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Mannosidosis: two brothers with different degrees of disease severity

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Two siblings with different degrees of mental retardation, skeletal dysplasia, coarse facies, delayed speech, motor incoordination, recurrent respiratory infections, and immunological abnormalities, were found to have deficient alpha-mannosidase activity. Cultured skin fibroblasts in one sib were markedly deficient in alpha-mannosidase while all other lysosomal enzymes tested were within the normal range. The more severely affected sib came to autopsy and was found to have "washed-out" appearing cortical neurons and marked histiocytosis effacing lymph node architecture and partially replacing the bone marrow. The post-mortem brain and liver samples demonstrated a deficiency in alpha-mannosidase relative to the elevations of other lysosomal enzymes. Although the patterns of abnormalities in the two cases closely match those of descriptions of "type II" and "type I" mannosidosis respectively, the variation should be due to genetic modifiers or environmental effects since the brothers must have shared similar alpha-mannosidase mutations. Immunologic abnormalities present in the more severely affected sib suggest that the differential survival seen in mannosidosis types I and II may be due to differences in their immune systems.

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Mannosidosis is a glycoprotein lysosomal storage disease characterized by coarse facies, dysostosis multiplex, hepatosplenomegaly, lenticular opacities, psychomotor retardation and recurrent upper respiratory infections (Kjellman et al. 1969, Autio et al. 1973, Arbisser et al. 1976, Aylsworth et al. 1976, Booth et al. 1976, Desnick et al. 1976, Spranger et al. 1976, Kistler et al. 1977, Vidgoff et al. 1977, Bach et al. 1978, Letson & Desnick 1978). Affected individuals have a decrease in the acidic alpha-mannosidase isozymes, which results in the accumulation of mannose-rich oligosaccharides in their tissues and urine.

Considerable heterogeneity has been found among patients with biochemically proven mannosidosis. The current literature reflects the belief that there are two forms of mannosidosis, a severe, Mannosidosis I, and a mild, Mannosidosis II, forms (Booth et al. 1976, Bach et al. 1978). We present two sibs whose findings suggest that the difference may not be due to allelic variation at the structural locus for alpha-mannosidase.

Materials and Methods

Autopsy Studies

Hematoxylin and eosin stained sections of formalin fixed tissue were routinely prepared of postmortem visceral specimens

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from Case 1. The brain was fixed in formalin and microscopic sections were prepared by paraffin embedding and frozen sections, and stained with hematoxylin and eosin, cresyl violet luxol fast blue-eosin, phosphotungstic acid hematoxylin, sudan IV, sudan black, oil red 0, nile blue sulfate, and by the periodic acid Schiff Reaction (PAS).

Enzyme Assays

β-galactosidase activity and β-glucuronidase activity were measured using the p-nitrophenol substrates as previously detailed (Hieber et al. 1980). The activities of α-mannosidase, α-fucosidase, and β-hexosaminidase were determined using the p-nitrophenol substrates and citrate-phosphate buffer, as described by Thomas et al. (1973). Activity of α-glucosidase was assayed using the p-nitrophenol substrate and citrate-phosphate buffer, as described by Fluharty et al. (1973).

Cultured skin fibroblasts were grown in Eagle's minimal essential medium containing 10 % fetal calf serum in 25 cm^2 Falcon flasks. For enzyme analysis cells were harvested by trypsinization, washed 2 times with 0.9 % NaCl and resuspended in 0.5 ml of 0.9 % NaCl. The cells were disrupted by 3 to 4 cycles of freezing and thawing in a dry ice-acetone mixture. Aliquots of the lysates were analyzed for enzyme activity by the procedures described above and for protein content (Lowry et al. 1951). Homogenates (10 % w/v) of tissue samples were prepared in 0.9 % NaCl. The homogenates were then centrifuged at 27,000 × g for 20 min and the supernatants assayed for enzymatic activities and for protein content as above.

Case Reports

Case 1

P.P., a 19-year-old Caucasian male, was admitted for evaluation of intermittent fevers to 107°F and supraclavicular lymphadenopathy. The patient was the product of a normal pregnancy and delivery. He was troubled with frequent upper respiratory infections associated with high temperatures in his first 3 years of life, at which time he was institutionalized. On examination at his admission to the institution the patient was only able to say a few words. He had just started to feed himself and walk with support. While at the institution the patient had approximately two severe respiratory infections each year. Psychological evaluation 1 year prior to admission showed that the patient had a score of SQ 9 on the Vineland Social Maturity Scale (profound mental retardation).

Family history revealed a less severely, but similarly affected, male sibling (Case 2). The patient also had a sister with "curvature of the spine" and a normal brother. Both parents were healthy, of English extraction, and came from the same small town in Kentucky (population c. 3000). No history of consanguinity was elicited. There was no other history of a similar disorder.

Physical exam revealed a severely mentally retarded young Caucasian male, 142 cm tall, and weighing 44 kg, who was unable to walk or sit up without assistance. He had a coarse voice and was unable to speak. His head was very large and asymmetrically scaphocephalic with normal pinnae. His face was characterized by hypertelorism, a low flat nasal bridge, small nose, and prominent massive mandible. He was without patulous lips, sagging skin, or macroglossia. The patient's mouth showed a narrow, high-arched palate and dental malocclusion. His teeth were not wide-spaced. There were no corneal opacities. The patient's neck was short with prominent posterior cervical and supraclavicular lymphadenopathy. The patient had a barrel chest with scoliosis and a flared rib cage. Cardiac examination revealed a grade III/VI systolic left ventric-

ular outflow murmur heard at the apex and radiating into the neck. The liver and spleen were not palpable and there was no evidence of inguinal or ventral hernia. The patient's upper extremities were thin with decreased muscle mass. Muscle tone was normal. He was without flexion contractures and had full range of motion in all upper extremity joints. His hands were essentially normal except for trace edema. His lower extremities showed spastic paraparesis with flexion contractures at both hips and knees. The feet were pronated with trace edema to the ankles. He had clubbing of his toes. The skin was smooth and soft. Neurological examination revealed cranial nerves II–VII and IX–XII to be grossly intact. Response to various sounds could not be elicited. The patient responded to pain in all four extremities. His deep tendon reflexes were 2 plus bilaterally in his upper extremities and 4 plus at the knees, with bilateral Babinski signs.

On admission, the patient had a normochromic, normocytic anemia with a hemoglobin of 7.0 g %. Serum iron was 39 μg % and total iron binding capacity was 175 μg %. Reticulocyte count was 1.4 %. He had only 2,600 WBCs/mm^3 with a large left shift on peripheral smear (63 PMNs, 25 stabs, 4 lymphocytes, 8 monocytes). No vacuolated lymphocytes were seen on peripheral smear. His prothrombin time was 100 % of control and his PTT was 54.5 s with a control of 31 s. He had 169,000 platelets/mm^3. Creatinine was 0.7 mg % with a serum urea nitrogen of 23 mg %. The patient was anergic with hypogammaglobulinemia, low T rosettes, low CH_{50}, and normal C3 and C4. Admission EKG, urinalysis, and chest X-ray were unremarkable.

A gallium scan showed increased uptake in the right supraclavicular area. Aspiration of a right knee effusion was sterile and consistent with Pigmented Villonodular Synovitis. Bone marrow biopsy and aspirate from the right iliac crest were felt to show erythroid hyperplasia, but were otherwise normal. A right supraclavicular lymph node biopsy showed marked alteration of lymph node architecture, owing to a lack of follicular centers and paracortical T zone. There was cellular proliferation with large vacuolated histiocytes scattered among rare lymphoid cells. Several large Reed-Sternberg-like cells were seen, but the histological picture was not that of Hodgkin's disease.

An EEG had been performed approximately 1 year prior to this admission and showed 14 and 6 s spike seizure activity in both hemispheres with an abnormal slow background both waking and sleeping. Lumbar puncture revealed CSF glucose of 57 mg/100 ml with a serum glucose of 109 mg/100 ml and CSF protein of 22 mg/100 ml. A computerized tomogram scan showed that the entire ventricular system was generous in size. Some cerebral sulci, including those along the inter-hemispheric fissure, were prominent. This combination suggested ventricular enlargement secondary to loss of cerebral substance or developmental brain deformity. No intra-cerebral calcifications were seen.

The patient was treated with various parenteral antibiotics from the 4th to the 15t he hospital day without change in his temperature which regularly spiked to 104–105°F orally in the evening. Antibiotics were discontinued when all cultures continued to be negative for significant organisms. A supraclavicular lymph node biopsy was performed on the 22nd hospital day. The patient was somnolent after the procedure and developed heart failure with increasing peripheral and pulmonary edema. His fever persisted and his condition deteriorated over the ensuing 6 days. The patient died on the 28th hospital day.

Radiographic findings. The skull vault was thickened with very prominent supraorbital

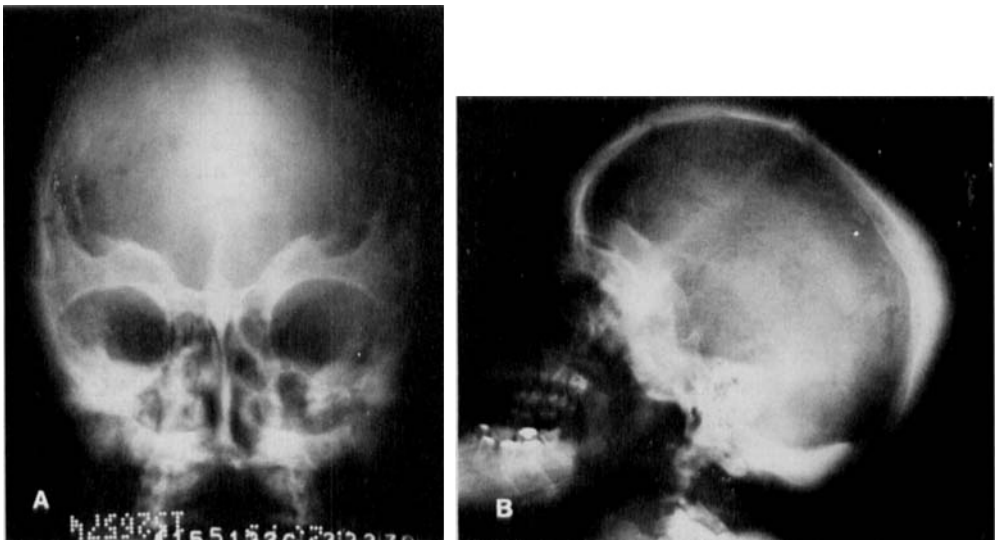
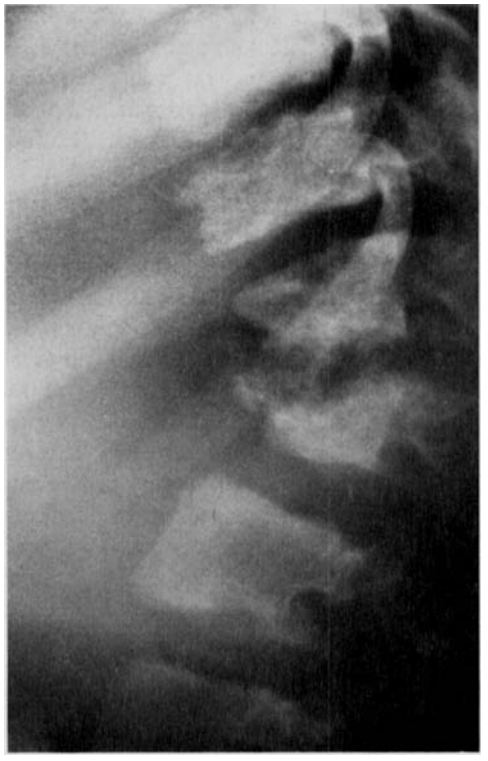


Fig. 1A & 1B. (Case 1) Radiographs of skull, AP and lateral. Note the marked thickening of the cranial vault, particularly in the occipital region and in the frontal area. The supraorbital region is particularly thickened.



ridges which were densely ossified (Fig. 1). The mandible was large. The pelvis was deformed with irregular steep acetabulae, coxa valga deformity bilaterally and small iliac wings. There was marked anterior wedging of L1 and L2 with some flattening of the vertebrae above this level (Fig. 2). The ribs were somewhat broad and had an unusual deformity with a "coathanger" appearance. The remaining bones were not remarkable. There was some bowing of the tibias. The hand bones were relatively normal with no widening of the medullary spaces. The bone age was retarded; approximately 13 years according to the male standards of Greulich and Pyle. Some small metaphyseal irregularities were seen in the middle phalanges of the hand. In the knees,

Fig. 2. (Case 1) Radiograph of spine. There is anterior wedging of L1 and L2 with irregularity of the joint space and considerable beaking. There is some flattening of the vertebrae above this level as well. The proximal ribs appear thickened and bow inferiorly.

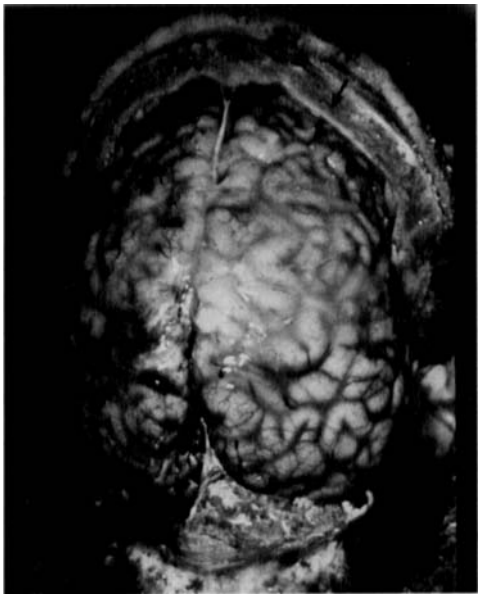


Fig. 3. Head with top of skull removed at autopsy shows the greatly thickened frontal (arrow) and parietotemporal skull. The brain, in the fresh state, shows a little more connective tissue in the leptomeninges at the vertex than usual in a teenage subject. White marks are highlights from photographic flash.

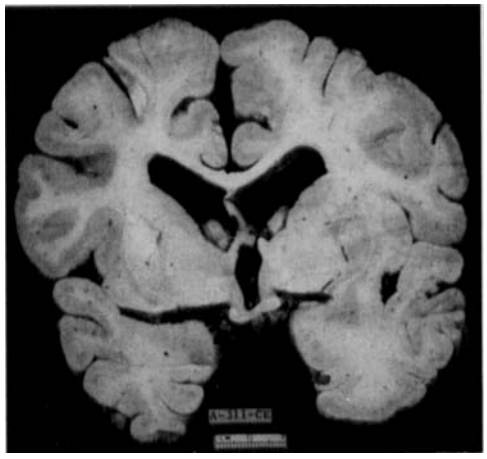


Fig. 4. Frontal section of the fixed brain in a plane through the optic chiasm showing enlarged lateral ventricles and widening of some sulci.

some accessory ossification was seen below the patella.

Autopsy findings. Dissection showed a skull thickened to 1.5 cm over the vertex and in the frontal and parietotemporal regions. The brain weighed 1420 g and it showed slightly increased connective tissue in the leptomeninges over the vertex of the cerebral hemispheres. Some gyri in several regions were wider than usual, but otherwise the appearance of the brain was not remarkable (Fig. 3). The lateral ventricles were enlarged, the cerebellar hemispheres were smaller than normal, and the substantia nigra was pale but pigmented (Fig. 4). The lymph nodes of the cervical, axillary, abdominal and inguinal region were enlarged,

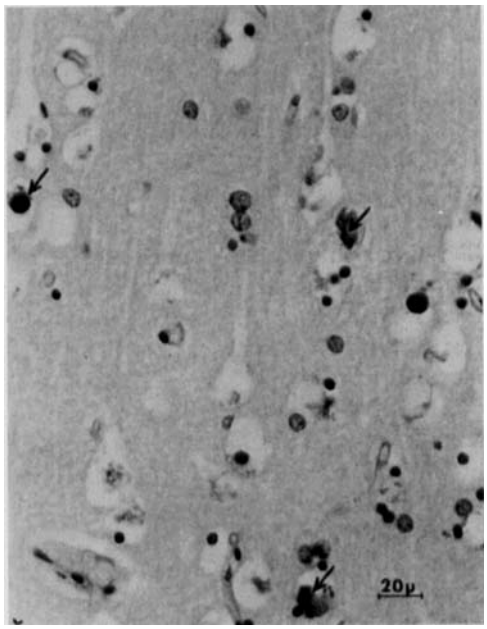


Fig. 5. Microscopic section of paraffin-embedded motor cortex stained for PAS reaction product and with hematoxylin shows virtually washed out nerve cells, but with some abnormal aggregates of PAS stained material in the cytoplasm (arrows). Most nerve cells show stippled foci of faintly PAS-stained material, interpreted as lipofuscin.

up to about 3 × 2 × 2 cm, especially in the abdominal aortic region.

Histological examination showed that the cytoplasm of most nerve cells was moderately distended and in most instances presented a "washed-out" appearance. PAS stains, however, showed that some cells contained cytoplasmic aggregates of PAS positive staining material (Fig. 5). Many cells also showed small foci of stippled material that contained PAS reaction product and gave a faintly positive lipid stain (Fig. 6). This material was interpreted as lipofuscin. A very few nerve cells retained virtually normal appearance and staining reactions. There was significant loss of Purkinje neurons in the cerebellum.

Microscopically, most of the enlarged lymph nodes were composed almost entirely of large, somewhat pleomorphic, polygonal histiocytes in a matrix of fairly dense connective tissue. Other lymph nodes were filled with large round mononuclear cells with pale-staining cytoplasm that was finely granular. The cytoplasm failed to stain for PAS-positive material, or for lipids with oil red 0. Samples of bone marrow and spleen showed diffuse infiltration with histiocytes like those in most of the lymph nodes. Hematopoietic tissue was diminished in the bone marrow samples. There were very few lymphocytes in the lymph nodes, spleen, marrow, or lamina propria and Peyer's patches of the intestine.

Both pre- and postmortem blood cultures grew *Klebsiella pneumoniae*. The immediate cause of death was considered to be septicemia.

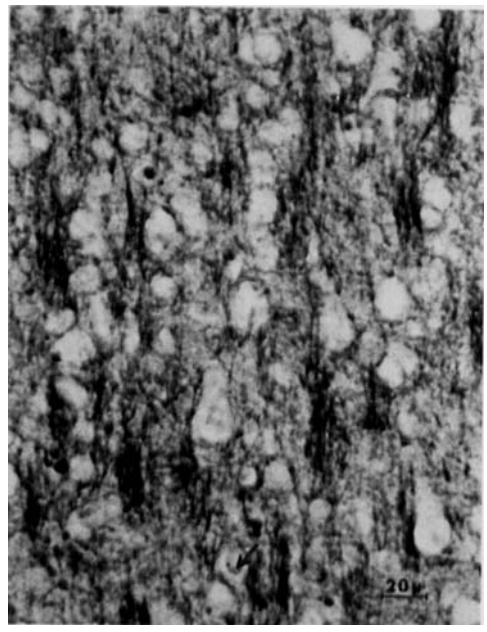


Fig. 6. Frozen section of formalin-fixed cortex stained with oil red 0 for lipid shows well-stained vertically oriented, normal appearing myelinated fibers and a few droplets of artefactitious lipid positive material. Arrow indicates a stippled focus of faintly lipid positive material, interpreted as lipofuscin, in the cytoplasm of a nerve cell which otherwise appears washed out.

Case 2

M.P., the 17-year-old male sib of P.P., lives at home with his parents and has attended a school for trainable retarded children since he was 5 years of age. He was the 8 pound 2 ounce full-term product of a normal delivery. The patient spoke words at 2½–3 years of age. At the time of his brother's admission he was able to read at an early elementary level. The patient's past medical history was remarkable for several hospitalizations for dental extractions, restorations, and enucleation of granulomata at the apices of his teeth. He had also been troubled with frequent upper respiratory infections and episodes of otitis media. He had a tonsillectomy and adenoidectomy when 4 years of age and a repeat adenoidectomy with bilateral myringotomies at age 11. During this last procedure he had a cyanotic episode which resolved without known sequelae. Microscopical examination of adenoid tissue showed numerous large histiocytes with foamy cytoplasm. Material

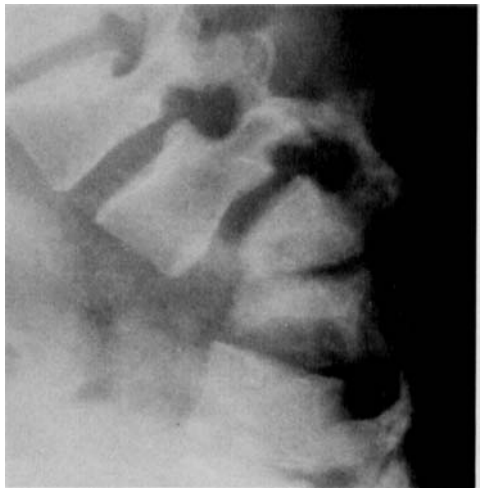


Fig. 7. (Case 2) Lumbar spine radiograph. Note the almost identical changes seen in Case 1.

Fig. 8. (Case 2) Cervical neck radiograph showing absence of ondontoid. On flexion films subluxation was noted.

in vacuoles was PAS negative and fat stain negative at that time.

On physical examination the patient was a well-developed, slightly obese, young Caucasian male, 167 cm tall and weighing 86 kg. He was normotensive and afebrile. He spoke in a normal voice without impediment. His facies resembled that of his brother, with a low flat nasal bridge, prominent mandible and slight hypertelorism. His head was symmetrical, did not seem large, and he had normal pinnae. He had unremarkable retinal fields and no corneal or lenticular opacities (although no slit-lamp examination was performed). He had a narrow, high-arched palate and dental malocclusion. His neck was short and broad without lymphadenopathy. There was marked kyphosis of the spine. The patient exhibited pectus carinatum. Cardiac examination showed a grade III/VI systolic left ventricular outflow murmur, loudest in the 2nd right intercostal space and radiating to the neck. Carotid upstroke was normal and there were no extra sounds. The patient's pulse was 90 with occasional extra beats. There was no abdominal organomegaly or evidence of hernia. Cranial nerves II–XII were grossly intact. He spoke in single words and short phrases and was unable to accomplish simple calculations. Sensory and motor examinations were normal, except for some impairment of cerebellar function. The patient walked with a flat-footed, shuffling gait and turned without assistance but used approximately 5 steps to make a 180° turn. He was unable to do heel and toe walking or serial apposition of the fingers. Extremities were unremarkable. He had full range of motion of all joints. There was slight cubitus valgus bilaterally.

The patient has a normal skin reaction to *Candida albicans*. His serum protein

Table 1

Lysosomal enzyme activities in patient and control postmortem tissues

Enzyme	Brain			Liver		
	nmol/mg protein/min			nmol/mg protein/min		
	Case 1	Control	Ratio P/C	Case 1	Control	Ratio P/C
β-galactosidase	0.34	0.15, 0.16	2.19	21.6	7.86, 4.64	3.46
β-glucuronidase	0.097	0.029, 0.031	3.23	30.5	10.2, 7.1	3.53
β-N-acetylhexosaminidase	10.9	1.64, 1.62	6.68	303	77, 19.7	7.76
α-glucosidase	0.464	0.040, 0.039	11.74	21.2	1.75, 0.73	17.1
α-L-fucosidase	0.067	0.025, 0.020	2.98	11.3	3.02, 2.26	4.28
α-L-mannosidase	0.013	0.010, 0.026	0.72	1.34	1.76, 2.73	0.60

electrophoresis and serum IgG, IgA, IgM, C3 and C4 levels were normal.

Radiographic findings. This sibling had much milder radiological manifestations than his brother. There was some thickening of the cranial vault, particularly in the occipital region. The supraorbital ridges were not prominent. The mandible was quite as large as in the brother. The beaking of L1 and L2 was almost identical to that of his brother (Fig. 7). The ribs were thick but did not have the "coat hanger" appearance. There was mild bowing of the long bones. One additional finding in this case was absence of the odontoid and subluxation of the atlantoaxial joint (Fig. 8).

Enzyme assays. Analysis of postmortem brain and liver samples from Case 1 showed increased values of the following lysosomal enzymes compared to controls: β-galactosidase, β-glucuronidase, β-N-acetyl-hexosaminidase, α-glucosidase, and α-L-fucosidase. There was a slight decrease in α-L-mannosidase compared to controls in both liver and brain (Table 1). This decrease became quite remarkable when contrasted to the levels of the other enzymes, i.e. brain α-mannosidase was 7–33 % of normal if the other enzymes were taken as the standard. Similarly, cultured skin fibroblasts from Case 2 (permission for skin biopsy of Case 1 was refused and an attempted postmortem skin culture was grossly contaminated) showed normal β-galactosidase, β-glucuronidase, and α-L-fucosidase levels compared to controls, but markedly decreased α-mannosidase activity at pH 4.0 (Table 2). The remaining alpha-mannosidase activity from Case 2 showed a shifted pH optimum (Fig. 9) as has been seen previously (Aylsworth et al. 1976).

Discussion

Biochemical evidence of alpha-mannosidase deficiency is thought to be necessary for the diagnosis of mannosidosis. This is due to the overlap of clinical findings among similar storage disorders and the variability of expression of this disease. In recent reviews

Table 2

Lysosomal enzyme activities in patient's cultured skin fibroblasts and controls

Enzyme	nmol/min/mg protein	
	Case 2	Controls
β-galactosidase	14.8, 15.5	12, 13.3, 17.3, 17.9
β-glucuronidase	3.24, 3.37	1.55, 3.24
α-L-fucosidase	7.04	2.91, 10.2
α-mannosidase (pH 4.0)	0.15	2.15, 2.73

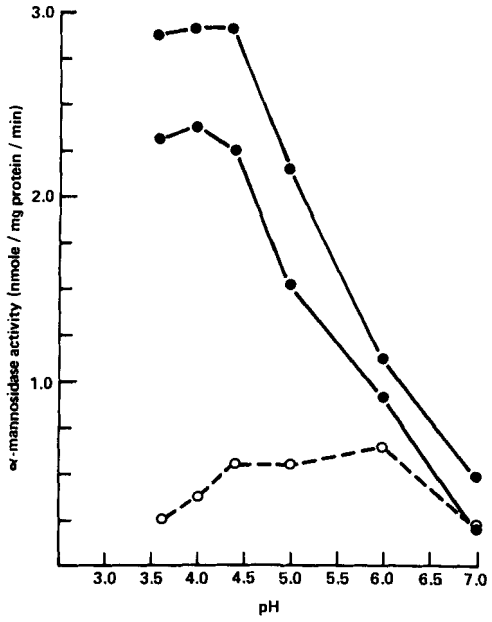


Fig. 9. pH optima of α-mannosidase in cultured skin fibroblasts from two controls contrasted with Case 2.

(Desnick et al. 1976, Kistler et al. 1977, Vidgoff et al. 1977) of the literature concerning this disease group, mannose-containing oligosaccharides in tissues, α-mannosidase deficiency in tissue or cultured fibroblasts, and vacuolated lymphocytes were universally present. The most common clinical findings among the 44 patients reviewed in order of decreasing frequency were: coarse facies, psychomotor retardation, deafness, hernias, frequent infections, and hepatomegaly. Cases described have varied from severely affected infants (Autio et al. 1973, Aylsworth et al. 1976) to young adults with more benign courses (Booth et al. 1976, Kistler et al. 1977). The age range is from 1 to 26 years of age with a median age of 5 (Öckerman 1967, Kjellman et al. 1969, Autio et al. 1973, Arbisser et al. 1976, Aylsworth et al. 1976, Booth et al. 1976, Desnick et al. 1976, Spranger et al. 1976, Kistler et al. 1977, Vidgoff et al. 1977, Bach et al. 1978, Letson & Desnick 1978). Patients with a milder course have had less severe mental retardation, minimal roentgenographic abnormalities, more normal stature and longer survival (Booth et al. 1976, Desnick et al. 1976, Grabowski et al. 1977, Kistler et al. 1977, Bach et al. 1978, Letson & Desnick 1978). Only approximately 50 % of patients (Öckerman 1967, Letson & Desnick 1978) have thickened calvaria. Flaring of the iliac wings, acetabular hypoplasia, coxa valga, and vertebral body abnormalities were somewhat more common in a review of 12 patients with mannosidosis (Spranger et al. 1976). Desnick et al. (1976) have separated the mannosidosis group into type I and type II homozygotes. Type I homozygotes are patients with severe disease and type II patients have more benign disease.

In addition to clinical heterogeneity, biochemical and roentgenographic heterogeneity have been described. Burton & Nadler (1978) found variable Km's for α-mannose among mutant skin fibroblast cell lines suggesting multiple allelic variations in α-mannosidase. Some type II homozygotes have been shown to have only a partial deficiency of α-mannosidase (Bach et al. 1978). Grabowski et al. (1977) demonstrated differential α-mannosidase stabilities with heat inactivation and different Km values at pH 4.4 in type I and II variants.

The characteristic light microscopic histological features of mannosidosis which have been described (Öckerman 1967, Kjellman et al. 1969, Autio et al. 1973, Dickersin et al. 1980) include PAS-positive cytoplasmic vacuoles in lymphocytes from peripheral blood, bone marrow, spleen and lymph nodes. Large storage cells with clear cytoplasm have been described throughout the central nervous system, in the retina, and myenteric plexus. In addition, coarse, darkly staining granulocyte granules have been seen.

The findings in Cases 1 and 2 are sum-

Table 3

Clinical and laboratory findings in two cases of mannosidosis

Age/Sex:	Case 1 19♂	Case 2 17♂
Deficient acidic α-mannosidase activity	+	+
Vacuolated lymph node histiocytes	+	+
Psychomotor retardation	+	Less marked
Coarse facies	+	Less marked
Frequent upper respiratory infections	+	+
Deafness	+	−
Organomegaly	Splenomegaly	−
Hernia	−	−
Joint disease	+	−
Lenticular opacities	−	−
Skeletal dysplasia	+	Less marked
Immune status:	↓ CH_{50} ↓ T Rosettes Hypogam. Anergic Normal C3, C4	+ Candida skin test − Mumps skin test Normal C3, C4

marized in Table 3. The pattern of abnormalities shown matches that of the type I and type II groups quite well (Desnick et al. 1976, Letson & Desnick 1978). Case 2 had less severe psychomotor retardation, dysostosis multiplex and facial dysmorphology. Unlike Case 1, his immunological assays were normal and he had no evidence of deafness or history of joint disease. Both brothers were without hepatomegaly or apparent ophthalmologic abnormalities. Enzymatic assays on postmortem tissue in Case 1 and cultured skin fibroblasts in Case 2 revealed decreased α-mannosidase activity in both instances. At autopsy, Case 1 was found to have splenomegaly, enlargement of the lateral ventricles of the brain, and generalized lymphadenopathy. Histologic examination revealed "washed-out" appearing cortical neurons with some abnormal PAS-positive cytoplasmic material, and a marked histiocytosis effacing lymph node architecture and partially replacing the bone marrow.

The enlarged histiocytes seen in the adenoids (Case 2) and postmortem material (Case 1) are consistent with the reported histological findings described above. Their negative reaction with PAS is, however, unusual. The absence of a positive PAS reaction in the postmortem material may be due to the histiocytosis being a proliferation secondary to infection with dilution of any PAS-positive material present. The "washed-out" appearance (Öckerman 1967) of cortical neurons with traces of PAS-positive material may be secondary to partial loss of stored mannose-rich material during tissue processing.

Several authors have reported mannosidosis occurring in multiple members of a sibship (Autio et al. 1973, Booth et al. 1976, Spranger et al. 1976, Vidgoff et al. 1977, Bach et al. 1978). In all but one of these sibships, the affected patients had very similar phenotypical findings. Spranger et al. (1976) described 6, 9, and 12-year-old sisters, the youngest of whom had less severe findings than her sibs. The findings in that case and in the brothers described here, tend to support the notion that the two types of mannosidosis characterized by

differing degrees of severity are not always due to allelic variation. Even with the possibility of false paternity, the likelihood of finding two different α-mannosidase homozygotes or compound heterozygotes in one family is several hundred to one. Since both brothers presumably shared the same α-mannosidase mutations(s), any difference in gene expression should be due to environmental effects or modifier genes acting differentially on the two sibs. Certainly the computerized tomographic scan and gross brain findings in Case 1 of some enlarged gyri, lateral ventricle enlargement, and small cerebellar hemispheres are not specific for mannosidosis. Similar findings are found in other brain disorders of pre- and perinatal origin. Consequently, it seems possible that some additional environmental or genetic insult led to the increased severity of mental retardation in Case 1. Wide variation in the severity of mucopolysaccharidosis II (Hunter's) has even been found between fraternal twins (Yatziv et al. 1977).

Desnick and his co-workers (1976) found significant abnormalities of neutrophil function and poor lymphocyte transformation in type I mannosidosis. The presence of poor immune function in Case 1 and normal function in Case 2 suggests that an immunological deficit may account for the differential survival in mannosidosis types I and II.

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