GAUCHER'S DISEASE — AN UNDERWRITING PROSPECTIVE

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I never think of the future. It comes soon enough.
Albert Einstein, Interview, Dec. 1930

Introduction

With increased availability of genetic screening, the number of insurance applicants with Gaucher's disease will undoubtedly increase. Some of these individuals will have no overt or minimal manifestations of disease; others will have disease of varying severity.

The frequent assumption that Gaucher's invariably follows an inexorably progressive course has not been supported by any longitudinal study.[1]

Historical

In 1882, for his medical school thesis, Phillipe Gaucher described an illness he believed to be an epithelioma of the spleen. Not until twenty years later was the pathology correctly described by Brill, Mandelbaum and Libman and called Gaucher's Disease.[1,2]

Clinical Classification

A detailed description of the types of Gaucher's is beyond the scope of this paper. Classically, three types are described. Type 2, acute neurologic, is usually fatal in infancy with an average age at death of 18 months.[2] Type 3, chronic neurologic, usually presents during childhood with diffuse progressive neurologic symptoms. There is a distinct subgroup whose sole neurological defect is a lateral gaze abnormality. Unfortunately, this subgroup usually has severe, progressive systemic involvement, especially lung and liver.[2]

Type 1 disease will comprise our applicant pool. It is characterized by marked heterogeneity of systemic, hematologic and skeletal manifestations. Neurologic disease is absent.

Biochemical Abnormality

Gaucher's is characterized by accumulation of glucocerebroside in the reticuloendothelial system. The genetic defect is a deficiency of the liposomal enzyme, glucocerebrosidase.[1]

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Severity Score Index (SSI)[1]

This can be used for objective classification and follow-up of the phenotypic manifestations of Gaucher's. The scoring criteria are primarily based on the extent of organ involvement.

Table
Severity Scoring Index for patients with Gaucher's disease.[1]

Cytopenia	Unsplenectomized	1
	If splenectomized	
	Leukopenia	1
	Anemia	1
	Thrombocytopenia	1
Splenomegaly*	None	0
	Mild	1
	Moderate	2
	Massive	3
Splenectomy		3
Hepatomegaly*	None	0
	Mild	1
	Moderate	2
	Massive	3
Liver function tests (GOT, alkaline phosphatase, LDH, GGT)	Normal	0
	Some abnormal	1
	All abnormal	2
Clinical signs of liver disease		4
CNS involvement		20
Other organ involvement (lungs, kidneys, etc.)		4
Bones: Choose one from each category		
Objective	No signs/symptoms	0
	X-ray or scan signs	1
Subjective	No pain	0
	Mild/occasional pain	2
	Chronic pain (not related to fractures)	3
Fractures	None	0
	Post-traumatic	1
	Aseptic necrosis or pathologic fractures	5

Abbreviations: GOT = glutamic oxaloacetic transaminase, LDH = lactic dehydrogenase, GGT = gamma glutamyl transferase, CNS = central nervous system.

*Organomegaly: mild – tip above umbilicus, moderate – tip between umbilicus and pelvic rim, massive – organ extends below pelvic rim.

Genetics

The gene for glucocerebrosidase is on chromosome 1q21;[2] transmission is autosomal recessive.[2] The clinical manifestations and mortality can be accurately correlated with genotypes, the four most common being 1226G/1226G, 1226G/84GG, 1226G/1448G and 1226G/unknown.[1] 84GG is second most common in Jewish patients; 1448G is second most common in non-Jewish individuals.[1] Other mutations include 764A, 1504A, 1297T, 1604A and the crossover, XOVR. Those with the 1226G/1226G genotype are most common, 61%. They have the best prognosis; on follow-up, there was no change in the severity score of any patient.[1] Their average age at first evaluation was 49, over twice the mean age of the entire group. The 1226G/1448G, 1226G/84GG and 1226G/unknown genotype have more severe clinical disease at a younger age. However, in each, the mean severity score increased only slightly (1-2) points on follow-up.

Patient Characteristics for Entire Study Group[1]

- Sex - 55% female, 45% male
- Jewish - 74%, non-Jewish 26%
- Mean age at diagnosis - 21 (range 8 mo - 70 yr)
- Mean age at first symptoms - 25 (range 8 mo - 70 yr)

Three patients were entirely asymptomatic and without any abnormal physical or laboratory findings when diagnosed. They were not included in the calculation of mean age at onset.

Clinical Manifestations[1]

Marked variability in clinical expression is the hallmark of Gaucher's.

The most common presenting symptoms were bleeding such as epistaxis, easy bruisability or prolonged bleeding after superficial trauma. Nearly one-third of patients were diagnosed while entirely asymptomatic following incidental findings of splenomegaly, thrombocytopenia or during family study. Skeletal presentations of pain and fractures were uncommon.

Over follow-up, bleeding manifestations became less prominent whereas bone problems became a major cause of morbidity. Individuals who developed major organ disease usually had signs and symptoms early in the disease course.

Laboratory Features[1]

Thrombocytopenia was most common, being present in 50% of patients. Forty two percent had mild anemia. A fewhad pancytopenia. Forty two percent of those splenectomized attained normal blood counts. Of those not splenectomized, only 31% had a normal count. About 20% had modestly elevated liver function tests. Prolonged prothrombin and partial thromboplastin times were noted in about 20%. Most patients had elevated acid phosphatase, ferratin and angiotension-converting enzyme levels. All individuals had low levels of leukocyte or fibroblast acid betaglucosidase; neither level correlated with disease severity.

Radiologic Abnormalities[1]

Most x-ray findings were detected in bone surveys. The classical "Erlenmeyer flask" deformity with widening of the distil femur was most common. Progressive changes were common and included avascular necrosis of the hip; some requiring replacement.

Ultrasound Findings[1]

Most usual was splenomegaly affecting about 45% of individuals. Seventy seven percent had hepatomegaly: 66% mild, 22% moderate and 12% severe.

Disease Progression[1]

Heterogeneity of Gaucher's requires emphasis. Within each type, the functional deficiency of glucocerebrosidase results in diverse clinical presentations and clinical courses.

The mean follow-up was 5.6 years (range 2-13 years). During this period, the Severity Score Index was repeatedly reassessed. Sixty-two percent showed no progression of either signs or symptoms. The average age of nonprogressors was 43 compared to 29 for those who experienced progression. In the progressors, only 17% had an increase in the severity score. Generally, the younger the presentation, the worse the prognosis. Progression of disease occurs in most cases during childhood, adolescence or early adulthood with a marked tendency for stabilization thereafter.[1]

Those with the genotype 1226G/1226G tended to have a later onset with milder clinical manifestations. During follow-up, they had no change in severity score. Those with 1226G/1448G and 1226G/84GG had more pathologic clinical presentations, yet severity scores only increased 0.5 and 1.15 respectively over the follow-

up period. There is a tendency in these individuals to have more severe disease at older ages.

The authors emphasized their patient population was seen in a referral center. Those with less severe disease remained in the medical community. Thus, the overall prognosis may be even more favorable in many cases.

Splenectomy usually improved and/or resolved the hematologic abnormalities especially thrombocytopenia.

Those with liver function abnormalities rarely developed end-stage liver disease.

About 50% of individuals developed significant skeletal problems; progression was highly variable. Most commonly affected were hips and vertebral column. In most cases bone disease developed before age 30 with stabilization thereafter.

Pulmonary disease engendered a very poor prognosis.

When underwriting an individual, the family history may be very helpful. The severity of disease is similar among siblings.[2]

Treatment

In selected patients, splenectomy can be highly effective, usually correcting thrombocytopenia or other cytopenias.[1] It also improves rate of growth in adolescents.[1] Its effect on progression of disease in other organs and skeleton is unclear. It does not appear to affect overall prognosis.[1]

Bone marrow replacement has been used in very severe cases. This corrects the enzyme deficiency, yet long-term reversal of signs and symptoms have been unspectacular.[2]

Enzyme replacement is currently indicated for moderate-to-severe disease; cost is between $100,000 and $250,000 yearly.

Barton, et al., reviewed the response to enzyme replacement in twelve patients.[3] Treatment reversed both signs and symptoms in patients regardless of genotype.

The time course of improvement appeared to be specific to the organ system with several months of treatment required before apparent response. Hematologic and visceral responses substantially preceded skeletal response.[3]

The hemoglobin response was usually dramatic and preceded a less dramatic increase in platelet count.[3]

Improvement in biochemical markers paralleled the hematologic response.[3]

Both of these responses occurred in conjunction with significant reductions in splenic volume.[3]

Systemically, most patients were objectively and subjectively improved.[3]

One can only conjecture that with continued treatment, these changes will be permanent, and ultimately, positively, affect both long-term morbidity and mortality. One must be cognizant of unknown risks of experimental, long term treatments.

Discussion

Genotype

The best, but potentially not available prognostic factor, is the genotype. The presence of 1226G connotes a favorable prognosis. Those with 1226G/1226G have the most favorable prognosis. Genotypes 1226G/84GG, 1226G/1448G and 1226G/unknown have a less optimal prognosis; nevertheless, many individuals with these genotypes may be insurable. In these latter groups, correlation with the Severity Score Index is essential for correct individual risk classification.

It would be tragic for the proposed insured if we, as an industry, were precluded by uniformated, emotion-base statute, to neither 1) access nor 2) use this genetic information in our underwriting. Those best risks would be denied the most favorable risk classifications.

Severity Score Index (SSI)

Applicants with severity scores five or less appear to be excellent risks. Those with higher SSI's, up to eleven, excluding bone, may be insurable risks. Demonstration of stability over time should lead to an even better risk classification.

Age

Older age at onset of signs and symptoms portends a better prognosis. This group had less severe symptoms and less progression. Many whose onset was at a younger age stabilized by adolescence or early adulthood. Care must be exercised in underwriting young individuals. One might not yet be able to ascertain the

correct type; some may develop type 3 or may not yet have manifested the maximal symptoms of disease.

Splenectomy

Several underwriting factors must be considered in splenectomized individuals. The basic premise is a splenectomized individual has more extensive disease. One must follow-up whether those hematologic abnormalities necessitating surgery have improved and if so, what risk remains from any residual abnormalities especially thrombocytopenia. Although splenectomy may favorably affect values on the complete blood count, there is no evidence it affects long-term prognosis.

Splenectomy can predispose one to bacterial sepsis, especially pneumococcal. *Medical Selection of Life Risks* recommends an additional debit for those splenectomized.[4] Since the risk of disseminated infection is greatest in childhood, I do not feel this extra debit is necessary for adults. New generation pneumococcal vaccines may negate this risk.

Enzyme Replacement

The long-term effect of genetically engineered glucocerebrosidase is as yet unknown. One must be optimistic it will effect an improvement in current status and prognosis. Those who are already insurable may be even better risks when treatment is established and results are known.

What affect enzyme replacement will have on those more severely affected, is unknown. Here conservatism is the wisest course of action.

References

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