A Rare Condition in Haematological Practice – Gaucher Disease

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Abstract

Gaucher disease, which is caused by an inherited glucocerebrosidase deficiency, is the most prevalent lysosomal storage disease worldwide. Estimated prevalence of Gaucher disease is 1:50,000 in most countries and the disease has its highest incidence in the Ashkenazi Jewish population. Type 1 (non-neuropathic) Gaucher disease is by far the most common form. Gaucher disease type 1 should be considered in cases of unexplained splenomegaly with or without bleeding diathesis, skeletal manifestations or hepatomegaly. Diagnosis is made by demonstrating decreased glucocerebrosidase activity in peripheral blood leucocytes. Dried blood spots can be used for screening but conventional enzyme assay on heparinised blood is essential. Patients with Gaucher disease may have extensive organ involvement despite relatively minor overt symptomatology. Evidence suggests that Gaucher disease may remain undiagnosed for years, leading to severe complications that are preventable or reversible with enzyme replacement therapy. These complications include avascular necrosis, severe bleeding, chronic bone pain, pathological fractures, growth failure, liver pathology and life-threatening sepsis. Most patients with Gaucher disease are initially evaluated by a haematologist–oncologist. Improved education is needed to enable prompt detection of Gaucher disease. An increased risk of multiple myeloma and haematological and non-haematological malignancies has been reported in type 1 Gaucher disease. This review aims to offer familiarisation with a rare disorder in haematological practice, focusing on adult patient management.

Keywords

Gaucher disease, glucocerebrosidase, cancer, haematological malignancy, multiple myeloma, monoclonal gammopathy of undermined significance (MGUS), diagnosis, splenomegaly, thrombocytopenia

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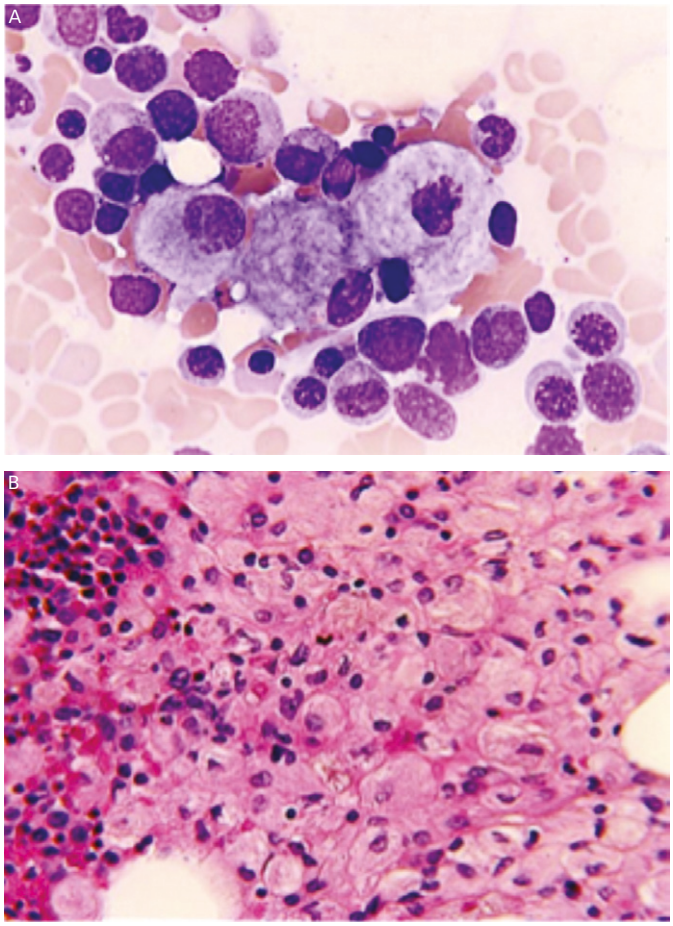
Gaucher disease (OMIM #230800) is an inherited deficiency of lysosomal enzyme acid ß-glucosidase (glucocerbrosidase, GBA1; EC 3.2.1.45) due to mutations in the glucocerebrosidase gene, *GBA1*.[1] Genetic mutations affect the enzyme's catalytic function, intracellular stability or subcellular trafficking.[2–4] Such enzyme deficiency results in the accumulation of glucocerebroside in lysosomes of macrophages (known as Gaucher cells, *Figure 1*), which are observed in many organs, primarily in the bone marrow, liver, spleen and lymph node parenchyma. The finding of an association between the GBA mutation in the heterozygous state and Parkinson's disease indicates that there may be pathogenic roles for GBA mutations beyond enzyme deficiency.[5–7]

Gaucher cells are typically 20–100 µm in diameter with eccentrically placed nuclei and cytoplasm with characteristic crinkles and striations.[8–10] However, untreated patients with type 1 Gaucher disease have recently been shown to display a considerable proportion of Gaucher cells with atypical cytomorphology.[11]

The glucocerebroside concentration in spleens can be increased 10 to 1,000-fold, but high levels may also be present in the bone marrow and liver.[12] Glucosylceramide accumulation leads to variable combinations of:[13]

- Splenomegaly with abdominal discomfort, often the presenting symptom of Gaucher disease.[14]
- Anaemia with chronic fatigue.[15]
- Spontaneous bruising and bleeding – due to thrombocytopenia and/or Gaucher disease-associated coagulopathy.[16] This is initially a result of enhanced blood cell clearance by the enlarged spleen. At a later disease stage, or in patients who have undergone a splenectomy, replacement of the bone marrow by Gaucher cells adds to cytopenia development.
- Hepatomegaly and abnormal liver function.
- Diverse bone disease manifestations, including chronic bone pain, acute bone crises, defective bone mineralisation, infarction, osteonecrosis, osteolysis and pathological fractures.[17] Skeletal disease affects more than 80 % of patients with Gaucher disease and can have a major impact on patient quality of life.[18,19]
- Impaired neutrophil function and neutropenia may cause an increased susceptibility to infection.[20]

Figure 1:Two Images from a Patient with Gaucher Disease Showing Bone (A) and (B) Abnormal Macrophages Infiltrating and Replacing the Normal Marrow Elements



Reproduced with permission from the ASH Image Bank ([A] Stanley Schrier, ASH Image Bank 2011:2011–1819; [B] Stanley Schrier, ASH Image Bank, 2011:2011–1820]).

Gaucher disease is classified into three broad phenotypes:[21] Type 1, non-neuropathic disease; Type 2, fulminant neuropathic disease that is fatal in infancy; and Type 3, chronic neuropathic disease, with an expected survival from childhood to mid adulthood.[22] An intermediate phenotype between types 2 and 3 has also been recognised.[23] The broadest spectrum in phenotypes in terms of age of onset, rate of progression and the organs affected occurs in Type 1 Gaucher disease.[24] Clinical phenotype cannot be discerned from the genotype[23] although early onset has been associated with more rapidly progressive and severe disease.[16] Type 1 Gaucher disease accounts for >90 % of all Gaucher disease patients. Gaucher disease occurs at a global prevalence of around 1 in 50,000 but is much more common in the Ashkenazi population, in which it is found in around one in 800–850 individuals.[15,25–28] Nearly 300 mutations have been identified, including frameshift mutations, point mutations, deletions, insertions and splice site mutations.[29] Four mutations N370S (c.1226A>G), L444P (C.1448T>C), 84GG (-c.84dupG) and IVS2+1 (c.27+1G>A) account for approximately 90 % of the disease causing alleles in the Ashkenazi Jewish population. In non-Jewish populations, the same four alleles account for approximately 50–60 % of the disease-causing alleles. Whereas strong correlations have not been identified between genotypes and the resulting phenotypes, several mutations are associated with a higher risk of neuronopathic forms of Gaucher disease (e.g., homozygosity for L444P or D409H, or the compound heterozygote L444P/D409H).[29] By contrast, the N370S mutation is commonly perceived to lead to minimal symptoms, although it could be associated with severe progressive bone disease and cancer risk when homozygous.[30] Genotypic data from affected patients show that presence of the single N370S allele is diagnostic of type 1 Gaucher disease. Alleles bearing the 84GG mutation are unable to direct systhesis of any protein and this mutation has therefore never been found in the homozygous state.[31] The combination of N370S and 84GG mutation leads to severe disease.[32] The most prevalent mutations in Caucasian patients are N370S and L444P.[33]

The model of Gaucher disease management is underpinned by prompt diagnosis taking place before the development of irreversible complications.[34] Enzyme-replacement therapy (ERT) (imiglucerase [Cerezyme®]; Genzyme Corporation, Cambridge, MA, US) ameliorates or reverses many systemic manifestations of Gaucher disease[35] and is considered the reference treatment for Gaucher disease type 1 and 3 patients. Other recombinant glucosidases include velaglucerase alfa (Shire HGT, Cambridge, MA, US) and taliglucerase alfa (Protalix Biotherapeutics, Carmiel, Israel and Pfizer, NY, US). However, ERT has been shown to correct only part of the coagulopathies in Gaucher disease and other therapeutic and supportive measures should be considered to treat and/or prevent bleeding.[36]

Diagnostic Delay

Despite the availability of treatment options, nearly one-quarter of type 1 patients with Gaucher[25] disease do not receive timely access to therapy, possibly due to the delays in obtaining a diagnosis after the onset of symptoms.[28,37] Concerns about safety of treatments may also account for this delay. Enzyme testing diagnosis of Gaucher disease is unequivocal; however, Gaucher disease is rare with a non-specific and heterogeneous manifestations, and minor overt symptomatology at onset, all of which hinders consideration of the disease in differential diagnosis. Aspiration biopsy of bone marrow is not a reliable diagnostic tool.[38]

Cytopenias and splenomegaly can lead to suspicion of haematological malignancy, especially in the presence of focal splenic lesions.[37] However, concomitant presence of hyperferritinaemia, polyclonal gammopathy, without neutropenia, but together with a more insidious onset may be useful in differentiating from malignancy.[22]

Early symptoms of Gaucher disease reflect the haematological characteristics such as splenomegaly, anaemia, thrombocytopenia and bleeding.[39] Therefore, patients with Gaucher disease are most likely to be referred to a haematologist for initial diagnosis, assessment and ongoing medical care. A global study of 406 haematologists–oncologists found that just 20 % considered Gaucher disease in the differential diagnosis, even in the presence of the classic symptoms of cytopenia, hepatosplenomegaly and bone pain.[37] Instead, the most likely diagnosis considered included leukaemia, lymphoma and multiple myeloma. The case series of patients who experienced a delay in diagnosis is summarised in *Table 1*. Of 136 patients surveyed, the average time from first appearance of Gaucher disease symptoms to diagnosis was 4.1±10.3 years. In particular, patients homozygous for the N370S glucocerebrosidase mutation appear especially vulnerable to diagnostic delays (see *Table 1*).

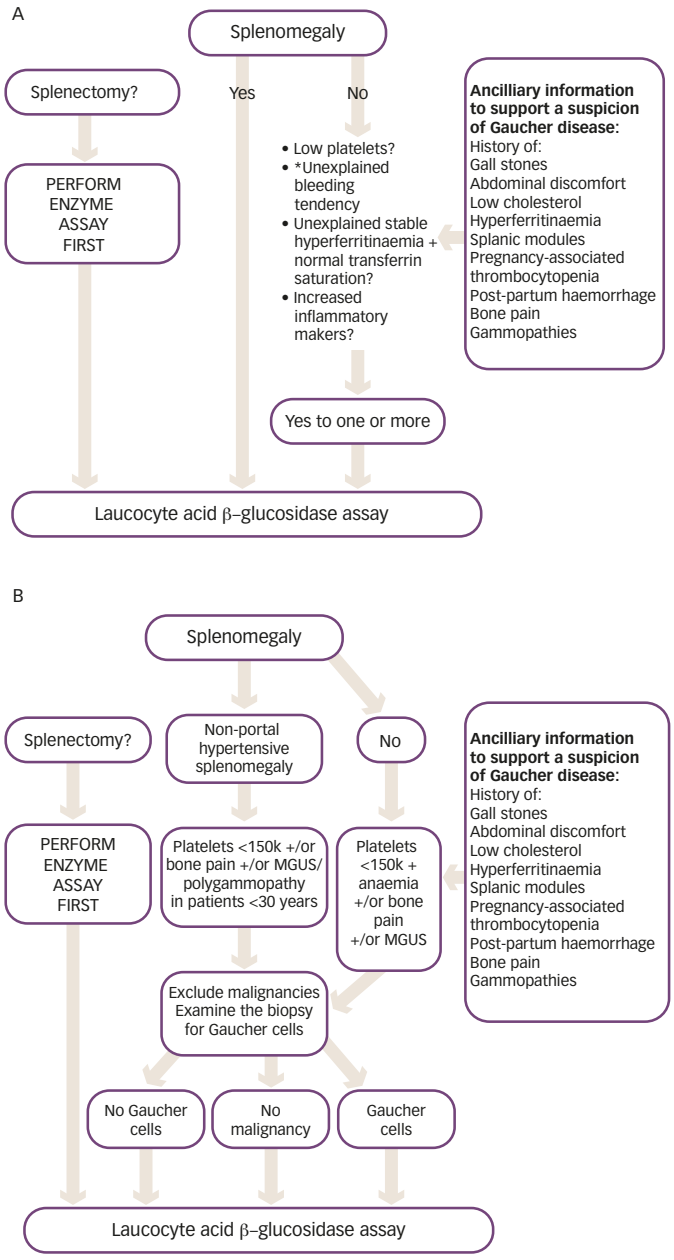
In a retrospective review of a single centre cohort of 86 patients, patients most commonly presented with symptoms related to visceral of haematological involvement.[22] The almost universal presence of

Table 1: Case Series of Patients Who Experienced a Delay in Diagnosis of Gaucher Disease

Patient Number	Age at Dx	Ethnic Group	GBA[a] Genotype	Initial Diagnosis	Time to Correct Diagnosis (Years)	Method of Initial Gaucher Disease Detection	Hb g/dl	Platelets x 1,000 u/l	Lv[b] XN	Sv[c] XN	Hermann Score	SSI[d]	Complication
1	70	AJ	N370S/N370S	Metastatic cancer, masses in the spleen	1	Bone marrow biopsy	12.0	140	1.1	4.5	2	4	Thrombocytopenia, post-surgical haemorrhage, systemic fungemia, fungal endophthalmitis
2	49	AJ	N370S/N370S	Fibromyalgia	1	Bone marrow biopsy	10.8	150	1	1.2	4	11	AVN of humeral head
3	29	AJ	N370S/N370S	Collagenosis	10	Liver biopsy	12.5	140	1.5	6	3	5	Bone pain, recurrent epistaxis, hepatic iron overload
4	19	AJ	N370S/L444P	Lymphoma	1	Splenectomy	14.0	280	1.2	–	4	[f]	AVN
5 (i)[e]	42	AJ	N370S/N370S	Cirrhosis/portal hypertension	1	Liver biopsy	13.3	109	1.14	2.42	1	4	Bone pain, hepatic iron overload
5 (ii)[e]	40	AJ	N370S/N370S	Pituitary adenoma	Post mortem	GBA genotype	[f]	[f]	[f]	[f]	[f]	[f]	Fatal septicaemia
6	70	AJ	N370S/N370S	'Frozen shoulder'	10	Bone marrow biopsy	10.8	26	1	5.45	5	11	AVN-bilateral humeral heads and femoral head, pathological fractures, Gaucheroma at T5 abdominal bleeding
7	71	AJ	N370S/N370S	Lymphoma	10	Splenectomy	12.9	281	1.1	–	4	9	Pathological fractures Multiple myeloma
8 (i)[e]	9	Hispanic	N370S/L444P	'Growing pains'	2	Mother Identified GD by Internet search	11.7	153	1.81	10.61	2	5	Hepatosplenomegaly, bleeding tendencies
8 (ii)[e]	7	Hispanic	N370S/L444P	'Growing pains'	2	Mother Identified GD by Internet search	11.1	86	2.07	8.25	1	4	Hepatosplenomegaly, bleeding tendencies
9	1.5	AJ	N370S/IVS2+1	Willebrand's disease/ red cell defect	8	Leukocyte acid b-glucosidase/ GBA genotype	11.2	164	1.7	7.57	1	4	Hepatosplenomegaly, thrombocytopenia, growth retardation
10	21	Hispanic	N370S/L444P	Liver disease	5	Liver biopsy	13.3	116	1.7	9.9	2	4	Severe anaemia (Hb 7.3 g/dl), menorrhagia
11	40	AJ	N370S/N370S	Liver disease	4	Liver biopsy	12.4	88	0.6	4.1	2	6	Hip pain
12	56	AJ	N370S/N370S	Osteoporosis	9	Bone marrow biopsy	13.7	123	1.34	5.74	5	12	Pathological fractures, severe bleeding post bone biopsy
13	34	Hispanic	N370S/L444P	Lymphoma	15	Splenectomy, liver biopsy	13.4	553	1.4	–	4	12	AVN, vertebral collapse, pulmonary hypertension

The table presents age, ethnic ancestry, initial diagnosis and time to correct diagnosis of Gaucher disease (GD). Results of comprehensive evaluation following diagnosis of GD are shown. Herman score is the skeletal disease severity score (1–5, 5¼ worst) as described previously.[21] Severity score index (SSI) as described by Zimran et al.[16,20] The last column lists complications before the diagnosis of GD. [a]gene mutations; [b]liver volume; [c]spleen volume; [d]severity score; [e]siblings; [f]no data. AJ = Ashkenazi Jewish; AVN = avascular necrosis; Dx = diagnosis; Hb = haemoblobin; GBA = glucocerebrosidase; N = normal. Reproduced with permission from Mistry et al.[37]

Figure 2: Diagnosis in People of Ashkenazi Jewish (A) and Non-Ashkenazi Jewish (B) Origin



**In patients with bleeding diatheses, coagulopathies such as factor XI deficiency common in Askenazim should be excluded. MGUS = monoclonal gammopathy of undetermined significance. Reproduced with permission from Mistry et al.[28]*

concomitant thrombocytopenia or splenomegaly means that the majority of patients were reviewed by haematologists. Fifty-six per cent of the patients presented primarily with features of thrombocytopenia or splenomegaly. The median time from onset of symptoms to diagnosis was 2 years (range 0.5–26 years) and 19 % experienced delays of ≥5 years. Bone marrow biopsies were performed in the majority of the cohort (68 %), despite the fact that they are not recommended in routine Gaucher disease diagnosis.

Preliminary findings from an observational study of 35 haematological centres in Italy showed that 18 % of all haematological first evaluations are positive for splenomegaly and/or thrombocytopenia and, among them, 11 % did not receive an appropriate diagnosis.[40]

Diagnostic Algorithms – Overview

A consensus meeting convened in Copenhagen to develop algorithms for Gaucher disease diagnosis and management.[28] In the publication containing the algorithms, which expands on ancillary concerns, the authors highlighted that it is advisable to test for Gaucher disease as a first-line investigation in patients of Ashkenazi Jewish ethnicity presenting with splenomegaly and cytopenia. The most common genotype in this ethnic group, N370S homozygosity, is frequently characterised by mild cytopenia and splenomegaly that may be difficult to detect, therefore ancillary information is helpful, including hyperferritinaemia, low high-density lipoprotein (HDL) cholesterol, premature gallstones or osteoporosis and gammopathy (see *Figure 2A*). In the non-Ashkenazi population where Gaucher disease is markedly less frequent compared with haematological malignancies, it is appropriate to consider Gaucher disease in differential diagnosis when malignancies have been ruled out (see *Figure 2B*). Bone marrow biopsy is usually undertaken in this setting and it should be routine to search for Gaucher cells as well as for haematological malignancies.

Routine bone marrow examination is not used in diagnosis; however, due to the risk of bleeding complications due to thrombocytopenia and coagulopathy,[41] and also the availability of a robust, less-invasive enzymatic test. The diagnostic test for Gaucher disease is the demonstration of low acid ß-glucosidase activity in peripheral blood leukocytes (normal range 2.1–2.5 µmol/l/hour).[42]

Gaucher Disease and Haematological Malignancies

Physicians need to be aware of the increased risk of haematological malignancy and actively look for signs of the disease.[15,39,43] The increased risk may possibly be due to potential chronic stimulation of the immune system associated with glucocerebroside storage in tissue macrophages.[43] Elevated glucosyceramide and complex glycosphingolipids have been proposed to be involved in cancer progression.[44] Other possible factors implicated in the pathophysiology of cancer in Gaucher disease include splenectomy, endoplasmic reticulum stress, genetic modifiers, altered iron metabolism and insulin resistance.[45]

A single-centre cohort study of 131 patients with Gaucher disease of mixed ancestry in Western Europe investigated cancer incidence and mortality compared with controls.[46] A 2.5-fold (95 % confidence interval [CI] 1.1–4.7) increased incidence of cancer was reported and a 12.7-fold (95 % CI 2.6–37.0) increased risk of haematological cancers. In particular, the incidence of multiple myeloma was highly elevated with a standardised rate ratio of 51.1 (95 % CI 6.2–184). In a retrospective cohort study, comparing the incidence and type of cancer in 48 patients with Gaucher disease with those of 511 control subjects without Gaucher disease, 10/48 (20.8 %) developed cancer compared with 35/511 (6.8 %) of the control population.[47] Data from the International Collaborative Gaucher Group (ICGG) reported an increased risk of multiple myeloma, although the patients with Gaucher disease did not seem to be at a highly increased risk of cancer, at least during early and middle age.[43]

Gaucher disease, as is the case with multiple myeloma, is associated with biclonal and triclonal gammopathies and monoclonal gammopathy of underdetermined significance (MGUS).[48] The risk of progression of MGUS to multiple myeloma or related disorders is about 1 % per year in the general population,[49] although it is not known if this rate also applies to patients with Gaucher disease. Immune

dysregulation in the bone marrow microenvironment is thought to be involved in the increased risk of MGUS and myeloma in patients with Gaucher disease.[50]

In a systematic literature review investigating malignancies and monoclonal gammopathy in Gaucher disease, based on the studies included, patients with Gaucher disease have an increased risk of cancer in general (pooled relative risk of 1.7 [95 % CI 1.27–2.31] and in particular, an increased estimated risk of multiple myeloma [25.0–51.1] and haematological malignancies [3.5–12.7]).[45]

An association between Gaucher disease and myelodysplastic syndrome has been reported but is rare.[51] Epidural haematoma in Gaucher disease is a rare manifestation that mimics malignant processes.[52]

Management and Enzyme Replacement Therapy (see *Table 2*)

Recommendations for the management of haematological malignancy have been published following proceedings of a European panel of experts in haematology that convened in Paris, France in 2006.[39] Bi-annual measurement of serum protein electrophoresis and immunofixation is recommended in those aged <50 years and annual measurement in older patients. There is overlap between some features of malignancy and Gaucher disease, including bone pain, splenomegaly and cytopenias, though the development of these features in otherwise stable patients should be followed by further investigation. The potential role of ERT in the prevention of malignancies warrants investigation. ERT may also improve peripheral blood counts to facilitate chemotherapy.[50]

The coincidence of Gaucher disease and multiple myeloma does not exclude the patient from receiving ERT.[39] There is, however, a paucity of data on the impact of continuing Gaucher-specific treatment during cancer treatment. Therefore, it is advisable to personalise the decision of continuing or interrupting the Gaucher disease treatment according the clinical status of the patient, life expectancy and treatment burden.

Newer treatment strategies for Gaucher disease that are under investigation include substrate reduction therapy, chaperone therapy, gene therapy and receptor-interacting protein kinase-3 inhibitors.[50,53]

Risk Factors

Age is an important risk factor for cancer in patients with Gaucher disease and may prove more pronounced in people with Gaucher disease than in the general population; the risk of cancer in patients with Gaucher disease compared with the risk in age-matched controls was higher in a cohort with mean age >40 years[46] than in cohorts with a mean age <40 years.[30,54] Other risk factors include splenectomy, immune dysregulation and impaired proteasomal degradation and of mutant glucocerebrosidase variants and genetic modifiers.

Table 2: Main General Recommendations for the Screening and Management of Haematological Malignancy in Patients with Gaucher Disease

1. To determine the immunoglobulin profile at diagnosis and monitored every 2 years (patients <50 years) or every year (patients ≥50 years)
2. If MGUS is found, general MGUS guidelines should be followed
3. If monoclonal protein concentration exceeds 15 g/l a bone marrow aspirate should be carried out to check for transformation to multiple myeloma
4. Check for the presence of main risk factors that have been hypothesised to play a role in the pathophysiology of haematological malignancy. If present, patients should be monitored more frequently. Those risk factors treatable should be corrected:
   - Splenectomy
   - Immune dysregulation
   - Altered iron metabolism (recent evidence suggests that iron chelation treatment may be considered as an option for patients with iron overload and increased inflammatory cytokines[55]
   - Insulin resistance
5. Case by case requires personalised attention
6. Based on type of malignancy developed, clinicians should follow the specific published guidelines
7. A cost–benefit balance for each clinical case should be considered

MGUS = monoclonal gammopathy of undetermined significance.

Mortality

The single-centre cohort study of 131 patients with Gaucher disease reported an increased mortality risk of hepatocellular carcinoma (relative mortality 101.4, 95 % CI 12.3–366.1) but no significant increase in mortality for multiple myeloma (mortality risk 7.6, 95 % CI 0.92–202.0) and all cancers (relative risk 3.0, 95 % CI 0.96–6.9).[46]

Conclusions

Evidence suggests that patients with Gaucher disease may go undiagnosed for years, which leads to severe complications that are preventable or reversible with ERT. Such complications include avascular necrosis, severe bleeding, chronic bone pain, pathological fractures, growth failure, liver pathology and life-threatening sepsis. Gaucher disease, although a rare disorder, has the potential to influence understanding of more common disorders, including Parkinson's disease and certain malignancies. Most patients with Gaucher disease are initially evaluated by a haematologist–oncologist. Increased risk of multiple myeloma and haematological and non-haematological malignancies has been reported with type 1 Gaucher disease. The precise relationship between Gaucher disease and cancer is still unclear, however, and needs further investigation. ■

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