WIDESPREAD ABNORMALITIES OF RADIOCOLLOID DISTRIBUTION IN PATIENTS WITH MUCOPOLYSACCHARIDOSES

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Mucopolysaccharidoses (MPS) are inherited disorders of lysosomal enzymes. We have examined the sites of accumulation of intravenously injected ^{99m}Tc-sulfur colloid in order to assess the regional distribution of phagocytic function in ten patients with MPS: three with Type I (Hurler), five with Type II (Hunter), one with Type III (Sanfilippo), and one with Type VI (Maroteaux-Lamy). Increased lung uptake was observed in 22 of 40 studies (55%) on the five patients with MPS Type II but in none of the 38 studies on patients with other MPS types. All MPS patients had diffuse reticuloendothelial (RE) marrow hypoplasia, despite normal or nearly normal hematocrits and hemoglobin levels, suggesting dissociation of the phagocytic and erythropoietic elements of the marrow. The eight patients with MPS Types I and II all had hepatomegaly and increased splenic uptake. Seven of these patients also had splenomegaly. The two patients with MPS Types III and VI did not have hepatosplenomegaly. These studies indicate that the lysosomal enzymic defect of MPS results in widespread abnormalities of the distribution of phagocytic function in the liver, spleen, bone marrow, and probably the lung as well.

The mucopolysaccharidoses (MPS) are diseases caused by inherited enzyme deficiencies, which result in the accumulation of mucopolysaccharides within cells and body fluids in varying degrees. MPS are subdivided according to the urinary mucopolysaccharide excreted, mode of inheritance, and clinical features (*1*). Serial ^{99m}Tc-sulfur colloid liver–spleen and bone marrow studies were done to monitor the clinical response of ten patients with MPS of various types who were given a series of plasma infusions in an attempt to correct the enzyme deficiency (*2,3*). Although the effects of treatment remain inconclusive, the findings with regard to the radiocolloid distribution, both before and during treatment, were of interest and have not been reported previously.

METHODS

Of the ten patients, three had MPS Type I; five, Type II; one, Type III; and one, Type VI. All patients had a ^{99m}Tc-sulfur colloid liver–spleen and bone marrow study before receiving plasma infusions. Subsequently, the patients returned periodi-

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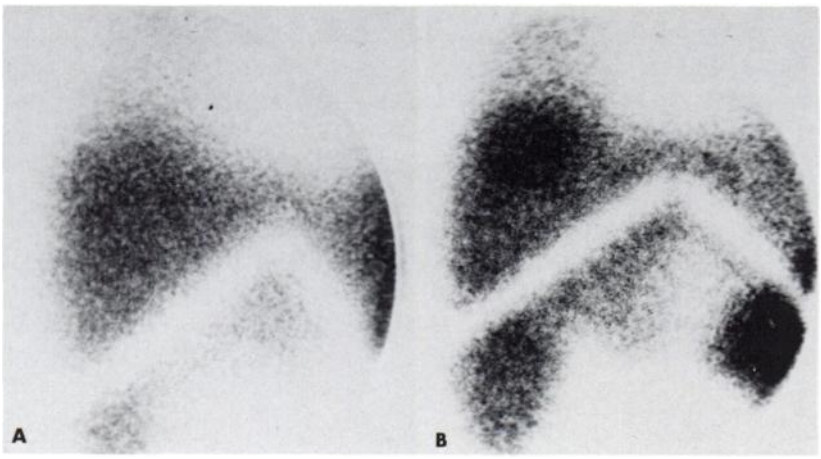

FIG. 1. Mild (A) and moderate (B) increased lung uptake of ^{99m}Tc-sulfur colloid in two patients with mucopolysaccharidosis Type II (Hunter).

TABLE 1. RESULTS OF LIVER–SPLEEN AND BONE MARROW STUDIES ON PATIENTS WITH MUCOPOLYSACCHARIDOSES

			Liver–spleen*				Bone marrow	
Patient	MPS type	Age/Sex	Studies	Lung uptake†	Hepato-splenomegaly	Spleen > liver‡	Studies	Diffuse hypoplasia
1	I	1/F	15	None	Mild	Yes (11/15)	12	Yes
2	I	1/F	9	None	Moderate	Yes	9	Yes
3	I	5/F	12	None	Moderate	Yes	13	Yes
4	II	2/M	4	Moderate (2/4)	Moderate	Yes	3	Yes
5	II	4/M	11	Mild (2/11)	Moderate (liver only)	Yes (5/11)	8	Yes
6	II	6/M	10	Mild (6/10)	Moderate	Yes	10	Initially normal, became hypoplastic
7	II	10/M	7	Moderate (6/7)	Marked	Yes	7	Yes
8	II	16/M	8	Moderate (6/8)	Moderate	Yes	7	Yes
9	III	18/F	1	None	None	Yes	1	Yes
10	VI	2/F	1	None	None	No	1	Yes
			78				71	

* Fractions are given to indicate the number of positive studies in patients in whom the finding was not present on all studies.
† Mild and moderate refer to predominant degree of lung uptake in corresponding patients.
‡ Refers to splenic density as compared to liver density in the anterior scintigram.

TABLE 2. INCIDENCE OF INCREASED LUNG UPTAKE IN MPS PATIENTS AND CONTROL PATIENTS

MPS type	No. of patients	No. of studies	Lung uptake (%)
II	5	40	22 (55)
I, III, VI	5	38	0 (0)
Control group	**Patients done same day as**	**No. of studies**	**Lung uptake (%)**
1	MPS II with lung uptake	84	13 (15)
2	MPS II without lung uptake	68	2 (3)
3	MPS other than Type II	121	7 (6)
Total	All MPS types	273	22 (8)

cally, usually monthly, for ^{99m}Tc-sulfur colloid studies and infusions. The duration of the study for each patient ranged from 1 to 26 months, with an average of 13.5 months.

A ^{99m}Tc-sulfur colloid dose of 5 mCi/m^2 body surface area was used for the bone marrow studies, and a dose of 3 mCi/m^2 was used when only a liver–spleen study was done. The bone marrow study consisted of anterior and posterior rectilinear scans of the whole body, and scintillation camera views, with preset time, of the lateral skull, anterior shoulders, anterior and posterior pelvis, and anterior femurs. In addition, a 100,000-count scintigram of a ^{57}Co sheet source was taken as an image-density reference. The liver–spleen study consisted of anterior, posterior, and both lateral scintillation camera views.

The ^{99m}Tc-sulfur colloid studies were interpreted by one of us (WCK) without knowledge of MPS type. With the imaging technique employed (*4*), normal liver–spleen studies usually show no activity within the lungs, or at most barely detectable activity. Increased lung uptake was determined from the anterior and posterior views and classified as mild, moderate, or marked (Fig. 1). The classification *mild* was used when the lung activity was only a small fraction of that in the liver and spleen. The classification *moderate* was used when the border between the lung and liver or spleen began to be obscured. In this study activity in the lung was never *marked*, i.e., never comparable to that in the liver.

The bone marrow studies were classified as normal, hyperplastic, diffusely hypoplastic, or centrally hypoplastic. Liver and spleen size were interpreted visually with the help of a costal-margin marker on one anterior view. Increased splenic uptake relative to the liver was determined from the anterior view.

RESULTS

Lung uptake of radiocolloid. Increased (mild or moderate) lung uptake of ^{99m}Tc-sulfur colloid was observed in all five patients with MPS Type II (Table 1). These patients had a total of 40 studies of which 22 revealed increased activity within the lungs (Table 2). There were 12 studies with mild lung uptake and 10 with moderate lung uptake. None of the five patients showed increased lung uptake on every occasion, and there was no consistent temporal pattern with the occurrence of lung activity, and no relationship to treatment. The five patients with other MPS types, namely, I, III, and VI, had no increased lung uptake in any of the 38 studies. The difference between the Type II and Type I MPS patients was significant below the 0.001 level. However, the dif-

ferences between the MPS Type II and MPS Types III and VI were not significant because the latter two patients had only one study each. The difference between the incidence of lung uptake among the MPS Type II patients (55%) and among all patient controls examined with the same preparation of colloid as the MPS patients (8%) was significant below the 0.001 level. The fact that all MPS Type II patients were males is explained by the x-linked recessive mode of inheritance for this type, but the fact that the other five MPS patients were all females is probably coincidental and not related to the absence of lung uptake in these patients.

Radiocolloid variability. The average number of liver–spleen studies per day was five, with no instances of increased lung uptake in all patients on any one day. The contribution of radiopharmaceutical variability to the occurrence of increased lung uptake was evaluated by determining the frequency of lung uptake in three groups of patient controls studied under the following circumstances: (A) on days when MPS Type II patients had lung uptake, (B) on days when MPS Type II patients did not have lung uptake, and (C) on days when MPS patients other than Type II were studied (Table 2). The difference between Groups 1 and 2 was significant at the 0.05 level while the difference between Group 3 and Groups 1 and 2 combined was not significant.

Bone marrow studies and hematologic findings. The bone marrow studies revealed diffuse hypoplasia of recticuloendothelial (RE) marrow in all studies on all patients, with one exception. Patient 8, MPS Type II, had a normal pattern initially that became progressively hypoplastic. Examples of a normal pediatric bone marrow study, and of diffuse hypoplasia in Patient 3, MPS Type I, are shown in Fig. 2. Hematologic values were available on all patients except Patient 9. The remaining patients had normal or nearly normal hematocrits and hemoglobin levels except Patient 10, who had a microcytic hypochromic anemia with a hematocrit of 29. This anemia was probably secondary to poor eating habits and iron deficiency.

Three of the five MPS Type II patients were consistently neutropenic (less than 3,000 neutrophils/mm^3), with the degree of neutropenia correlating with the frequency and degree of lung uptake and with the patient's age. The other two MPS Type II patients, 5 and 6, did not have neutropenia, but they had only three white blood counts, two of which were not at times when they showed lung uptake. For all

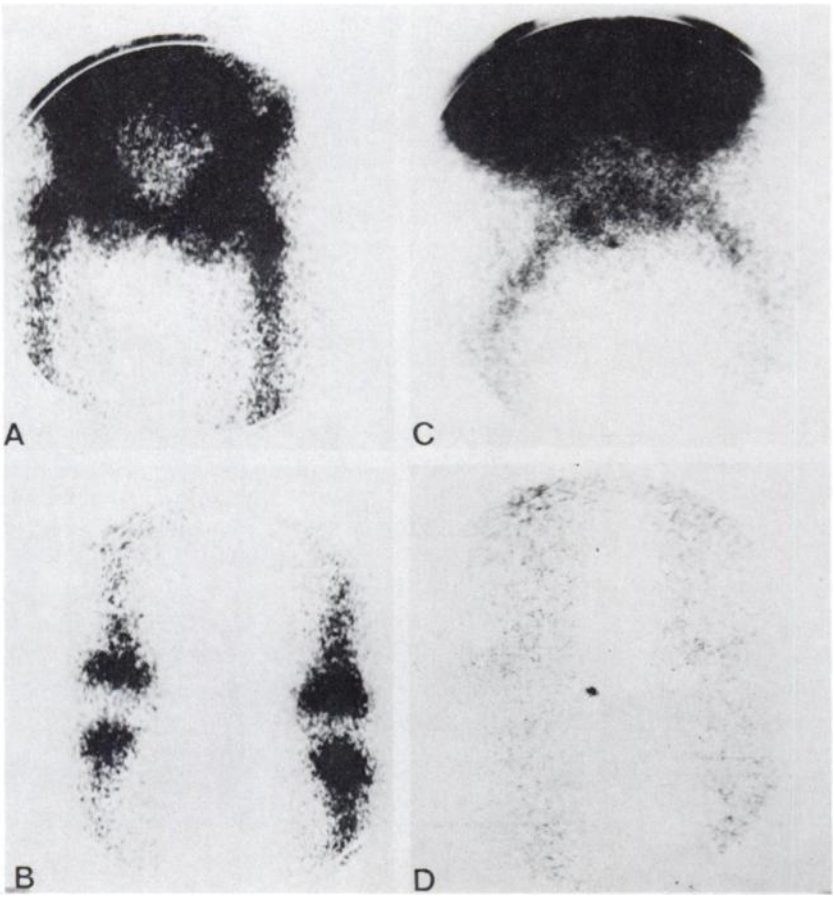

FIG. 2. Bone marrow images of pelvis and knees in 6-year-old normal patient (A and B) and in 5-year-old MPS Type I (Hurler) patient with diffuse hypoplasia of bone marrow (C and D).

MPS Type II patients the correlation coefficient between neutropenia and frequency of lung uptake was 0.55, and between neutropenia and age was 0.68, but neither of these were significant at the 0.05 level in this small number of patients. Three of the four MPS patients other than Type II had normal neutrophil counts, and the fourth, Patient 1, was mildly neutropenic.

Liver–spleen studies and liver function tests. The liver–spleen images revealed hepatosplenomegaly in all patients with MPS Types I and II except Patient 4, who had hepatomegaly only. The single studies of MPS Type III and VI did not show hepatosplenomegaly. In anterior scintigrams, increased splenic uptake of ^{99m}Tc-sulfur colloid, relative to the liver, was present in all patients except the one with MPS Type VI. This finding tended to be progressive in Patients 1 and 4 (Table 1), who did not show increased splenic uptake on every study. Examples of increased splenic uptake in MPS Types I and II are shown in Fig. 3. All liver function tests were within normal limits.

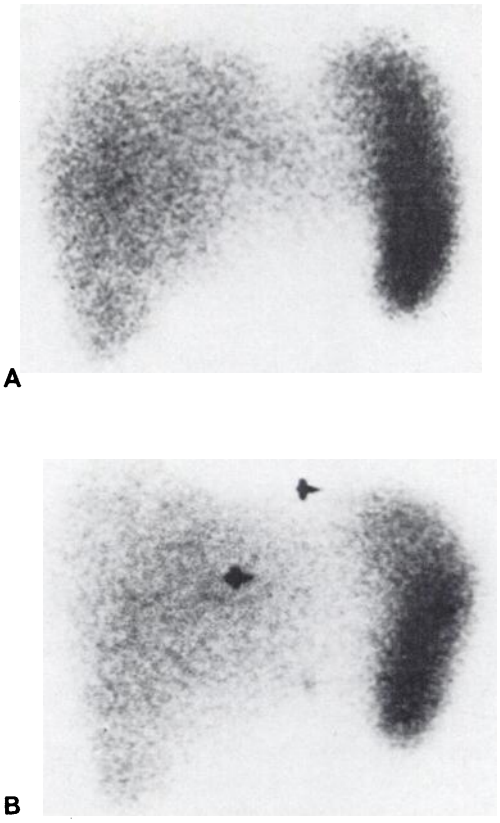

FIG. 3. (A and B) Hepatosplenomegaly and increased splenic uptake of ^{99m}Tc-sulfur colloid on anterior views in patients with mucopolysaccharidoses Types I and II, respectively.

DISCUSSION

The mucopolysaccharidoses are a group of inheritable diseases resulting from lysosomal enzyme deficiencies and characterized by accumulation of mucopolysaccharides in tissue lysosomes and body fluids including the urine (*5*). The accumulation occurs in a wide variety of cells and increases with time, resulting in progression of the disease with increasing age. Mucopolysaccharides are synthesized in fibroblasts and excreted extracellularly. Some of the substance passes into the blood stream and appears in the urine. Other cells take up the mucopolysaccharides by endocytosis, i.e., pinocytosis and phagocytosis, with subsequent accumulation in lysosomes (*6*). The process is particularly prominent in RE cells and is reflected in the widespread abnormalities in radiocolloid studies found in this investigation.

All ten patients with MPS had diffuse hypoplasia of the RE marrow despite the fact that erythron abnormalities are not a feature of MPS in general, and the peripheral erythrocyte findings were normal or nearly normal in the present study with one exception. Dissociation of the degree of involvement of different marrow elements has previously been reported in severe hematologic disorders (*7*) and following irradiation (*8*). In these cases, however, the RE marrow was usually preserved while the erythropoietic marrow was impaired—exactly the opposite of the findings in MPS. While radioactive iron studies were not done in our MPS patients, the nearly normal peripheral RBC findings suggest that the erythropoietic marrow was relatively normal.

Hepatosplenomegaly is usually present in MPS Types I and II. This condition is usually only slight to moderate in MPS Type III and, while it is a common finding in MPS Type VI after the age of 5, our patient was studied at age 2 (*1*). The hepatosplenomegaly is secondary to accumulation of mucopolysaccharides in the lysosomes of the hepatocytes and in macrophages of the liver and spleen (*9*). Nevertheless, there is usually little functional impairment of the liver in MPS (*1*), and in our patients no significant abnormalities of liver function were found.

Increased splenic uptake of ^{99m}Tc-sulfur colloid was present in all patients except the one with MPS Type VI. This finding occurs most often in cases of diffuse hepatic parenchymal disease, neoplasm, and diabetes mellitus (*10*). In MPS it is probably related to diffuse hepatic parenchymal disease and splenomegaly.

The increased lung uptake of colloid was of particular interest. It has been observed in a number of diseases including malignant lymphomas (*11,12*), metastatic carcinomas (*12*), intra-abdominal infections (*12*), cirrhosis (*13*), and liver transplants (*13*). In the present study, significant lung uptake

occurred in 55% of studies on the five patients with MPS Type II (Hunter), but in none of 38 studies on the other five MPS patients. Increased lung uptake is generally associated with a poor prognosis in cancer and cirrhosis (*12*), yet MPS Type II (Hunter) has a significantly better prognosis than MPS Type I (Hurler). Among the MPS Type II patients, however, the frequency and degree of lung uptake tended to increase with age and thus with progression of the disease.

The mechanism of increased lung uptake is not definitely known, although there are data against the involvement of a plasma factor (*14*) and for gradual accumulation of the ^{99m}Tc-sulfur colloid in the lung which would favor a phagocytic mechanism rather than embolization of macroaggregates (*11*). In animals, increased lung uptake has been produced by the intraperitoneal injection of endotoxin (*15,16*), and autoradiographic examination of the lungs of these animals demonstrated that the ^{99m}Tc-sulfur colloid was associated with cells (*15*). Therefore, the evidence to date suggests increased RE activity in the pulmonary capillary bed. It has been suggested that the increased pulmonary RE activity may reflect a monocytosis (*17*) and, in general, there is a similarity between the diseases associated with lung uptake (*12*) and those associated with monocytosis (*18*). However, a significant monocytosis was not found in the MPS Type II patients, although neutropenia, which was prevalent among these patients, is a known cause of monocytosis (*19*).

The many studies done on each patient who had increased lung uptake allowed us to test for colloid variability. The 15% incidence of lung uptake in control patients, done on days when MPS Type II patients had lung uptake, was significantly different from the 3% incidence of lung uptake among patient controls done on days when MPS Type II patients did not have lung uptake. The overall incidence of lung uptake among these patient controls, however, was not significantly different from the incidence among patient controls studied on days when MPS patients other than Type II were studied. These findings support the concept that variation in ^{99m}Tc-sulfur colloid preparations influences the incidence of lung uptake in addition to endogenous factors.

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