

19.1 Introduction

The oligosaccharidoses are a group of lysosomal storage disorders characterized by defects of glycoprotein degradation due to the deficiency of specific lysosomal enzymes (Fig. 19.1). All are inherited as autosomal recessive traits.

The diagnosis is suggested by the clinical picture. Two general features of lysosomal storage diseases need to be considered. First, although some signs are quite specific or even pathognomonic, an overlap in the clinical presentation often exists between the oligosaccharidoses and other lysosomal storage disorders, and the mucopolysaccharidoses (see Chap. 17). Second, the same enzymatic defect can be responsible for different clinical presentations, variable age of onset, severity and organ involvement. Section 19.4 summarizes the clinical features observed in oligosaccharidoses and related disorders with an early (infantile) presentation, and symptoms described in the late onset types. The same enzymes are responsible for both the early and late onset variants.

Once a lysosomal storage disorder has been considered in a differential diagnosis, a laboratory evaluation must be initiated in order to define biochemically the diagnosis. Two types of urinary screening tests are easily accessible to look for the abnormal excretion of either oligosaccharides or mucopolysaccharides. If positive, this suggests either a disorder in the metabolism of oligosaccharides or of the mucopolysaccharides. The final diagnosis always requires specific enzymatic confirmation in the appropriate biological material (generally leukocytes or cultured skin fibroblasts extracts, rarely plasma). When the screening tests are negative but suspicion is still high, the resolution of the diagnosis may be provided by various assays of lysosomal enzymes, selected on the basis of a thorough clinical examination. A clinical approach, combined with simple laboratory tests, is suggested in the diagnostic flow-charts (see Figs. 19.2, 19.3). Due to the extreme phenotypic variability of many of these disorders, all proposed diagnostic flow-charts cannot replace the critical evaluation of the astute clinician.

The features of lysosomal storage disorders do not meet the requirements for mass screening programs of patients. However, an approach based on the detection of markers, such as lysosomal-associated membrane proteins (LAMP-1 and LAMP-2), has been recently proposed for mass screening of patients with lysosomal storage diseases. Carrier screening programs have been proposed or implemented in populations where a certain disorder is particularly frequent. Examples are aspartylglucosaminuria in Finland or Tay-Sachs disease and Gaucher disease, quite common among Ashkenazi Jews (carrier frequency of 0.032 and 0.10, respectively).

Until a few years ago no efficacious treatment was available for lysosomal storage disorders and a biochemically defined diagnosis was requested only for the genetic counseling, eventually leading to a prenatal diagnosis in pregnancies at risk. Recently, exciting progresses have been made in the treatment of lysosomal storage disorders, based on bone marrow transplantation or enzyme replacement, as in Gaucher disease and other lysosomal storage disorders. In this respect, any patient with a suspicion of lysosomal storage disease is a potential candidate for new therapeutic strategies and deserves a precise diagnosis.

19.2 Nomenclature

No.	Disorder	Enzyme/protein defect	Chromosome localization	McKusick number
Oligosaccharidoses				
19.1.1	α -Mannosidosis type I	α -Mannosidase	19cen-q12	248500
19.1.2	α -Mannosidosis type II			
19.2.1	β -Mannosidosis infantile	β -Mannosidase	4q22-q25	248510
19.2.2	β -Mannosidosis juvenile/adult			
19.3	Fucosidosis	α -Fucosidase	1p34	230000
19.4.1	Sialidosis severe infantile	α -Neuraminidase	6p21.3	256550
19.4.2	Sialidosis mild infantile (mucopolipidosis I)			
19.4.3	Sialidosis adult			
19.5.1	Galactosialidosis (early infantile)	"Protective protein"/cathepsin A deficiency	20q13.1	256540
19.5.2	Galactosialidosis (late infantile)	(Secondary β -galactosidase and α -neuraminidase deficiencies)		
19.5.3	Galactosialidosis (juvenile/adult)			
19.6	Aspartylglucosaminuria	Aspartylglucosaminidase	4q32-q33	208400
19.7.1	α -NAGA deficiency type I (Schindler disease)	α -N-acetylgalactosaminidase	22q11	104170
19.7.2	α -NAGA deficiency type II (Kanzaki disease)			

No.	Disorder	Enzyme/protein defect	Chromosome localization	McKusick number
Related disorders				
19.8.1	GM1 gangliosidosis (early infantile)	β -Galactosidase	3p21.33	230500
19.8.2	GM1 gangliosidosis (late infantile)			
19.8.3	GM1 gangliosidosis (adult)			
19.9.1	GM2 gangliosidosis variant B, infantile (Tay-Sachs disease)	β -Hexosaminidase A (β -subunit)	15q23-q24	272800
19.9.2	Variant B, late onset			
19.9.3	Variant 0, infantile (Sandhoff disease)	β -Hexosaminidase A and B (α -subunit)	5q13	268800
19.9.4	Variant 0, juvenile/adult			
19.9.5	Variant AB	β -Hexosaminidase activator	5q31.3-q33.1	272750
19.10	Mucopolipidosis II (I-cell disease)	N-acetylglucosamine 1-phosphotransferase (secondary multiple lysosomal enzyme deficiencies)	4q21-q23	252500
19.11	Mucopolipidosis III	N-acetylglucosamine 1-phosphotransferase (secondary multiple lysosomal enzyme deficiencies)	4q21-q23	252500
19.12	Mucopolipidosis IV	Mucolipidin (receptor-stimulated cation channel)	19p13.3-p13.2	252650
19.13.1	Gaucher disease Type 1 ("adult", chronic nonneuronopathic)	β -Glucocerebrosidase	1q21	230800
19.13.2	Type 2 (acute neuronopathic)			
19.13.3	Type 3 (subacute neuronopathic)			
19.13.4	Gaucher disease (SAPC deficiency)	SAPC	10q22.1	176801
19.14.1	Niemann-Pick disease type A	Sphingomyelinase	11p15.4-p15.1	257200
19.14.2	Niemann-Pick disease type B			
19.14.3	Niemann-Pick disease type B (adult)			
19.15.1	Niemann-Pick disease type C (acute)	Abnormal intracellular cholesterol transport	18q11-q12	257220
19.15.2	Niemann-Pick disease type C (classic)			
19.15.3	Niemann-Pick disease type C (adult)			
19.16.1	Krabbe disease infantile	β -Galactocerebrosidase	14q31	245200
19.16.2	Krabbe disease late onset			
19.17	Multiple sulfatase deficiency	Posttranslational modification of a cysteine in at least 12 sulfatases		272200

19.3 Metabolic Pathway

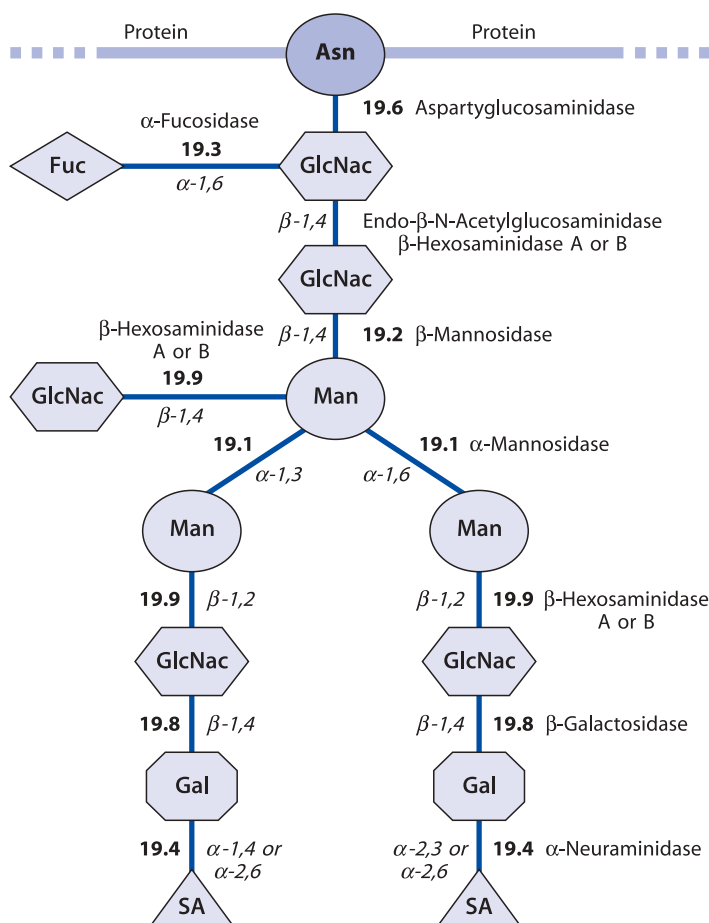


Fig. 19.1. Degradation of complex oligosaccharides

The degradation of a hypothetical complex oligosaccharide by lysosomal enzymes known to be deficient in human diseases. This is only an example of a complex molecule which can accumulate in oligosaccharidoses. The numbers in bold indicate the diseases (listed in Sect. 19.2) in which the defect in the cleavage of a specific glycosidic bond (in italics) is present. A variety of oligosaccharides can accumulate in body fluids and tissues as a consequence of the enzymatic defects; however, structural studies of the storage compound are not relevant to the diagnosis. The demonstration of an abnormal oligosacchariduria by thin-layer chromatography (TLC) is the only established screening test for this group of diseases. The final diagnosis relies upon the demonstration of the specific enzyme defect. Asn = asparagine; Fuc = fucose; GlcNac = N-acetylglucosamine; Man = mannose; Gal = galactose; SA = sialic acid (modified according to ref. [1]).

19.4 Signs and Symptoms

Table 19.1. Oligosaccharidoses with early infantile presentation

System	Symptoms/markers	Disorders								
		19.1.1	19.2.1	19.3	19.4.1	19.4.2	19.5.1	19.5.2	19.6	19.7.1
Clinical course	Age (yr) at onset	<1	1–2	<1–2	<0.5	<1–3	<0.3	1–3	1–5	<1
	Age (yr) at death	<10	a	<10–a	<1–7	10–20	<2	a	a	
Frequency		100 cases	10 cases	100 cases	<20 cases	<50 cases	20 cases	<20 cases	100 cases; Finnish: 1:17000	very rare
Facies	Hurler-like phenotype	++	+	+	++	++	++	++	+	
	Macrocephaly	+			±	±	±	+		
	Microcephaly								±	
Skeleton	Short stature/growth disturbance	±	±	+	+	+	++	+	±	
	Disostosis multiplex	++		+	++	++	+	+	±	
	Vertebral changes	++		+	++	++	+	+	+	
	Osteolysis/osteonecrosis									
Eye	Corneal opacities	+		±	+	±	+	±		
	Lens opacities	+			+	+		±	±	
	Cherry-red spot				±	++	±	+		
	Optic atrophy									+
Ear	Hearing loss	++	++	±	±	++	±	+		+
CNS	Mental retardation	+	+	+	++	+	++	+	+	++
	Progressive neurological course/dementia	+		+	+	+	+		+	++
	Seizures		+	+	+	+		±		+
	Startle reaction to sound									±
	Myoclonus					+				+
	Ataxia	+				+				+
	Pyramidal signs spasticity		+	+		+			±	+
	Hypotonia			+	+	+			±	+
	Ophthalmoplegia/strabismus									+
Cardiac	Hypertrophy/valvular thickening					+	+	+	+	
Renal	Kidney involvement/edema				++		++			
Liver	Hepatomegaly	+		±	++	+	+	+		
Spleen	Splenomegaly	+		±	++	+	+	+		
GI	Hernias	+		±	+	+	+	+	+	
Dermatologic	Angiokeratoma			+						
Special laboratory	Vacuolar lymphocytes/foamy bone marrow histiocytes	+		+	++	++	++	++	+	
	Reduced nerve conduction velocity					+				
	Increased acid phosphatase									

a, Adulthood; blank, not reported.

Table 19.2. Other lysosomal storage disorders with early (infantile) presentation

System	Symptoms/markers	Disorders					
		19.8.1	19.8.2	19.9.1	19.9.3	19.9.5	19.10
Clinical course	Age (yr) at onset	<0.5	0.5–2	<0.5	<0.5	<0.5	0–1
	Age (yr) at death	<2	3–10	2–4	2–4	2–4	5–8
Frequency		rare		1:300000 Non-Jewish 1:4000 Jewish	1:300000	very rare	rare
Facies	Hurler-like phenotype	+					++
	Macrocephaly	±		+	+		
	Microcephaly						
Skeleton	Short stature/growth disturbance	+					++
	Disostosis multiplex	+	±				
	Vertebral changes	+	+				++
	Osteolysis/osteonecrosis						
Eye	Chondrodysplasia punctata						
	Corneal opacities						+
	Lens opacities						
	Cherry-red spot	+		+	+	+	
	Optic atrophy						
	Retinal degeneration						
Ear	Hearing loss	+					
CNS	Mental retardation	++	++	++	++	++	+
	Progressive neurological course/dementia	++	+	++	++	++	+
	Seizures	+	+	++	++	++	
	Startle reaction to sound	+	+	++	++	++	
	Myoclonus					++	
	Ataxia		+				
	Pyramidal signs/spasticity		+				
	Hypotonia	+				+	+
	Ophthalmoplegia/strabismus						
Cardiac	Hypertrophy/valvular thickening						++
Renal	Kidney involvement/edema	±					
Liver	Hepatomegaly	+			±		++
Spleen	Splenomegaly	+			±		±
GI	Hernias						+
Dermatologic	Angiokeratoma						
	Ichthyosis						
Special laboratory	Vacuolar lymphocytes/foamy bone marrow histiocytes	+	+		±		+
	Reduced nerve conduction velocity						
	Increased acid phosphatase						

a, Adulthood; blank, not reported.

19.11	19.12	19.13.2	19.13.3	19.14.1	19.14.2	19.15.1	19.15.2	19.16.1	19.17
2-4 a rare	0-1 rare	<1 <2 1:500000	<1-20 1:100000	0-1 <5 rare	0.3	0.2 <8 1:150000	0-20 <1-a	<0.5 1-2 1:100000	<1 3-10 50 cases
								±	+
								+	+
+									+
+									+
+			++						+
±	++								±
									+
				+	±	+			+
	+							±	
±	+	++		++	±	++	++		+
±	+	++	++	+		+		++	+
		++	+				+	+	
			++					++	
		++	+	+		+		++	
	+			+				+	
	+	++	++				+		
+									
		++	++	++	++	+	+		
±		++	++	++	++	+	+		
±									
		++	++	++	++	++	++		+
+									
								+	
		++	++						

Table 19.3 (continued)

System	Symptoms/markers	Disorders											
		19.1.2	19.2.2	19.4.3	19.5.3	19.7.2	19.8.3	19.9.2	19.9.4	19.13.1	19.14.3	19.15.3	19.16.2
Cardiac	Hypertrophy/valvular thickening				++								
Renal	Kidney involvement/edema												
Liver	Hepatomegaly	+								++	+	±	
Spleen	Splenomegaly	+								++	+	±	
GI	Hernias				+								
Dermatologic	Angiokeratoma		±		+	+							
	Ichthyosis												
Special laboratory	Vacuolar lymphocytes/foamy bone marrow histiocytes	+		+	++		±			++	++	±	
	Reduced nerve conduction velocity												±
	Increased acid phosphatase									++			

a, Adulthood; blank, not reported.

19.5 Laboratory Diagnosis

The diagnosis of oligosaccharidoses and related disorders relies upon the assay of the deficient enzymatic activities. For all of them DNA analysis is also available and, if required, can be used. For mucopolipidosis IV an enzymatic assay is not available, but molecular analysis is feasible and can be used for prenatal diagnosis.

Disorder	Enzyme defect ^c	Material		Oligosaccharides (U) ^d
		Postnatal diagnosis	Prenatal diagnosis	
19.1	α -Mannosidase	WBC, FB	CV, AFC	↑
19.2	β -Mannosidase	WBC, FB	CV, AFC	↑
19.3	α -Fucosidase	WBC, FB	CV, AFC	↑
19.4	α -Neuraminidase	FB	CCV, AFC	↑
19.5	α -Neuraminidase and β -galactosidase (secondary deficiencies)	FB ^b	CCV, AFC	↑
19.6	Aspartylglucosaminidase	WBC, FB	CV, AFC	↑
19.7	α -N-Acetylgalactosaminidase	WBC, FB	CV, AFC	↑
19.8	β -Galactosidase	WBC, FB	CV, AFC	↑
19.9	β -Hexosaminidase A and B	P, WBC, FB	CV, AFC	↑ ^a
19.10	N-Acetylglucosamine 1-phosphotransferase	FB	CV	↑
	Multiple lysosomal enzyme activities (secondary deficiencies)	FB ^b	CCV, AFC	
19.11	N-Acetylglucosamine 1-phosphotransferase	FB	CV	↑
	Multiple lysosomal enzyme activities (secondary deficiencies)	FB ^b	CCV, AFC	
19.13	β -Glucocerebrosidase	WBC, FB	CV, AFC	
19.14	Sphingomyelinase	WBC, FB	CCV, AFC	
19.15	Abnormal cholesterol esterification	FB	CCV, AFC	
19.16	β -Galactocerebrosidase	WBC, FB	CV, AFC	
19.17	Multiple sulfatase activities	P, WBC, FB	CV, AFC	

^a Only in GM₂ gangliosidosis, variant 0 (Sandhoff disease).

^b Diagnosis is also based on high levels of some extracellular enzyme activities (β -hexosaminidase, arylsulfatase A, α -mannosidase, etc.) in plasma or amniotic fluid supernatant.

^c Diagnostic tests. The diagnosis of this group of lysosomal storage disorders relies upon the demonstration of a profound deficiency of a specific enzymatic activity, assayed in the appropriate material (as indicated in this table). Since assay conditions are very variable in relation to type of substrate, source of enzyme, etc. no reference values are given here. The physician should refer to the normal range of enzymatic activity under established assay conditions, as provided by the diagnostic laboratory. The interpretation of the results is generally clear-cut, since enzymatic activities in controls are much higher than in patients, but can overlap with the heterozygote range. An apparently normal enzymatic activity can be found in vitro for some variants of lysosomal disorders due to in vivo deficiency of an activator of the enzyme: this is seen, for example, in some cases of Sandhoff disease and Gaucher disease and requires a more complex and careful laboratory workup. Enzymatic pseudodeficiencies have also been reported for some lysosomal storage diseases, such as metachromatic leukodystrophy and GM₂ gangliosidosis.

^d Screening tests: Thin-layer chromatography of urinary oligosaccharides is the most useful, simple and reliable screening test for this group of diseases (see Chap. D for the interpretation).

19.6 Diagnostic Flow Charts

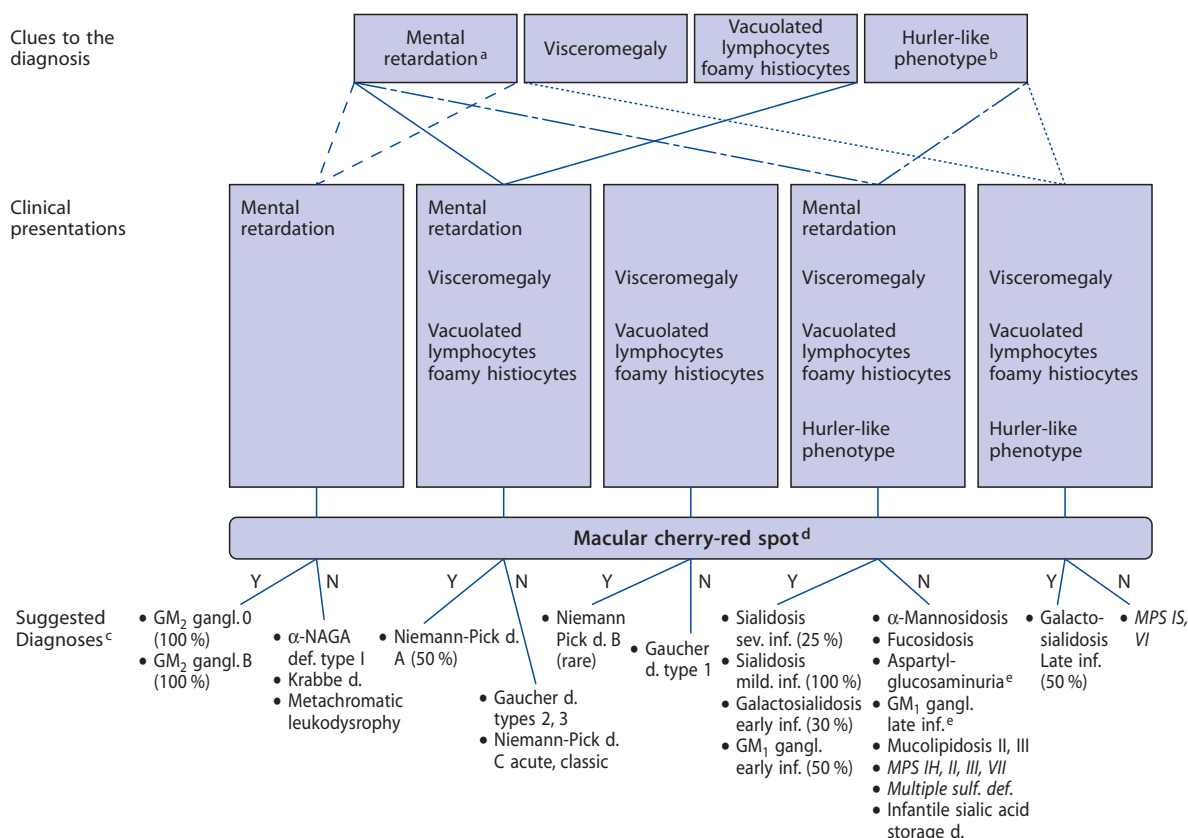


Fig. 19.2. Clinical approach to the diagnosis of oligosaccharidoses and related lysosomal disorders with early (infantile) onset. ^a Associated with CNS involvement of various types. ^b Facial dysmorphism and/or skeletal (vertebral) involvement suggestive of dysostosis multiplex. ^c Bold: conditions associated with abnormal oligosacchariduria; italics: conditions associated with abnormal mucopolysacchariduria. ^d The percentage of patients showing macular cherry-red spot (when present) is indicated in parentheses. ^e Absence of visceromegaly

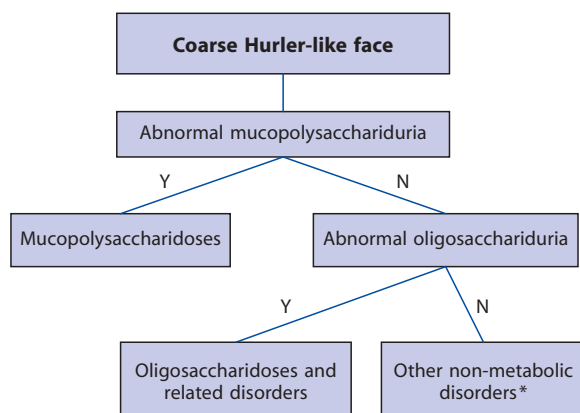


Fig. 19.3. Diagnostic flow-chart for patients with coarse Hurler-like face. *Coffin-Lowry syndrome (MIM 303300); Coffin-Siris syndrome (MIM 135900); frontometaphyseal dysplasia (MIM 305620); Sotos syndrome (MIM 117550); Williams syndrome (MIM 194050); multiple neuroma syndrome (MIM 171400); pachydermoperiostosis (MIM 167100); acromegaloid facial appearance syndrome (MIM 102150); Costello syndrome (MIM 218040); Patterson David syndrome (MIM 169170); Schinzel-Giedeon syndrome (MIM 269150); Fountain syndrome (MIM 229120); Pallister-Killian syndrome (MIM 601803); Simpson-Golabi-Behmel syndrome (MIM 312870); congenital hypothyroidism. Sialic acid storage disease, a lysosomal transport defect (Chap. 20) should also be considered in the differential diagnosis

19.7 Summary

Oligosaccharidoses are inherited diseases showing relevant clinical overlap with other related lysosomal disorders. Analysis of undegraded and accumulated metabolites is used as a screening test only, for oligosaccharidoses as well as for mucopolysaccharidoses. A profound deficiency of a specific enzyme has to be demonstrated for a biochemically defined diagnosis of these diseases. Progresses in molecular genetics have already modified the approach to prenatal, postnatal and heterozygote diagnosis. In the next future they are expected to lead to new forms of treatment, including gene therapy.

References

1. Scriver C.R., Beaudet A., Valle D., Sly W.S. (eds.), The metabolic and molecular bases of inherited disease. McGraw-Hill, New York, U.S.A., 2001, 8th edition. Chap. 138, 139, 140, 141, 144, 145, 146, 147, 149, 151, 152, 153
2. Durand P., O'Brien J.S., Genetic errors of glycoprotein metabolism. Edi-Ermes, Milan, Italy, 1982.
3. Warner T.G., O'Brien J.S., Genetic defects in glycoprotein metabolism. Ann. Rev. Genet., 17: 395–441, 1983