ethnic origin	Pan-ethnic / Ashkenazi Jews	Pan-ethnic	Pan-ethnic/ norrbottnian Sweden		
Age at onset	Infancy to adulthood	Perinatal/ birth/ infancy	Childhood/adolescence		
Progression	Variable	Rapid, death by 2 yrs of age	Variable		
Neurological manifestations	Absent	Bulbar & oculomotor paresis	++ to +++ Progressive myoclonus & dementia	+ to ++ Horizontal supranuclear gaze palsy	+ Impaired horizontal ocular saccades, corneal opacities
Splenohepatomegaly	+ to +++	++	+	+++	+
Skeletal disease	+ to +++	-	+/-	++ to +++	+
Pulmonary disease	+ to +++	+++	++ to ++	++ to +++	+/-
Cardiac valvular disease					cardiac/aortic valvular calcification

other storage disorders. Type 3 disease is relatively more common in India as compared to Western populations [11]. The earliest and most common neurological manifestation in these patients includes oculomotor apraxia. This ocular sign must be evaluated in each patient at every clinic visit as it may help to distinguish between Type 1 and type 3 GD [4]. A perinatal lethal variant is a severe manifestation presenting *in utero* or at birth as non-immune hydrops fetalis, isolated fetal ascites, collodion baby and hepatosplenomegaly [8,12]. A high index of suspicion is important to delineate this phenotype in such cases to help families through appropriate genetic counseling.

The multisystem involvement in GD may result in complications that involve multiple organ systems [10,13-18]. These are common to all types of GD with the exception of neurological disease that is typically seen in type 2 and type 3 GD with milder manifestations in the latter (***Box* 1**). Multispecialty referral is tailored dependent on the manifestations and complications encountered in the patient.

RECOMMENDATIONS

Investigations in a Suspected Patient

Enzyme diagnosis: The gold standard for diagnosis of Gaucher disease is acid β-glucocerebrosidase enzyme assay in blood leucocytes; Gaucher disease patients have levels ≤10% of controls. The sample should be collected in ethylenediaminetetraacetic acid (EDTA) or heparin vacutainers. An alternative that overcomes logistical difficulties in sending blood samples across long distances to arrive in good condition at the laboratory is dried blood spots (DBS). This is the recommended sample for GD diagnosis in India [19]. Collection of sample needs to be optimal to avoid false results. Cultured skin fibroblasts may occasionally be required for enzyme activity estimation in cases where the blood reports are ambiguous; latter may arise in rare cases of Gaucher disease due to saposin deficiency or *GBA* mutations that lead to trafficking defect of the mutant enzyme (*i.e.*, G202R) [20] or when the differential diagnosis include Niemann Pick type C disease, a disorder that may be associated with falsely low acid β-glucosidase activity [21]. Carrier-testing by assay of enzyme activity is unreliable because of overlap in enzyme activity between carriers and non-carriers [22].

BOX 1 COMPLICATIONS IN GAUCHER DISEASE

- Hypersplenism and pancytopenia
- Splenic rupture
- Bleeding diathesis due to thrombocytopenia and acquired coagulopathy
- Fractures and collapsed vertebral bodies, avascular osteonecrosis, chronic bone pain and bone crisis
- Hepatic fibrosis, portal hypertension
- Hepatopulmonary syndrome
- Hematological malignancies - multiple myeloma, hepatocellular carcinoma
- Parkinson's disease with Lewy body dementia
- Progressive neurodegenerative disease in Gaucher disease type 2 and 3

Molecular diagnosis: Molecular testing and identification of the *GBA* mutation confirms the diagnosis and in addition the genotype information aids prognostication, carrier-testing and prenatal diagnosis. These benefits are especially valuable in managing Gaucher disease in India due to high prevalence of L444P mutation, homozygosity for which is associated with neuronopathic disease, type 2 or type 3 [5]. We recommend GBA mutation analysis before initiation of therapy. However, there are >300 known *GBA* mutations catalogued in Gaucher disease and full gene sequencing is required when one or both alleles are other than L444P [23]. Based on published data and experience with patients followed in India, initial testing for L444P and full sequencing of the entire coding regions of G*BA* only when the patient tests negative for this common mutation in either of the two alleles is cost-effective.

Role of tissue biopsy: The common presentation of hepatosplenomegaly with the hematological manifestations in GD patients overlaps other disease phenotypes for which bone marrow aspiration/biopsy are indicated. Gaucher cells in the marrow are classically described in GD; however, their presence or absence does not confirm or preclude the diagnosis of GD. Distribution of Gaucher cells is patchy and not uniform and likely to be missed, especially in aspiration biopsy. Moreover, pseudo-Gaucher cells have been described in disorders unrelated to GD *i.e*., thalassemia, HIV, mycobacterial infection in immunodeficient patients, and hematological malignancies [24-26]. Hence incidental finding of Gaucher cells during work-up of patients mandates enzyme activity measurement. At times, patients undergo liver biopsy after initial presentation with hepatosplenomegaly and mildly elevated liver enzymes. We do not recommend liver biopsy in Gaucher disease for diagnosis due to prohibitive bleeding risk from thrombocytopenia and coagulopathy. It is recognized that patients undergo splenectomy for a misdiagnosis of malignancy or another disorders [27]. We strongly advise that any patient who is considered for splenectomy for splenomegaly of

uncertain diagnosis, mandatory enzymatic testing for lysosomal storage disorders like Gaucher and Niemann Pick disease be performed. This is important as splenectomy in Gaucher disease leads to acceleration of disease in the skeleton, liver and the lungs [28].

Biomarkers in GD: The expert group recommends serial biomarker measurement for longitudinal follow up of all patients to assess disease status. Chitotriosidase and CCL18 have been validated as representative of total body burden of Gaucher cells [29]. The most widely used biomarker in GD is chitotriosidase that is secreted by Gaucher cells. Although serum chitotriosidase is also elevated in several other lysosomal diseases and in thalassemia, the extraordinary elevations of chitotriosidase up to 1000-fold are only seen in Gaucher disease. A relative disadvantage is the presence of a polymorphism in the cognate gene *CHIT1*; about 6% of most ethnicities are homozygous for a null polymorphism and have undetectable chitotriosidase level. Some 30% of individuals are heterozygous for the polymorphism and their chitotriosidase is approximately one-half of that in patients homozygous wild type for the polymorphism [30]. In patients homozygous for null *CHIT1* polymorphism, *CCL18/PARC* that is not subject to genetic variation is a useful alternative biomarker. However, currently this is not available in India. Recently, glucosylsphingosine has been validated as key biomarker of Gaucher disease, that directly reflects root-cause of the disease, and is involved in mediating disease pathophysiology [31].

Management

Management of Gaucher disease needs a multidisciplinary approach and is best coordinated at a center with expertise in this complex disease. The multidisciplinary team generally includes a hematologist, geneticist, gastroenterologist, pediatrician, neurologist, occupational therapist and orthopedic surgeon.

Baseline Assessments

After confirmation of diagnosis, baseline evaluation to establish the extent and severity of the disease is recommended (***Table* II**). This incorporates an exhaustive general physical and neurological examination. Recommended investigations include a complete and differential blood count, liver function tests, serum calcium, 25-hydroxy-vitamin D, coagulation profile, biomarkers, assessment of liver and spleen size and bone by magnetic resonance imaging (MRI), if feasible. Ultrasound scanning for spleen and liver volumes and focal defects in the parenchyma is less expensive [32]. For children, a routine MRI of femurs to assess for marrow infiltration is not recommended due to normal cellular marrow in this age group that cannot be distinguished from pathological infiltration. However, when a patient

TABLE II RECOMMENDED ASSESSMENTS AT BASELINE AND ON FOLLOW-UP IN INDIAN CHILDREN WITH GAUCHER DISEASE

Assessment	*Baseline*	*6 monthly*	*Yearly*	*As indicated*	*After treatment goals attained*
Physical examination including a detailed	√	√			
neurological evaluation	√	√			
Liver size	√	√			
Spleen size	√	√			
Hemoglobin	√	√			Yearly
Total leukocyte count	√	√			Yearly
Platelets	√	√			Yearly
Dual-energy *X*-ray Absorptiometry	√		√		Every 3 years
Ultrasound abdomen	√		√		As indicated
Radiographs spine and pelvis	√		√		As indicated
MRI spine and femur neck (optional)	√		√		As indicated
Chitotriosidase	√		√		
*Pulmonary (optional)					
- Pulmonary function test					
- Computed Tomography chest				√	
Cardiac (2D Echocardiography)				√	

**A better evaluation of pulmonary arterial hypertension diagnosis can be established by a serial doppler echocardiography; Pulmonary function test (above 6 years of age) and CT chest are indicated to evaluate for the uncommon complication infiltrative lung disease which may be clinically evident by progressive breathlessness in the absence of severe anemia.*

complains of pain, MRI is extremely useful to assess for avascular osteonecrosis.

Baseline plain chest and spinal radiograph should be performed to assess for pulmonary infiltration and early spinal deformity, which occur commonly in L444P homozygous patients. DEXA scan to document bone mineral density is ideal due to prevalent osteopenia and fragility fractures in GD, and should be performed if resources are available. Appropriate assessment for pulmonary vascular involvement includes Doppler 2D echocardiography (recommended only in asplenic patients) and high resolution CT Scan chest (HRCT) as there is high risk of pulmonary hypertension in splenectomized Gaucher disease patients. Further follow-up is indicated based on presence of elevated right ventricular systolic pressure in baseline echocardiography [33].

Disease-specific Management

The disease specific management of GD includes enzyme replacement therapy (ERT) and substrate reduction therapy (SRT).

Enzyme Replacement Therapy: The development and availability of ERT since 1991 as a treatment modality has transformed the natural course of the disease in patients affected with GD. Therapy with ERT significantly ameliorates organomegaly and improves hematological manifestations [34-36], as also the skeletal manifestations, prevent avascular necrosis, and reverse, growth failure in Gaucher disease type 1 [37-39]. A longitudinal cohort study of 25 children with GD1 and GD3 with 14 years follow-up reinforced previous reports and showed sustained improvement in hemoglobin, platelet count and bone pain [40]. Generally, patients with Gaucher disease in India are more severely affected than in the West with earlier onset and more severe disease manifestations. Treatment with ERT should be considered even if avascular osteonecrosis has occurred, as studies have shown that risk of such complications is reduced with ERT [41,42]. However, in setting of progressive neurological symptoms such as seizures and or/ neuroregression, ERT is not recommended, as it cannot cross the blood brain barrier. ERT with the recombinant enzyme, Imiglucerase is approved in India and is used for the treatment of patients with a confirmed diagnosis of type 1 GD and the visceral manifestations of type 3 GD. As the cost of therapy is high, stringent criteria have been formulated and are recommended to identify patients who would best benefit from ERT and optimize the outcome of therapy. ***Box* 2** lists the criteria for initiation of ERT.

Although one or more criteria are needed to initiate therapy, in clinical practice most patients commonly present with significant multisystem involvement and have a combination of features making early intervention important. Waiting for the manifestations to progress before initiation will limit the benefit of the treatment and may lead to further deterioration with time [43]. The therapeutic goals that can be attained with ERT should be discussed at length with the patient and the family. In addition to the criteria to initiate enzyme replacement therapy, it is important to discuss with the family and the patient, the need to have life-long intravenous infusions every other week in hospital setting. The final decision on the candidacy of a patient for ERT needs assessment by the physician, that the family and patient will comply with this regimen. In our experience we have noted that some families cannot / are not willing to cope with this additional burden of frequent hospitalization and in this setting it is not wise to embark on enzyme treatment.

Administration of ERT: ERT is a lifelong therapy and administered as an intravenous infusion once every 14 days. Being a recombinant enzyme and requiring reconstitution before infusion, precautions as mentioned in the pack insert should be strictly adhered to achieve the optimum activity of the drug. The standard dose for ERT at initiation is 60 units per kg bodyweight. However,

BOX 2 CRITERIA FOR INITIATION OF ENZYME REPLACEMENT THERAPY

ERT should be initiated in all symptomatic patients with one or more of the following features:

- Failure to thrive (height and weight less than the 5th centile of age after excluding other causes)
- Splenohepatomegaly causing mechanical discomfort or splenic infarctions
- Severe cytopenia (Bicytopenia at least):-
  - Hemoglobin <8 mg/dL) due to GD and not to other causes
  - Platelets <60,000/µL
  - Leucocyte count <3,000/mm^3
- Symptomatic bone disease (bone pain, bone crisis), or active bone disease (osteopenia, fractures, marrow infiltration, infarction, osteonecrosis)
- Prior splenectomy (history of splenectomy is a marker for disease severity and such patients carry a high risk of avascular necrosis and osteonecrosis)
- Symptomatic pulmonary involvement (evidence of pulmonary hypertension on 2D echocardiography, or evidence of Infiltrative lung disease on CT chest)

due to the heterogeneous nature of the disease manifestations, individualized dose modifications on a specific need-basis may be required [43]. If drug availability is limited, an initial dose of 30 units per kg may be used for less severely affected children, but should be increased if treatment goals are not met [44]. The weight of the patient is checked at each assessment and the dose adjusted according to the bodyweight. Total dose to be administered at each infusion can also be partly adjusted based on the need to avoid wastage of the reconstituted drug as the drug is expensive and under no circumstances should be wasted. Pre-infusion medication with antihistaminic/antipyretics is not routinely recommended unless there is history of infusion related reactions. Use of low-protein binding 'in-line' filters of 0.2 microns size is recommended for infusion.

Recommendations on Therapeutic Goals

The multisystem nature of the disease necessitates organ-specific therapeutic goals for patients on treatment. It is essential to set realistic expectations on improvement of the disease phenotype and discuss this with the family prior to initiation of therapy. Patients are followed up based on the clinical features at the time of presentation with a detailed evaluation at each visit to assess the improvement of disease manifestations as a response to therapy. ***Table* III** details the therapeutic goals for patients with GD and their expected timelines of achievement with therapy.

Adverse events with ERT: The ERT in GD is generally well tolerated with few reported adverse events [45,46]. Most adverse events reported are mild and include nausea, vomiting, fever, rash, headache, dyspepsia, diarrhea, headache and dizziness. Local infusion-site reactions may include itching, swelling and discomfort. Anaphylactic reactions have been reported in rare cases and necessary emergency medications must be available prior to infusion in cases at risk. Management of infusion-related reactions include stopping the infusion temporarily and administration of antihistaminic and/or antipyretics. In such cases, the infusion can be restarted slowly after the infusion-related reaction settles down. Severe reactions may need management with steroids.

Indian Experience with Enzyme Replacement Therapy

ERT with Imiglucerase has been in use in India since last 15 years. 75 GD patients have received therapy with Imiglucerase. It has been found to be highly effective and safe, with marked reversal of growth failure, cytopenia, visceral disease and amelioration of skeletal disease [9]. Timely initiation of ERT in these patients has improved the general well-being, growth, and prevented development and progression of complications [47].

Substrate reduction therapy: Substrate reduction therapy (SRT) for GD is based on the principle of using inhibitor of glucosylceramide synthase, the rate-limiting enzyme in synthesis of glucosylceramide to balance residual activity of acid β-glucosidase due to *GBA* mutations. Eliglustat tartrate is an oral SRT that is a powerful and specific inhibitor of glucosylceramide synthase and was approved in US and many other countries as first-line oral therapy in adults with GD type 1 following an extensive clinical trial program since 2007 involving >400 patients. It has shown good safety profile and proven to reverse hematological visceral and skeletal disease, similar to ERT [48]. This promises to be a good option in India, where logistics of life-long 2-weekly intravenous infusions can be challenging, especially in rural areas with limited facilities. For all therapies in GD, excellent compliance is essential.

Supportive Management

This is an extremely important part of management of patients with GD, especially children affected with the disease. It includes correction of nutritional anemia, vitamin D deficiency and improvement of the nutritional status of the paient. Bisphosphonates can be administered if severe osteopenia co-exists. Immunization with vaccines as per the National guidelines and the recommended immunization schedule for splenectomized patients should be followed [49]. We have frequently encountered patients who present dependent on blood transfusions for severe anemia. This is marker of severe end-stage disease and each blood transfusion rarely lasts more that 2-3 weeks and transfused blood cells massively add to the load of glycolipids leading to rapid acceleration of the disease. Dependency on blood transfusion is an urgent indication for ERT with the goal to eliminate the need for blood transfusion. We also recommend withholding splenectomy if therapy with ERT/SRT is feasible in a particular patient, unless it is required as a life-saving measure.

Follow-up and Monitoring

All patients with GD, irrespective of the disease-specific treatment, must be followed up for evaluation of the disease status [32,50]. This should include assessment of all systems likely to be affected in GD. The recommended type and frequency of assessment is shown in ***Table* II**.

Hematopoietic Stem Cell Transplantation

Experience with hematopoietic stem cell transplantation (HSCT) is limited to about 50 cases of neuronopathic and non-neuronopathic GD. With the availability of ERT and its safety and efficacy profile, stem cell transplantation is

TABLE III THERAPEUTIC GOALS [43,44]

Clinical Parameters	*Treatment Goals*	*Timeframe to response*
Symptoms	Feeling of wellbeing, decrease fatigue and irritability	6 - 12 months
	Decreased abdominal distension, improved appetite	
Anemia[1]	Increase of hemoglobin ≥10.0 gm/dL	1-2 years
	Eliminate blood transfusion dependency	1-2 years
Thrombocytopenia[1]	Increase platelet count to prevent surgical, obstetric and spontaneous bleeding	1 year
	Baseline platelet count between 60,000 - <120,000/μL:	
	- approach normal levels	
	- the platelet count should increase by 1.5- to 2.0-fold/ approach normal levels	1 year
	- approach normal levels	2 years
	Baseline platelet count < 60,000/μL:	
	- the platelet count increase by 1.5-fold	1 year
	- continue to increase but normal counts may be unattainable	2-5 years
Hepatomegaly[1]	Decrease in liver size[2]	
	Reduce the liver volume	
	- by 20 to 30 %; and	1-2 Years
	- by 30 to 40 %	3-5 years
Splenomegaly[1]	Avoid splenectomy in all patients[3]	
	Alleviate symptoms - abdominal distension, early satiety, new splenic infarction detected by ultrasound	1 year
	Reduce the spleen volume	
	- by 30 to 50 %; and	1 year
	- by 50 to 60 %	2-5 years
Bones	In all patients: lessen or eliminate bone pain and prevent bone crises	1-2 years
	Prevent fractures; attain bone mineral density commensurate with their age (z-score not t-score)[4]	1-2 years
Growth	Achieve normal weight and height as assessed by WHO growth charts for Indian children upto 10 years of age and BMI thereafter	Within 3 years
	Achieve normal onset of puberty	
Quality of life	Clear improvement in quality of life	1-2 years

[1]Treatment responses may vary depending on associated co-morbidities and individual response to therapy. In some cases the liver and spleen may not regress to the normal size; [2]Ideal volumetric measurement of liver and spleen size is by MRI of liver and spleen. In pediatric patients, the need for sedation and cost of MRI limits its use. Ultrasound is observer dependent but is inexpensive and easily available in India and may be used for serial assessment of liver and spleen size and echotexture in India. Practical modality for monitoring of liver and spleen size is by measuring spans on ultrasonographic examination. However, where facilities are available, objective laid down criteria using MRI evaluation of organ volumes (in multiples of normal) should be followed; [3]Splenectomy is known to worsen bone disease in patients with GD and is associated with an increased susceptibility to infection; [4]Ideal bone mineral density would be attained after correction of associated risk factors affecting bone density like co-existing Vitamin D deficiency.

currently not in general use. A cochrane meta-analysis on the role of HSCT in GD [51] concluded that there were no clinical trials that have assessed HSCT safety and efficacy with that of the approved therapies for GD. A recent review [53] of the follow-up data of patients who underwent HSCT has suggested the need to re-evaluate this modality in selected patients in GD. However, there are no conclusive guidelines recommending the use of HSCT in GD [52]. Our group's consensus opinion is that BMT is not the treatment of choice for type 1 GD due to the associated risk of complications and mortality.

Genetic Counseling and Prenatal Diagnosis

GD is an autosomal recessive disorder with a 25% risk of recurrence in each pregnancy. Pre-test and post-test counseling must be done to ensure that the family understands the risk of disease in each pregnancy, the reproductive options to prevent recurrence, implications of giving birth to a child with GD, and the options available to them if the fetus is identified to be affected.

Currently this is the most important and effective strategy in India to reduce the burden of disease and is commonly requested through all disease phenotypes. A prerequisite to prenatal testing is confirmation of the diagnosis in the affected child by enzyme testing and preferably also mutation identification. Most commonly, chorionic villus sampling is performed at 11-13 weeks of gestation. Prenatal fetal testing is conventionally performed by measurement of enzyme activity in uncultured chorionic villi tissue. Cultured amniotic fluid cells (15-18 weeks) or cord blood (19-20 weeks) can also be used if the family comes in late gestation. Ideally biochemical results should be correlated with mutation studies if the latter are available. It is important to be aware that maternal tissue contamination should be excluded as per guidelines for any prenatal testing. Option for termination of pregnancy is available to the family upto 20 weeks of gestation according to Medical Termination of Pregnancy Act, in case the fetus is affected. Molecular testing is the technique of choice for carrier detection too. It should be offered to extended family members, especially in communities where consanguinity is common. Experience from India related to prenatal diagnosis of lysosomal storage disorders, importance of confirmation of proband diagnosis, and identification of the familial mutations has previously been reported [53,54].

When a child in a family is diagnosed with Gaucher disease, siblings should be screened. Those found to be affected but pre-symptomatic should be monitored to assess rate of progression, if any. There is wide phenotypic variation even among siblings; hence, pre-symptomatic diagnosis is not in itself an indication for therapy. These children should be monitored at 6-monthly intervals for development of cytopenia, splenomegaly and skeletal disease.

CONCLUSION

GD is an inherited pan-ethnic and the most common LSD that commonly manifests in childhood. Detection of β-glucocerebrosidase activity in leucocytes/cultured skin fibroblasts is considered as the most efficient and reliable

KEY MESSAGES FOR DIAGNOSIS AND MANAGEMENT OF GAUCHER DISEASE IN INDIA

- A high index of suspicion is essential for timely diagnosis.
- Leucocyte acid β-glucosidase activity is mandatory for establishing the diagnosis of Gaucher disease and can easily be performed by collecting 4-5 drops of blood on filter paper (similar to that available for newborn screening).
- *GBA* gene analysis for mutations is recommended to confirm the diagnosis and help identify patients at risk of neuronopathic disease.
- Initial screen for L444P mutation is recommended. In the absence of one of two L444P mutations, full sequencing of the entire coding regions of *GBA* is recommended.
- Prenatal testing is best performed by initial genotype determination in the affected proband, confirmation of obligate carrier state in the parents or by testing in family member under investigation.
- Bone marrow biopsy is not essential for diagnosis and the absence of Gaucher cells in the bone marrow does not exclude the diagnosis of Gaucher disease. Liver biopsy or splenectomy should not be performed in Gaucher disease.
- Chitotriosidase is a useful biomarker for serial monitoring of individual patients receiving ERT; it should be used in the context of other clinical indicators of disease activity. Chitotriosidase levels should not be used to compare disease severity among different patients.
- ERT should be considered in patients with Type 1 and Type 3 GD to address the visceral, hematological and skeletal manifestations. The clinical spectrum of L444P in India is extremely variable and detailed assessment for neurological involvement is important before consideration for ERT. ERT is not recommended in Type 2 Gaucher disease or severe type 3 Gaucher disease as the enzyme does not cross the blood brain barrier.
- The need for lifelong therapy and the commitment of the time, money and effort should be discussed in detail with the patient and the caregivers prior to initiation of therapy to ensure compliance.
- The optimum dose of ERT needs to be individualized in patients and will depend upon the body weight and response to ERT.
- Supportive therapy is of paramount importance in patients on or off definitive therapy.
- Genetic counseling forms the mainstay of prevention of future affected births.

method of establishing the diagnosis of GD. Enzyme replacement therapy is proven to be the standard of care in the therapeutic management of symptomatic patients with GD. The dosing regimen is personalized based on the achievement of therapeutic goals. These guidelines provide a systematic and standard framework to the treating physicians and other healthcare providers for the management of GD.

Acknowledgements: Dr Shashi Dhawan, Dept of Pathology, Sir Ganga Ram Hospital, New Delhi for her inputs. We also pay tribute to Late Prof SS Agarwal for steering the group and formation of the ICMR LSD Task Force. We would also bring to record the hard work of the patient support society, Lysosomal Storage Disorders Support Society (LSDSS) details of which can be found at *http://www.lsdss.org/*

Competing Interests: PKM has received research support from Genzyme, Shire and Pfizer. He has received funding from NIH R01 AR 065932, Gaucher Generation Program Senior Investigator Award, Genzyme Center of Excellence Award for Translational Research in Gaucher disease. He is on the DSMB of NIH Pediatric Acute Liver Failure Study Group (PALF) and serves on NIH Study Sections.

PSK has received research/grant support from Genzyme Corporation (Sanofi Aventis), Valerion Therapeutics, Shire Pharmaceuticals, Roche, Pfizer, Alexion, NIH, FDA, and PCORI.

PKM has received travel support/honoraria for lectures from Genzyme, Shire and Pfizer. He is member of the North American and International Boards of the ICGG Registry. He is the Chair of Project Hope Humanitarian Program for Gaucher disease.

PSK has received consulting fees and honoraria from Genzyme Corporation (Sanofi Aventis), Shire Pharmaceuticals, Alexion Pharmaceuticals, Amicus Therapeutics and Roche. She is a member of the Pompe and Gaucher Disease Registry Advisory Board for Genzyme Corporation; Scientific Advisory Board for Shire Pharmaceuticals; and Registry Board Member for Alexion Pharmaceuticals. She also serves on the Data Safety Monitoring Board for PTC Therapeutics. Duke University and the inventors of the method of treatment and precursors of the cell lines used to generate the enzyme (rhGAA) used commercially have received royalties pursuant to the University's policy on inventions, patents, and technology transfer. This potential conflict for Duke University has been resolved through monetization.

RDP, MB, MM, AN, SJ and ICV are advisors within the Indian Compassionate Access Program (INCAP) of Genzyme Corporation (Sanofi Aventis) but do not receive any compensation for serving.

NG, MK, SRP - No Conflicts of interest except that some of the Gaucher's disease patients attending our hospital are getting Enzyme Replacement therapy under INCAP on Humanitarian initiative

RDP, SK, AS, SA, AB, LB, AD, SD, APD, AG, LL, SN, IP, VHS, and JS are members of the Genzyme Corporation (Sanofi Aventis) Scientific advisory board and do not receive any compensation for serving, and the association is purely academic.

REFERENCES

1. Mistry PK, Sadan S, Yang R, Yee J, Yang M. Consequences of diagnostic delays in type1 Gaucher disease: The need for greater awareness among hematologists-oncologists and an opportunity for early diagnosis and intervention. Am J Hematol. 2007;82:697-701.
2. Cox TM, Schofield JP. Gaucher's disease: clinical features and natural history. Baillieres Clin Haematol. 1997;10:657-89.
3. Nair S, Boddupalli CS, Verma R, Liu J, Yang R, Pastores GM, *et al*. Type II NKT-TFH cells against Gaucher lipids regulate B-cell immunity and inflammation. Blood. 2015;125:1256-71.
4. Mistry PK, Belmatoug N, Vom Dahl S, Giugliani R. Understanding the natural history of Gaucher disease. Am J Hematol. 2015;90:S6-S11.
5. Ankleshwaria C, Mistri M, Bavdekar A, Muranjan M, Dave U, Tamhankar P. Novel mutations in the glucocerebrosidase gene of Indian patients with Gaucher disease. J Hum Genet. 2014;59:223-8.
6. Agarwal S, Lahiri, K, Muranjan M, Solanki N. The face of lysosomal storage disorders in India: a need for early diagnosis. Indian J Pediatr. 2015;82:525-9.
7. Sheth JJ, Ankleshwaria CM, Mistri MA, Nanavaty N, Mehta SJ. Splenomegaly, cardiomegaly, and osteoporosis in a child with Gaucher disease. Case Rep Pediatr. 2011;2011:564868.
8. Weiss K, Gonzalez A, Lopez G, Pedoeim L, Groden C, Sidransky E. The clinical management of type 2 Gaucher disease. Mol Genet Metab. 2015; 114:110-22.
9. Nagral A, Mewawalla P, Jagadeesh S, Phadke SR, Verma IC, Puri RD, *et al.* Recombinant macrophage targeted enzyme replacement therapy for Gaucher disease in India. Indian Pediatr. 2011;48:779-84.
10. Nagral A. Gaucher disease. J Clin Exp Hepatol. 2014;4: 37-50.
11. Burrow TA, Barnes S, Grabowski GA. Prevalence and management of Gaucher disease. Pediatric Health Med Ther. 2011;2:59-73.
12. Aggarwal S, Jain SJMN, Das BA, Tandon A, Dalal A. Molecular studies on parents after autopsy identify recombinant GBA gene in a case of Gaucher disease with ichthyosis phenotype. Am J Med Genet A. 2015;11:2858-60.
13. Wenstrup RJ, Roca-Espiau M, Weinreb NJ, Bembi B. Skeletal aspects of Gaucher disease: a review. Br J Radiol. 2002;75:A2-12.
14. Lachmann RH, Wight DG, Lomas DJ, Fisher NC, Schofield JP, Elias E, *et al*. Massive hepatic fibrosis in Gaucher's disease: Clinico-pathological and radiological features. QJM. 2000;93:237-44.
15. Mistry PK, Taddei T, vom Dahl S, Rosenbloom BE. Gaucher Disease and malignancy: A model for cancer pathogenesis in an inborn error of metabolism. Crit Rev Oncog. 2013;18:235-46.
16. Arends M, van Dussen L, Biegstraaten M, Hollak CE. Malignancies and monoclonal gammopathy in Gaucher

disease; a systematic review of the literature. Br J Haematol. 2013;161:832-42.
17. Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. Lancet Neurol. 2012;11:986-98.
18. Abrahamov A, Elstein D, Gross-Tsur V, Farber B, Glaser Y, Hadas-Halpern I, *et al*. Gaucher's disease variant characterised by progressive calcification of heart valves and unique genotype. Lancet. 1995;346:1000-03.
19. Verma J, Thomas DC, Sharma S, Jhingan G, Singh A, Hsiao KJ, *et al*. Inherited metabolic disorders: Quality management for laboratory diagnosis. Clinica Chimica Acta. 2015;447:1-7.
20. Schmitz M, Alfalah M, Aerts JM, Naim HY, Zimmer KP. Impaired trafficking of mutants of lysosomal glucocerebrosidase in Gaucher's disease. Int J Biochem Cell Biol. 2005;37:2310-20.
21. Lo SM, McNamara J, Seashore MR, Mistry PK. Misdiagnosis of Niemann-Pick disease type C as Gaucher disease. J Inherit Metab Dis. 2010;33:S4 29-33.
22. Gort L, Coll MJ. Diagnosis, biomarkers and biochemical alterations in Gaucher's disease. Med Clin (Barc). 2011;137:12-6.
23. Hruska KS, LaMarca ME, Scott CR, Sidransky E. Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene (GBA). Hum Mutat. 2008;29:567-83.
24. Cozzolino I, Picardi M, Pagliuca S, Ciancia G, Luigia L, Pettinato G, *et al*. B-cell non-Hodgkin lymphoma and pseudo-Gaucher cells in a lymph node fine needle aspiration. Cytopathology. 2016;27:134-6.
25. Sharma P, Das R, Bansal D, Trehan A. Congenital dyserythropoietic anemia, type II with SEC23B exon 12 c.1385 A '! G mutation, and pseudo-Gaucher cells in two siblings. Hematology. 2015;20:104-7.
26. Chatterjee T, Dewan K, Ganguli P, Das S, Sharma A, Sahni AK, *et al*. A Rare case of hemoglobin E eemoglobinopathy with Gaucher 's disease. Indian J Hematol Blood Transfus. 2013;29:110-2.
27. Mistry PK, Sadan S, Yang R, Yee J, Yang M. Consequences of diagnostic delays in type 1 Gaucher disease: The need for greater awareness among hematologists-oncologists and an opportunity for early diagnosis and intervention. Am J Hematol. 2007;82: 697-701.
28. Cox TM, Aerts JM, Belmatoug N, Cappellini MD, vom Dahl S, Goldblatt J, *et al*. Management of non-neuronopathic Gaucher disease with special reference to pregnancy, splenectomy, bisphosphonate therapy, use of biomarkers and bone disease monitoring. Inherit Metab Dis. 2008; 31:319–36.
29. Aerts JMFG, Hollak CEM, van Breemen M, Maas M, Groener JEM, Boot R. Identification and use of biomarkers in Gaucher disease and other lysosomal storage diseases. Acta Pædiatrica. 2005;94:43-6.
30. Stein P, Yang R, Liu J, Pastores GM, Mistry PK. Evaluation of high density lipoprotein as a circulating biomarker of Gaucher disease activity. J Inherit Metab Dis. 2011;34:429-37.
31. Murugesan V, Chuang WL, Liu J, Lischuk A, Kacena K, Lin H, *et al*. Glucosylsphingosine is a key biomarker of Gaucher disease. Am J Hematol. 2016;91:1082-9.
32. Elstein D, Hadas-Halpern I, Azuri Y, Abrahamov A, Bar-Ziv Y, Zimran A. Accuracy of ultrasonography in assessing spleen and liver size in patients with Gaucher disease: comparison to computed tomographic measurements. J Ultrasound Med. 1997;16:209-11.
33. Lo SM, Liu J, Chen F, Pastores GM, Knowles J, Boxer M, *et al*. Pulmonary vascular disease in Gaucher disease: clinical spectrum, determinants of phenotype and long-term outcomes of therapy. J Inherit Metab Dis. 2011;34:643-50.
34. Hollak CE, Maas M, Aerts JM. Clinically relevant therapeutic endpoints in type I Gaucher disease. Inherit Metab Dis. 2001;2:97-105.
35. Hughes DA, Gonzalez DE, Lukina EA. Velaglucerase alfa (VPRIV) enzyme replacement therapy in patients with Gaucher disease: Long-term data from phase III clinical trials. Am J Hematol. 2015:90:584-91.
36. Zimran A, Gonzalez-Rodriguez DE, Abrahamov A, Elstein D, Paz A, Brill-Almon E, *et al.* Safety and efficacy of two dose levels of taliglucerase alfa in pediatric patients with Gaucher disease. Blood Cells Mol Dis. 2015;54:9-16.
37. Mistry PK, Weinreb NJ, Kaplan P, Cole JA, Gwosdow AR, Hangartner T. Osteopenia in Gaucher disease develops early in life: Response to Imiglucerase enzyme therapy in children, adolescents and adults. Blood Cells Mol Dis. 2011;46:66-72.
38. Weinreb N, Barranger J, Packman S, Prakash-Cheng A, Rosenbloom B, Sims K. Imiglucerase (cerezyme) improves quality of life in patients with skeletal manifestations of Gaucher disease. Clin Genet. 2007;71:576-88.
39. Weinreb NJ, Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, *et al*. Effectiveness of enzyme replacement therapy in 1028 patients with type 1 Gaucher disease after 2 to 5 years of treatment: a report from the Gaucher Registry. Am J Med. 2002;113:112-9.
40. Grabowski GA. Phenotype, diagnosis, and treatment of Gaucher's disease. Lancet. 2008;372:1263-71.
41. Mistry PK, Deegan P, Vellodi A, Cole JA, Yeh M, Weinreb NJ. Timing of initiation of enzyme replacement therapy after diagnosis of type 1 Gaucher disease: Effect on incidence of avascular necrosis. Br J Haematol. 2009;147:561-70.
42. Charrow J, Andersson HC, Kaplan P, Kolodny EH, Mistry P, Pastores G, *et al.* Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. J Pediatr. 2004;144:112-20.
43. Mistry PK, Cappellini MD, Lukina E, Ozsan H, Mach Pascual S, Rosenbaum H. *et al.* A reappraisal of Gaucher disease-Diagnosis and disease management algorithms. Am J Hematol. 2011;86:110-5.
44. Kaplan P, Baris H, De Meirleir L, Di Rocco M, El-Beshlawy A, Huemer M, *et al.* Revised recommendations for the management of Gaucher disease in children. Eur J Pediatr. 2013;172:447-58.
45. Pastores GM. Recombinant Glucocerebrosidase (Imiglucerase) as a therapy for Gaucher disease. Bio Drugs. 2010;24:41-7.

46. Zimran A, Pastores GM, Tylki-Szymanska A, Hughes DA, Elstein D, Mardach R, *et al*. Safety and efficacy of velaglucerase alfa in Gaucher disease type 1 patients previously treated with imiglucerase. Am J Hematol. 2013;88: 172-8.
47. Muranjan M, Patil S. Outcome for Gaucher disease in India: Lessons from prevalent diagnostic and therapeutic practices. Indian Pediatr. 2016;53:685-8.
48. Lukina E, Watman N, Arreguin EA, Dragosky M, Iastrebner M, Rosenbaum H, *et al*. Improvement in haematological, visceral and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood. 2010;116:4095-8.
49. Vashishtha VM, Choudhury P, Kalra A, Bose A, Thacker N, Yewale VN, *et al.* Indian Academy of Pediatrics (IAP) recommended immunization schedule for children aged 0 through 18 years—India, 2014 and updates on immunization. Indian Pediatr. 2014;51:785-800.
50. Weinreb N, Taylor J, Cox T, Yee J, vom Dahl S. A benchmark analysis of the achievement of therapeutic goals for type 1 Gaucher disease patients treated with imiglucerase. Am J Hematol. 2008;83:890-5.
51. Somaraju UR, Tadepalli K. Hematopoietic stem cell transplantation for Gaucher disease. Cochrane Database Syst Rev. 2012;7:CD006974.
52. Ito S, Barrett AJ. Gauchers disease–a reappraisal of hematopoietic stem cell transplantation. Pediatr Hematol Oncol. 2013;30:61-70.
53. Prajnya R, Rehder C, Phadke SR, Bali D. Prenatal diagnosis of Pompe disease: enzyme assay or molecular testing? Indian Pediatr. 2011;48:901-2.
54. Verma J, Thomas DC, Sharma S, Jhingan G, Saxena R, Kohli S, *et al*. Inherited metabolic disorders: prenatal diagnosis of lysosomal storage disorders. Prenat Diagn. 2015;35:1137-47.

Annexure I

Members of the Gaucher Disease Task Force (in alphabetical order): Satinder Aneja, Ashish Bavdekar, Lalit Bharadia, Meenakshi Bhat, Ashwin Dalal, Sumita Danda, Anand P Dubey, Apurba Ghosh, Neerja Gupta, Sujatha Jagadeesh, Madhulika Kabra, Seema Kapoor, Priya S Kishnani, Lokesh Lingappa, Mamta Muranjan, Pramod K Mistry, Abha Nagral, Sheela Nampoothiri, Inusha Panigrahi, Shubha R Phadke, Ratna Dua Puri, Anupam Sachdeva, Sankar V Hariharan, Jayesh Sheth, Ishwar C Verma .