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Radionuclide Assessment of Gaucher's Disease

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Gaucher's disease involves multiple organs and may present with variable severity. The scintigraphic appearance of the reticuloendothelial system and bone are described in three patient's with Gaucher's disease. Scintigraphic abnormalities reflected the severity of organ involvement and correlated well with the patients' clinical status. Scintigraphy appears useful for the evaluation and followup of patients with Gaucher's disease.

J Nucl Med 19: 1333–1336, 1978

Gaucher's disease causes diffuse abnormalities of the reticuloendothelial system, affecting the spleen, liver, and bone marrow. Little attention has been paid to the scintigraphic appearance of this disease. Diffusely decreased uptake of Au-198 by the liver has been reported in one case (*1*). Gaucher's disease is also included in the differential diagnosis of splenomegaly (*2*). This paper describes the scintigraphic findings in three patients with varying severity of Gaucher's disease.

MATERIALS AND METHODS

Liver-spleen scintigraphy was performed 15 min after the i.v. administration of Tc-99m-labeled sulfur colloid. Microscopic analysis was performed routinely on each batch before injection. Seventy-five to 80% of the colloid particles were found to be between 0.25 and one micron in diameter. In normal patients, hepatic uptake was slightly greater than that in the spleen, and bone-marrow uptake was not visible on the images obtained with Polaroid Type 107 film.

Bone scintigraphy was performed with Tc-99m-labeled methylene diphosphonate. Scintigrams were performed approximately 3 hr after i.v. injection of 18–20 mCi of the tracer.

Patient 1 is a 42-year-old Jewish woman with Gaucher's disease initially diagnosed at age 21 during a hospitalization for acute appendicitis. Following an uncomplicated appendectomy, a bone-marrow biopsy was performed. Microscopic analysis revealed numerous Gaucher cells. The patient's twin sister was also affected with Gaucher's disease.

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The patient had intermittent back pain 2 years before the present admission, and radiographs of the lumbosacral vertebrae showed only mild degenerative changes, not characteristic of Gaucher's disease. Following conservative therapy and change of work habits, the symptoms largely disappeared. Recently, the patient had some left knee pain with motion, thought by her orthopedist to be characteristic of degenerative changes. Physical examination demonstrated hepatosplenomegaly but no other unanticipated findings.

Liver-spleen and bone scintigraphy were performed as part of a baseline study. The liver-spleen scintigram (Fig. 1) showed moderate enlargement of the liver and spleen. The tracer uptake in the liver was moderately inhomogeneous with marked shift of activity to the spleen. The bone marrow was not visualized. The bone scan (Fig. 2) showed asymmetry of uptake in the distal femoral shaft, with increased uptake in the left femoral condyle, left tibial plateau, and in the right ankle. In addition, there was a suggestion of increased cortical and metaphyseal uptake in the left distal femoral diaphysis. These abnormal findings corresponded to the site of the patient's symptoms (pain with motion).

Patient 2 is a 20-year-old Jewish woman with Gaucher's disease diagnosed at age 7. The history revealed recurrent episodes of abdominal pain and pulmonary infections. Multiple nosebleeds due to thrombocytopenia had been successfully treated by splenectomy at age 9. Liver function in May 1974 showed LDH 173, SGOT 57, alkaline phosphatase 84, normal bilirubin, PT, PTT, and platelets.

The patient was admitted to the hospital in June 1976 with the recent onset of left hip pain. Hepatomegaly was found at physical examination. Serum enzyme activities were: SGOT 47, LDH 74, alkaline phosphatase 7.4, and SGPT 33. The CBC, PT, PTT, and platelets were all normal. Blood cultures were negative. The liver-spleen scan (Fig. 3) showed the liver measuring 15 cm in its vertical axis at the midclavicular line, with inhomogeneous tracer uptake but without focal defects or shift of activity to the bone marrow. The spleen was absent. The bone scan (Fig. 4) showed decreased tracer uptake in the left femoral head and increased uptake in the proximal tibia and distal femur. The latter had an Erlenmeyer-flask appearance as well. Several hip radiographs performed at that time showed no abnormalities. The radiograph of the femur confirmed the Erlenmeyer-flask appearance and cortical thinning of the distal femur (Fig. 5). The pelvis and the lumbar and thoracic spine were all scintigraphically and radiographically normal.

The patient was treated conservatively. Followup radiographs of the pelvis and hip 5 mo later showed no evidence of avascular necrosis in the femoral head.

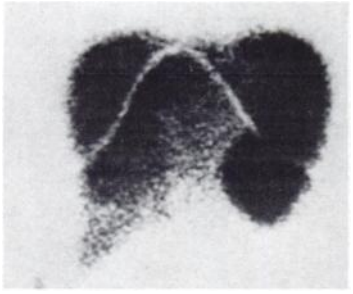

FIG. 1. Liver-spleen scintigram in Patient 1, showing hepatosplenomegaly and marked shift of radiocolloid to the spleen.

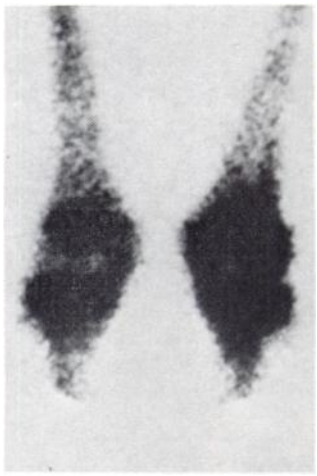

FIG. 2. Bone scintigram of both knees obtained from Patient 1. There is asymmetry and increased cortical and metaphyseal uptake.

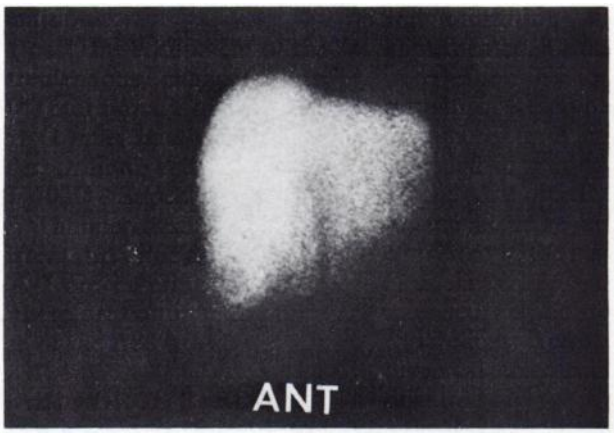

FIG. 3. Liver scintigram obtained from Patient 2 shows slight hepatomegaly with mild inhomogeneity.

Patient 3 was a 7-year-old white boy diagnosed as having Gaucher's disease, type 3, at age 2½. Hepatosplenomegaly was noted at that time. A bone-marrow biopsy produced Gaucher cells, and the diagnosis was subsequently confirmed biochemically. The patient's older brother also had Gaucher's disease. At the time of the initial diagnosis, our patient was asymptomatic with normal developmental milestones. At age 3, left-leg pain led to the radiologic finding of an Erlenmeyer-flask lesion in the distal femur. A month later, destructive changes in the femoral neck were also noted. At age 4, anemia and thrombocytopenia due to hypersplenism led to splenectomy. The spleen weighed 550 g, measured 10 × 15 cm, and showed numerous Gaucher cells. During the next year, multiple bony fractures, especially in the femur and vertebrae, necessitated several hospitalizations. At age 5, the patient experienced severe hematemesis with markedly abnormal liver function tests. Severe portal hypertension was documented angiographically (*3*). An end-to-side shunt was performed between the portal vein and inferior vena cava. During the operation, the liver

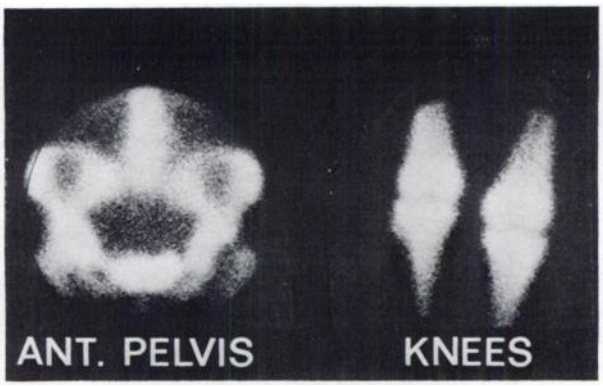

FIG. 4. Bone scintigram obtained from Patient 2. Decreased uptake is seen in left femoral head (left). Increased uptake is noted in distal femur on anterior view of knees (right).

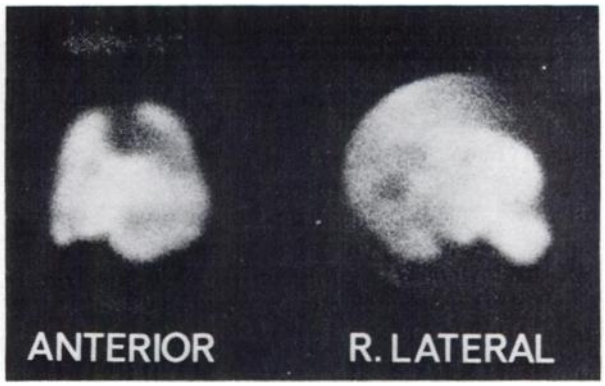

FIG. 6. Liver scintigram in Patient 3 shows hepatomegaly with multiple areas of decreased tracer uptake; also marked shift of radiocolloid to lung.

was found to be grossly nodular, with enlarged left lobe. The biopsy showed wide fibrous bands and massive infiltration by Gaucher cells in the central lobular region. Liver-spleen scintigraphy performed 3 weeks later showed a greatly enlarged liver with the left lobe larger than the right (Fig. 6). Multiple focal areas of decreased tracer uptake included a large area in the left lobe measuring 2.5 by four cm, and two in the right lobe, measuring 1.5 by 1.5 cm and three by three cm. Considerable tracer activity was present in the lungs, but no central marrow activity was seen. A repeat study using a new batch of sulfur colloid to rule out technical artifacts gave the same findings. Hepatic angiography performed the following day demonstrated a number of tortuous vessels in the liver, with several areas of hypovascularity compatible with cirrhosis. On the portocavogram, the shunt was found to be nonfunctioning. The patient followed a progressively downhill course and died 22 mo later.

At autopsy, the liver was twice the expected normal weight. No regenerative nodules were seen. Small amounts of residual liver parenchyma were preserved about the portal spaces but heavy fibrous bands obscured the central lobular areas. Typical Gaucher cells were found in the scar tissue, in the hepatic sinusoids and at other visceral sites. Histologic examination suggested that the portal hypertension was secondary to portal-vein obstruction rather than to the infiltrative Gaucher cells (*3*). The bone marrow was massively infiltrated by Gaucher cells. Plasma cells were increased but megakaryocytes were scarce.

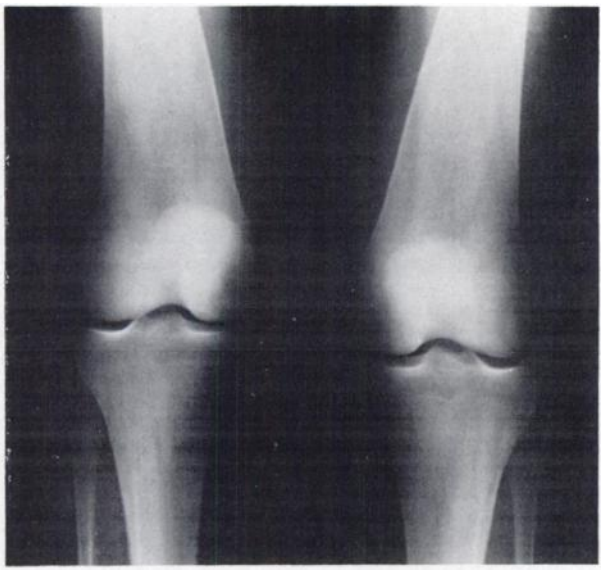

FIG. 5. Radiograph obtained from Patient 2, demonstrating Erlenmeyer-flask appearance and cortical thinning of distal femur.

DISCUSSION

Gaucher's disease is an autosomal recessive disorder caused by a deficiency of beta glucosidase, an enzyme that catabolizes glucosyl ceramide (a metabolic product of many cells) into glucose and ceramide. The glucosyl ceramide accumulates in the body and is stored in the reticuloendothelial cells. The disease usually affects families of Jewish origin, but other ethnic groups may occasionally be affected (*4*).

Depending on the degree of beta-glucosidase deficiency, Gaucher's disease manifests a range of severity, differing in the age of onset, the severity of symptoms, and the prognosis. Diagnosis is usually made by marrow or spleen aspiration. Typical Gaucher cells are 20–80 microns in diameter, round, oval, or spindle-shaped, with eccentric nuclei. Confirmatory diagnosis is done by tissue lipid analysis (*5*).

Classically, there are two forms of Gaucher's disease. The acute infantile form produces abnormal neurologic manifestations and death within the first 1½ years. The more common chronic, nonneurologic form may begin insidiously during childhood or adolescence with slowly progressive splenomegaly over a period of years. The earliest symptoms usually arise from the enlarged spleen or bone-marrow infiltrate. Massive infiltration by Gaucher cells causes hepatomegaly. Bone-marrow infiltration causing pathologic fractures of the long bones and vertebrae is noted in later stages of the disease. Anemia, leukopenia, and thrombocytopenia may be related to hypersplenism and, in late stages, bone-marrow insufficiency. Repeated episodes of pulmonary infection may occur, particularly if the disease shows clinical manifestations in childhood (*4*).

The first patient in this report was essentially asymptomatic. The second patient had hypersplenism, liver function abnormalities, skeletal changes, and pneumonia. The third patient had multiple bony fractures and complications of portal hypertension and died of hepatic failure.

Since Tc-99m sulfur colloid is phagocytized by the same

reticuloendothelial cells that store the body's excess glucosyl ceramide, it is not surprising that the first patient showed inhomogeneous and decreased hepatic uptake. Interestingly, the hepatocellular dysfunction was not apparent from the serum liver function tests. The liver-spleen scan showed only mild hepatomegaly with slight inhomogeneity of tracer uptake. Apparently the liver had sufficient reticuloendothelial reserve so that no shift of activity to the marrow or lungs was seen.

In the third patient, the picture was that of end-stage liver disease. Since the patient was surgically asplenic, the reticuloendothelial system in the lungs took over a significant portion of the phagocytic activity (*6*). No bone-marrow activity was observed because the marrow was heavily infiltrated by Gaucher cells. The absence of central bone-marrow uptake in the face of severe hepatic disease, with shift of colloid to other reticuloendothelial sites, indicates suppressed reticuloendothelial marrow function and is consistent with massive Gaucher-cell infiltration of the marrow. Frank liver failure with portal hypertension, as seen in this case, is rare in Gaucher's disease (*3*). Only six other such cases have been reported.

About three-fourths of adult patients affected with Gaucher's disease have radiographically demonstrable skeletal abnormalities. Distal femur involvement causing an "Erlenmeyer flask" configuration is most frequent (*7*). This finding is caused by the expansion of marrow space by the infiltrating Gaucher cells and remodeling of the bone cortices in the metaphyseal and diaphyseal regions (*7*). Vertebrae, hips, shoulders, tubular bones, and pelvis are the next most frequently involved bones (*7,8*). Since the process is slow and chronic, only moderately increased uptake would be expected in the absence of complications such as pathologic fractures.

The decreased tracer uptake in the left hip corresponded to one of the patient's major clinical complaints, although no abnormalities were detected on the serial hip radiographs. Patients with Gaucher's disease commonly have dull pain (attributable to the packing of marrow by Gaucher cells) and episodes of acute bone pain with fever simulating osteomyelitis (*9*). Gaucher's disease also causes avascular bony necrosis (*7*). Since revascularization of the ischemic areas, if prompt enough, has been known to leave no evidence of radiographic bony abnormalities, we feel that the "bone crisis" in Gaucher's disease, as documented on the bone scan in the second case, represented a transient episode of bone ischemia similar to the transient bone ischemia that may occur in sickle-cell anemia.

In the first patient, the normal tracer uptake in the lumbosacral area and the increased uptake in the left knee area correctly reflected the patient's clinical status. The radiographs of the lumbar spine 2 years previously showed degenerative changes. Repeat radiographs would not have been able to distinguish between acute and chronic bony changes.

Though chemical analysis of glucosyl ceramide levels in the serum provides an approximate index of the severity of Gaucher's disease, it does not provide information on organ involvement. The liver-spleen and bone scans identified the organ abnormalities and delineated the extent of involvement not observable with other noninvasive methods.

Recently, successful treatment of this storage disease by enzyme replacement therapy has been reported (*10*). Glucosidase can be purified rapidly and with high yield from human placental tissue (*11,12*). Whether the enzyme is entrapped in the patient's own red blood cells or is given in free form, no adverse reactions were found in four patients treated by this method (*11,13*). The level of accumulated glucocerebroside decreases in the liver and blood over long periods of time (*11,13*). A decrease in liver size has also been reported (*14*). Serial liver-spleen and bone scans may be useful in the followup of therapy.

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