SESSION II

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Catabolic disorders of complex carbohydrates

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Summary

The various disorders caused by heritable defects in complex carbohydrate catabolism comprise two groups;

(A) The mucopolysaccharidoses, six main and several subtypes are described.

(B) The mucopolidoses (oligosaccharidoses), at least nine types being recognized.

Whilst most of these are now well defined by clinical and biochemical studies, much of the sequence of events from the intrinsic metabolic error to their clinical features remains obscure. Most are transmitted as autosomal recessive conditions, a mode of inheritance often, as with these disorders, associated with enzymic deficiencies. All patients display the Hurler phenotype, but this, as also the characteristic bone changes, varies widely in severity both within and between the specified types of disease.

The radiological abnormalities—dysostosis multiplex—indicate the broad disease complex and are rarely type-specific; diagnostic precision needing knowledge of both clinical and biochemical examinations. In several types mental development is normal and bone changes are mild, so permitting confusion with other forms of bone dysplasia or disease.

THIS review includes disorders arising from deranged metabolism of the mucopolysaccharides (MPS), glycoproteins and glycolipids. Although by the Paris classification this group of conditions was moved from disorders of unknown pathogenesis to those of known pathogenesis, this is something of a misstatement. We know that in these diverse ailments there is pathological storage of complex carbohydrates, which is intracellular and lysosomal, owing

to the absence or defective action of enzymes concerned with carbohydrate metabolism; but we still do not understand why the excessive deposition of these substances in fibroblasts and chondrocytes results in these types of bone dysplasias and not in any other form of osseous disease. Why, for example, in Hurler disease, or any other particular form, is there this characteristic type of bone dysplasia and not some other pattern? What makes the second lumbar vertebra hook-shaped, or the sella so large, or the diaphyses so expanded is quite unknown. The pathogenic sequence from the storage phenomenon to the morphological manifestation is still unexplained. The bone dysplasia, however, is one of the cardinal symptoms in all disorders of complex carbohydrate metabolism.

It must be emphasized that the dysplastic bone changes in all these carbohydrate metabolic disorders are qualitatively identical and non-specific, although specific in the sense that when the radiologist notes this dysostosis multiplex it invariably indicates some derangement of catabolism of complex carbohydrates.

The bone changes, however, with few exceptions do not permit precise diagnosis of the type of dysplasia present, further differentiation requiring knowledge of the clinical state and the results of biochemical investigations.

“(A) The mucopolysaccharidoses

These are listed in Table 1. The last edition of McKusick's book (1972) showed six main types, there are now seven, but type V remains vacant because Scheie disease has been moved to type I, as it is known to be caused by a deficiency of the same enzyme as in Hurler disease. So there are six recognized types of mucopolysaccharidoses, in most of which

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TABLE 1. The current classification of the mucopolysaccharidoses and some associated biochemical changes

Type		Enzyme defect	Major storage substance
I-H	Hurler	α -L-iduronidase	Dermatan sulphate Heparan sulphate
I-S	Scheie		
I-H/S	Hurler-Scheie compound		
II	Hunter (severe and mild)	Iduronate sulphatase	Dermatan sulphate Heparan sulphate
IIIA	Sanfilippo A	Heparan sulphate sulphamidase	Heparan sulphate
IIIB	Sanfilippo B	α -N-acetylglucosaminidase	Heparan sulphate
IV	Morquio	N-acetylgalactosamine-6-sulphatase?	Keratan sulphate
V	—	vacant	—
VI	Maroteaux-Lamy (severe and mild)	N-acetylgalactosamine-4-sulphatase	Dermatan sulphate
VII	Glucuronidase deficiency (severe and mild)	β -glucuronidase	Dermatan sulphate Heparan sulphate

allelic or non-allelic mutations give rise to various subtypes.

Type I Hurler; Scheie; Hurler-Scheie compound

Hurler disease is the classic type I with the typical dysmorphism that has unfortunately been described as gargoylism. These patients have severe mental retardation with corneal opacities. The condition is an autosomal recessive and caused by a deficiency of the enzyme α -L-iduronidase. Heparan sulphate and/or derman sulphate are stored in most of these mucopolysaccharidoses. α -L-iduronidase acts upon these sulphated carbohydrates splitting off a terminal L-iduronate radicle and, when deficient, intracellular and intralysosomal accumulation of short chain MPS with L-iduronate at the non-reducing end takes place. Thus heparan sulphate and derman sulphate cannot be catabolized normally, since they are usually, but not invariably, broken down by *exo*-glycosidases which attack the end of the molecular chains. This excess of short and long chain heparan sulphate and derman sulphate when released from the cells is excreted in the urine, providing a convenient diagnostic test.

In Scheie disease, which is morphologically dissimilar, the patients do not have the gargoyle-like facies, but have coarse facial features. They are not mentally retarded, but do have corneal opacities, and the disorder again is an autosomal recessive. It

is still unexplained why the Hurler patients are mentally subnormal and the Scheie patients mentally normal, the former having a short life span of about only 10 years, but both with a similar type and degree of α -L-iduronidase deficiency.

There is a third form of type I which McKusick (1972) thinks is a compound. Patients have one Hurler allele and one Scheie allele together, which theoretically should result in a type with intermediate severity and clinical phenotype. This is what is observed.

Comparing facial appearances, those with Hurler-Scheie compound are peculiar, impish, but not so ugly as those with Hurler disease, and may be distinguished from the Scheie type. Mentally, the patients are moderately retarded.

The frequency of the so-called Hurler-Scheie compound can be calculated to be only slightly less than that of Hurler disease which is about 1 in 100 000, and that of Scheie disease which is approximately 1 in 500 000; whilst that of the presumed compound is about 1 in 125 000. It is also possible that this 'Hurler-Scheie compound' is due to another allelic mutation. Nevertheless, even if the patients already reported as compounds should be disproved and shown to be affected by other allelic mutations, some such form must exist with one Hurler gene and one Scheie gene and a considerable frequency in the population.

Type II Hunter

In Hunter disease, there are two types caused by defective action of iduronate sulphatase. The first step in the degradation of sulphated mucopolysaccharides is the removal of the sulphate radicle, and when this does not take place, the mucopolysaccharide cannot be further broken down. There are both severe and mild varieties probably caused by allelic mutations on the X-chromosome, and patients with the mild disorder may survive to adult life. Corneal opacities are usually absent in this disorder although exceptionally they may occur.

Type III Sanfilippo

There are at least two non-allelic mutations in Sanfilippo disease. Type A is about four times as common as Type B from which it is clinically and radiologically indistinguishable. Type A is caused by deficient heparan sulphate sulphamidase which normally removes a sulphate radicle from heparan sulphate. Type B is caused by a defective glucosaminidase (Table 1). In both disorders some loss of the appropriate enzyme is demonstrable in clinically normal heterozygotes and prenatal diagnosis is possible, as in the other mucopolysaccharidoses and mucopolipidoses.

Type IV Morquio

Again there are severe and mild forms, patients with the former being much shorter than the latter. The patients do not have contractures but show laxity of the ligaments. This contributes to the most severe complication in Morquio disease which is compression of the upper cervical spinal cord due to atlanto-axial instability (Fig. 3).

In Morquio disease, the enzyme defect is still unsure, but has been claimed to be a hexosamine-6-sulphatase which Matalon *et al.* (1974) described as galactosamine-6-sulphatase. Since keratan sulphate, the major storage substance in Morquio disease, contains no galactosamine-6-sulphate, the nature of the actual enzyme defect remains uncertain.

Type VI Maroteaux-Lamy

There are again two variants manifest as severe and mild phenotypes. Both variants are caused by deficiency of the enzyme *N*-acetylgalactosamine-4-sulphate which is concerned with the degradation of dermatan sulphate. This substance, unaccompanied by larger amounts of heparan sulphate, is excreted in the urine in this disorder. Patients are usually mentally normal. Amongst the author's cases, one severely afflicted man aged 21 years was blind, with buphthalmos and a huge tongue but a well preserved mentality; another female patient of similar age did not have these defects.

Type VII Glucuronidase deficiency

This is the most recently described type of mucopolysaccharidosis. The metabolic defect was explained in a single patient as being due to deficiency of the enzyme β -glucuronidase by Sly *et al.* (1973). The disorder is heterogeneous with allelic mutations leading to varying phenotypes, one boy aged 2 years being mentally retarded whilst another patient, aged 14 years, was reported to be mentally normal. Only four patients with this condition have been diagnosed.

(B) Mucopolipidoses and related conditions

The second big group of disorders of complex carbohydrates includes conditions in which patients do not excrete acid mucopolysaccharides in the urine. Instead, oligosaccharides are excreted in most of them and the group has been named the 'oligosaccharidoses' (Maroteaux and Humbel, 1976). The various conditions are listed in Table 2.

Clinically, the patients share morphological features of both the mucopolysaccharidoses and sphingolipidoses. Since in most of them there is also storage of mucopolysaccharides and lipids, the term 'mucopolipidoses' was originally applied to all of them. For biochemical and nosological reasons, it now appears preferable to restrict this name to some specific entities within the whole group.

There are conditions in which the glycoprotein degradation is faulty and small amounts of glycopeptides are stored and excreted in the urine, such as mannosidosis and aspartylglucosaminuria (Table 2).

Intracellular accumulation of mucopolysaccharides, sphingolipids and glycopeptides occurs in GM_1 gangliosidosis, both in severe and mild forms, and in Sandhoff disease. The GM_1 -gangliosidoses are caused by a defective β -galactosidase and Sandhoff disease by an absent activity of hexosaminidases A and B. Since hexosaminidase B is apparently involved in mucopolysaccharide degradation, skeletal abnormalities must be expected in Sandhoff disease and indeed have been observed in the form of mild dysostosis multiplex.

In fucosidosis the degradation of glycopeptides, glycolipids, and possibly also of keratan sulphate is impaired. In fucosidosis, as in the other mentioned conditions, the excessive accumulation of multiple substances results from the fact that the defective enzymes have multiple substrates.

In another subgroup, the intracellular accumulation of multiple substrates results from the fact that more than one enzyme is defective. Thus, in mucopolysaccharidosis multiple sulphatases are deficient and acid mucopolysaccharides are excreted in the urine together with sulphatide. In mucopolipidosis II and III multiple lysosomal enzymes are lacking within the cells. This is probably due to an aberrant transport

TABLE 2. The mucopolidoses and related conditions (oligosaccharidoses)

Type	Enzyme defect	Substances stored or excreted
Mannosidosis	α -mannosidase	Mannosyl-oligosaccharides
Aspartylglucosaminuria	Aspartylglucosamine-amido-hydrolase	Glycoasparagines
GM ₁ -gangliosidosis (various forms)	β -galactosidase	GM ₁ -ganglioside, glycopeptides, keratan sulphate
Sandhoff disease	Hexosaminidases, A, B	GM ₁ -ganglioside, trihexoside-ceramide, mucopolysaccharides
Fucosidosis (infantile and adult)	α -fucosidase	Fucosphingolipids, fucoglycopeptides, keratan sulphate
Mucosulphatidosis	Multiple sulphatases	Mucopolysaccharides, sulphatide
Mucopolidosis I	N-acetyl-neuraminidase	Sialyloligosaccharides
Mucopolidosis II	Multiple lysosomal hydrolases	Glycopeptides, glycolipids, mucopolysaccharides
Mucopolidosis III	Multiple lysosomal hydrolases	Glycopeptides, glycolipids, mucopolysaccharides

mechanism in the cells, the enzymes not being transported into their proper place in the lysosomes. Mucopolidosis I which had been grouped with the other mucopolidoses mainly for clinical and cytological reasons now appears to be caused by a defect of a neuraminidase (Cantz, Gehler and Spranger, 1977).

(C) Radiological signs—all types

The skeletal changes occurring in all types of mucopolysaccharidoses and mucopolidoses are relatively uniform and have been termed 'dysostosis multiplex'. They are specific in the sense that their occurrence invariably indicates a disorder of complex carbohydrate catabolism. On the other hand, they are non-specific in the sense that they occur in all conditions caused by such a defect, although varying in severity and distribution (Spranger, Langer and Wiedemann, 1974).

In disorders with brain degeneration, e.g. Sanfilippo disease or mannosidosis, one may see non-specific thickening of the calvaria (Fig. 1a). Thickening of the leptomeninges or mucopolysaccharide-containing cysts may impede the free flow of cerebro-spinal fluid and result in hydrocephalus and widened or J-shaped sella with a depressed chiasma (Fig. 2a). Premature closure of the cranial sutures is quite common.

The ribs are wide and this appears to be one of the earliest signs of dysostosis multiplex, occurring as early as in the first 3 months of life.

The vertebral bodies are immature and the ovoid shape, normal in infancy, may persist beyond the

first year of life (Fig. 1b). There may be anterior and superior ossification defects (Fig. 2b). The lower portions of the ilia may be hypoplastic (Figs 1c, 2c). There are also short and wide metacarpals which may be proximally pointed, and bullet-shaped phalanges (Fig. 2d). In mild cases, there is only a slight

FIG. 1. Mild dysostosis multiplex.

(a) Thickened calvaria secondary to degenerative loss of brain tissue. The illustrated skull is from a patient with Sanfilippo disease but similar pictures may be found for instance in mannosidosis.

(b) Ovoid (immature) form of the vertebral bodies of a 4-year-old patient.

(d) Coarse bone structure: V-shaped dysplasia of the distal ends of the forearms.

(c) Mild hypoplasia of the lower portions of the ilia with slightly wide acetabular angles and small capital femoral epiphyses.

FIG. 2. Severe dysostosis multiplex.
(a) Wide, J-shaped sella; irregular thickening of the calvaria; premature synostosis of the coronal suture.

(c) Severe hypoplasia of the lower portions of the ilia with marked iliac flare; slanting of the acetabular roofs; coxa valga and dysplastic femoral epiphyses.

(b) Ovoid deformity of the dorsal bodies; anterosuperior hypoplasia of L-2, less pronounced of L-3 and L-4; retroposition of L-2.

(d) Marked shortening and diaphyseal expansion of the phalanges and metacarpals; proximal pointing of metacarpals II-V; epiphyseal deformities; V-shaped deformity of the distal ends of the forearm bones.

FIG. 3. Morquio disease. Flexion-extension views of the upper cervical spine show hypoplasia of the odontoid process and atlanto-axial hypermobility.

expansion of the shafts of the short tubular bones and in even milder cases only a somewhat coarsened, irregular bone structure of these bones is present. These are the most important skeletal changes of dysostosis multiplex varying in severity from one disorder to another.

In Morquio disease the bone changes are more specific and usually sufficiently characteristic to permit a radiological diagnosis. Generalized platyspondyly is present with anterior pointing of the vertebral bodies, which are anteriorly hypoplastic at the dorso-lumbar junction where they become displaced backwards. This may lead to acute gibbus sufficiently severe to compress the spinal cord in this region, producing one of the important complications of Morquio disease. Moreover, in this type of mucopolysaccharidosis the pelvic hypoplasia is marked with severe coxa valga and epiphyseal dysplasia. In the hands, in contrast with other mucopolysaccharidoses, there is diaphyseal constriction of the short tubular bones. Hand and pelvic changes differentiate Morquio disease from other skeletal dysplasias, notably spondyloepiphyseal dysplasia congenita.

A serious complication of Morquio disease is hypoplasia of the odontoid process which fails to fuse normally with the body of the second cervical vertebra (Fig. 3). This leads to hypermobility and

atlanto-axial instability which may be demonstrated in flexion and extension views of the upper cervical spine. This abnormal mobility may cause spinal cord compression which is present to some extent in most older patients with Morquio disease. To prevent this complaint, prophylactic spinal fusion has been advocated.

It must be stressed that some degree of odontoid hypoplasia is common in many disorders with platyspondyly. This defect alone is not responsible for the atlanto-axial instability: it is only when combined with undue ligamentous laxity, as in Morquio disease, that this severe instability obtains. The first clinical symptoms are usually mild, e.g. children cannot move their legs as quickly as they used to, or they may easily become tired.

Differential diagnosis of dysostosis multiplex

The non-specific nature of the osseous changes noted in disorders of complex carbohydrates has been emphasized. Further information, both clinical and biochemical is mandatory for differential diagnosis of distinct types of mucopolysaccharidoses or mucopolipidoses, particularly when the skeletal abnormalities are moderate or mild. Morquio disease, as mentioned, is an exception and its diagnosis is easier on radiographic than on biochemical grounds.

In a child with raised mucopolysacchariduria, severe bone changes may be encountered either with Hurler (type I-H) or Maroteaux-Lamy (type VI) disease. With less severe bone changes it may be either Hunter (type II) disease, and with mild bony defects only, either Sanfilippo (type III) or Scheie (type I) disease. A mucosulphatidosis may also be considered.

In a child with normal mucopolysacchariduria, severe bone changes are seen in GM₁-gangliosidosis (subtype I), in other defects of β -galactosidase and in mucopolidoses II and III. The bone changes in mucopolidoses I are moderately severe. They are mild in the other conditions listed in Table 2.

In infancy, there is never severe dysostosis multiplex in a mucopolysaccharidosis. Should such skeletal changes be observed, including widened ribs and marked vertebral defects, the diagnosis is either mucopolidoses II or GM₁-gangliosidosis type I and the urine is normal for mucopolysaccharides.

With the exception of Morquio disease, the bone changes of disorders of complex carbohydrate catabolism are not easily confused with those of other bone dysplasias. The pattern of bone changes

in Morquio disease, on the other hand, is so characteristic that the traditional confusion of Morquio disease with other short-trunk types of dwarfism should finally come to an end.

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