Disorders of the Skeletal System: Mucopolysaccharidosis, Part One

Uptodate

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Directed by Trevor A Scott.

Black-and-white
Duration: 00:39:17:21

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<Opening titles>

<Whiteman to camera>

Hello. The mucopolysaccharidoses are a group of genetically determined disorders, characterised by abnormal storage and excretion of complex carbohydrate polymers known as acid glycosaminoglycans. These disorders are due to deficiencies of specific lysosomal enzymes required for normal glycosaminoglycans degradation.

In this programme, we will discuss aspects of clinical and laboratory diagnosis, and in a subsequent programme outline pathogenesis, aspects of management and possible future trends. To begin Dr Rosemary Stephens will talk about the various clinical manifestations of these disorders. Dr Stephens.

<Stephens to camera>

Thank you. The diagnosis of a mucopolysaccharidosis is based on a pattern of findings, the most prominent being characteristic coarse, sometimes grotesque facial features, skeletal changes of dysostosis multiplex and an excessive urinary secretion of glycosaminoglycans otherwise known as mucopolysaccharides. Recent advances in biochemistry, tissue culture and histochemistry have made it possible to identify several distinct disease entities which were previously only suspected on clinical, genetic and radiological grounds.

<Stephens narrates over tables>

McKusick's 1972 classification summarises the present recognised types. <*Next table*> They all have an autosomal recessive mode of inheritance, except Hunter's disease which is inherited on an x-linked recessive gene.

In Hurler's disease, the enzyme α-L-iduronidase is deficient and excessive dermatan sulphate and heparin sulphate are secreted in the urine. The disease is evident in infancy and the baby is often unusually large in the first year but later becomes moderately dwarfed. By one year of age, delayed development is apparent and recurrent respiratory tract infections are a problem.

<Stephens narrates over series of slides>

By age two years, the full clinical picture has developed. The characteristic features can be seen in these children – coarse facial features with large frequently scaphocephalic shaped heads. <*Next slide*> The tongue is large and there is hypertrophy of the gums and bony alveolar ridges. Teeth are widely spaced, small, short and malformed, being peg-shaped.

<*Next slide*> Abundant coarse hairs on the head with a low hair line. Frequently there is excessive body hair, chiefly on the back and shoulders, short neck and broad and deformed chest with flaring of lower ribcage and retracted lower sternum. Kyphosis with gibbus in lower dorsal or upper lumbar spine. Protuberant abdomen, umbilical and inguinal herniae are common. Liver and spleen may be greatly enlarged.

Long bones are short and deformed, hands and feet are broad with short fingers and toes kept in semi-flexed position. This claw-hand deformity develops early and is established by three years of age. There is stiffness and limitation of movement in most joints, and with hip, knee and elbow joints partly flexed and trunk bent forward, the children have an ape-like posture.

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<Next slide> Progressive corneal clouding always occurs and may be present from infancy. The corneal opacities appear as a haze and can be seen as many grey, dust-like opacities on slit lamp examination. They are particularly dense at the periphery and in the deeper layers of the stroma. Increasing visual loss occurs. The voice is deep and hoarse. Persistent rhinitis with noisy mouth-breathing is invariably present and often accompanied by middle ear infections. Deafness is common.

<Stephens to camera>

Cardiac lesions are common and are due to deposition of mucopolysaccharides in the heart valves, coronary arteries and myocardium. Valvular lesions occur in the same order of frequency as in rheumatic heart disease. Severe and progressive mental retardation is present and is manifest from about six months of age. The children are docile and frequently affectionate. Death usually occurs before age ten years, often due to heart failure or a chest infection.

<Stephens narrates over table>

In Scheie's disease, the enzyme α-L-iduronidase is deficient and dermatan sulphate is excreted in excess in the urine. The disease is characterised by a gradual onset, normal or near normal intelligence, severe corneal clouding, pigmentary retinitis, broad short hands and feet with claw-hand deformity and stiff joints. Carpal tunnel syndrome may develop later in life. Aortic valve disease, especially aortic regurgitation is common and a frequent cause of death.

<Stephens to camera>

Patients are stocky build, muscular and of average or just below average height. The broad face with broad nose and flaring nostrils is unlike that of Hurler's disease. There is increased height to the mid-face and a square, protruding lower jaw. The liver, but not the spleen, may be enlarged. The disease can be compatible with relatively normal life to the sixth decade or longer.

<Stephens narrates over table>

In the Hurler-Scheie compound disease, patients are thought to have the Hurler gene on one chromosome and the Scheie gene on the other chromosome. Their fibroblasts do not show cross-correction with those of a Hurler patient or with those of a Scheie patient. The enzyme α-L-iduronidase is deficient and excessive dermatan sulphate and heparan sulphate are excreted in the urine.

<Stephens to camera>

The clinical features may suggest Hurler's disease but the course may be more gradual and is sometimes compatible with life to the early twenties at least, and with not so severe mental impairment.

<Stephens narrates over table>

Hunter's disease is named after Charles Hunter, a Winnipeg physician, who first described the disease in two brothers in 1917. It has an x-linked recessive mode of inheritance. Heparan sulphate and dermatan sulphate are excreted in excess in the urine, and recently the enzyme iduronic acid sulphate sulphatase has been found to be deficient in patients.

There are two recognised types: A, the severe form in which there is more rapid mental regression with death occurring before the age of fifteen years, and B, the

milder form which may be compatible with life to the fifties or later, and usually with reasonably good intelligence.

<Stephens narrates over series of slides>

Many clinical features are similar to those in Hurler's disease, but they tend to be less severe and the course is more gradual in many patients. Corneal opacities do not occur. Progressive deafness from about the age two years is usually more conspicuous. Thoracolumbar kyphosis is mild or absent. Recurrent upper respiratory tract infections are uncommon. Nodular skin lesions, up to 1 cm in diameter, may appear over the scapula and pectoral regions and the lateral surface of the upper arms.

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<*Next slide*> The skull is brachycephalic. At around three years of age, about half these patients deteriorate rapidly becoming severely retarded, often hyperactive with rapid worsening of physical deformities. Sometimes spastic quadriplegia develops. This four year old boy shows the features of the severe form. Children with a milder form may remain intellectually more normal, or near normal, for much longer and well into adult life, and physical deformities progress much more slowly.

The stature is small with ultimate height below 150 cm. The deformed trunk is relatively shorter than the extremities and the scapulae are very highly placed. This thirteen year old boy and this twenty-two year old man demonstrate the characteristic facial features of the milder form. The claw-hand deformity can be seen in the younger boy. Carpal tunnel syndrome is common <*next slide*> and trophic changes occur as shown in the man's hands. Cardiac abnormalities are frequent and the most common cause of death.

<*Next slide, table*> There are at least two biochemically distinct types of Sanfilippo's disease which are indistinguishable clinically. In Sanfilippo A disease the enzyme heparan sulphate sulphatase, and in Sanfilippo B disease N-acetyl-α-D-

glucosaminidase is deficient. In both, heparan sulphate is excreted in excess in the urine. The disease is characterised by severe progressive mental retardation and mild somatic changes. <*Next slide*> Heart lesions do not occur. There is no corneal clouding. There is mild or moderate hepatomegaly, and in less than 25% of cases the spleen is enlarged too. Skeletal abnormalities are usually minimal, but mild stiffness of some joints may occur.

<*Next slide*> These children may develop normally in the first two or three years and are often taller and stronger than their peers, usually being above the 90% percentile in the first decade. Body proportions remain normal throughout life. <*Next slide*> Between eighteen months and four years, there is an arrest of development. Skills are lost and by age eight years, the child is severely mentally retarded, frequently with restless, overactive, sometimes aggressive behaviour.

<*Next slide*> Around three years, some coarsening of facial features occurs which may resemble those in Hurler's or Hunter's disease, but are never so abnormal. The children have a dull, blank appearance.

<Stephens to camera>

In later childhood, spastic quadriplegia and sometimes seizures of various types may appear. Death from pneumonia may occur any time in childhood or early adult life.

<Stephens narrates over series of slides>

Morquio's disease was independently described by Morquio in Montevideo, Uruguay, and Brailsford in Birmingham, England, in 1929. The enzyme defect is probably a specific sulphatase. Increased amounts of keratan sulphate and of chondroitin sulphate are excreted in the urine. <*Next slide*> In the second or third year of life, retarded growth, severe chest deformity with sternal protrusion, lumbar-dorsal kyphosis, prominent joints, knock-knees, flat feet and awkward gait may appear. These deformities increase and the child is strikingly dwarfed, especially after the age of five. Usually the maximum height of up to 100cm is reached by eight years.

<*Next slide*> This picture shows a seven year old boy with characteristic deformities and semi-crouched position adopted, with hips and knees partially flexed and trunk bent forward. The neck is very short and the head tilted backwards. The lower part of the face is disproportionately long with a prominent chin and face profile is flat or dish-like. There is marked enamel hypoplasia of deciduous and permanent teeth, and they rapidly decay. Although movement is limited in large joints, hyperextensibility is present in the metacarpophalangeal and interphalangeal joints.

Intelligence is usually normal. By mid-childhood mild, diffuse corneal opacities, deafness and valvular heart disease, often aortic regurgitation, may appear. The liver is frequently enlarged, but not the spleen.

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Spinal cord compression often develops, either at the level of a gibbus or more commonly at the upper cervical level due to subluxation or dislocation of the atlas on the axis. Death occurs usually in the second decade, either from this complication or due to valvular heart disease or a respiratory tract infection. A few patients live till the fourth decade.

<*Next slide, table*> In Maroteaux-Lamy's disease, dermatan sulphate is excreted in excess in the urine, and the enzyme aryl sulphatase B is deficient. Patients have normal intelligence, smallness of stature with often severe skeletal deformities, severe corneal clouding, frequently becoming deaf and may develop cardiac lesions.

<*Next slide*> After age two years, sometimes the disease runs a rapid course, leading to severe deformities. <*Next slide*> In other children, the course is much milder, at least to mid-childhood. These pictures show the rather coarse facial features: large head and deformities including typical stance in a boy with a severe form. <*Next slide*> The girl has the milder form. She is rather small, has claw-hand deformities, severe corneal clouding and some deafness. The liver is enlarged and the spleen too in about half the cases. Cardiac involvement is common. Death is

usually due to a cardiac lesion or neurological complications secondary to hydrocephalus or spinal cord compression.

<*Next slide*> In mucopolysaccharidosis type VII, the enzyme β-glucuronidase is deficient and there is mildly raised urinary excretion of chondroitin sulphate. Children have unusual facial features, progressive skeletal deformities, […]

<Stephens to camera>

[…] including thoracolumbar kyphosis, hepatosplenomegaly and herniae from infancy. Small stature and mental retardation are evident by the second or third year. They may or may not have corneal clouding and a heart lesion. Now Dr Sutcliffe will tell you about the x-ray changes in these diseases. Dr Sutcliffe.

<Sutcliffe to camera>

Thank you. This talk will have to be confined to a very brief description of the x-ray changes in the skeleton. It is these which are so distinctive that they allow one to make or approach the diagnosis. If we could see the first x-ray?

<Sutcliffe narrates over series of x-rays using indicator>

This is the lateral skull film of classical Hurler's disease MPS 1H. It shows that the skull vault is large, there is tonic encephaly, the sella has a most distinctive shape referred to as J-shaped or shoe-shaped. There is very poor pneumatization of the mastoid processes and this tooth is in a very odd position. It is halfway up the ascending ramus of the mandible instead of its usual position anterior to the mandible.

<*Next x-ray*> This is a posterior-anterior film of the same skull showing the reason for the [?*unclear word*] encephaly which is premature fusion of the sagittal suture. You can see a dense ridge of bone up the sagittal suture which is closed. <*Next x-ray*> And the next film, the spine shows very distinctive features; there is hypoplasia of

one of the upper lumbar vertebra and it carries an inferior beak on its anterior margin. There is also posterior displacement of this vertebral body in relation to the one above. It is this which explains the gibbus.

<*Next x-ray*> This film shows other features: the ribs are a characteristic shape, having narrow posterior ends and then expanded anterior ends, described as oar-shaped. There is hypoplasia of the acetabular roof and of the supra-acetabular part of the iliac bone which is much narrower than normal. There is also coccyx-valgus deformity. <*Next x-ray*> Here we have an x-ray of the hands of Hurler syndrome showing the claw fingers and the very broad metacarpals with pointing of the proximal ends.

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<*Next x-ray*> Another feature which may be seen in any of the mucopolysaccharidoses is this great expansion of the medial end of the clavicles. <*Next x-ray*> Now if we could turn to the next film, this is MPS 1S, showing again the claw fingers, and in this condition one encounters cysts in many of the bones. Here you can see them in the carpal bones and they may occur anywhere in the vicinity of larger joints.

<*Next x-ray*> I'm going to omit films of the Hunter syndrome because the changes are very similar to MPS 1H, although they tend to develop later in life. I'll move on to MPS 3, Sanfilippo syndrome, and show that in this condition the sella is normal. A very striking feature is this thickening of the vault, particularly in the parietal and occipital regions. <*Next x-ray*> The changes in the long bone in the MPS 3 are slight and in the spine the deformity that we saw in MPS 1H is not present. The vertebral bodies are ovoid in shape.

<*Next x-ray*> If we could now move on to MPS 4, Morquio's disease, in this condition the sella is normal, but there are these very remarkable changes in the upper cervical spine. The odontoid process is completely missing in this case and as a result of this there is forward dislocation at the atlanto-axial joint. It is this which leads

to pressure on the cord and which may be a cause of death. <*Next x-ray*> The spine changes in Morquio's disease vary in the early years. The characteristic feature is fatty[?] spondyly with a central beak, but in the older years they may be very similar to those we saw in MPS 1H with an inferior beak. This is at the age of about two and a half years. Five years later <*Next x-ray*> there is universal fatty[?] spondyly and the beak is central in position in all these vertebral bodies.

<*Next x-ray*> The changes at the hips are very striking. There is severe coccyx-valgus deformity with subluxation of the femoral heads, and the femoral heads show fragmentation and may eventually disappear completely. <*Next x-ray*> And the hands, as in MPS 1H, there is proximal pointing of the metacarpals, but in distinction to MPS 1H there is still wasting of all the metacarpals – there is narrowing of the central path.

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<*Next x-ray*> If we now turn to MPS 6, the changes in this disease are severe dysostosis multiplex similar to MPS 1H. You can see in the pelvis that there are the changes as in MPS 1H, but one striking difference is these changes in the femoral head which look like Perthes disease. Also there is narrowing of the femoral necks with coccyx-valgus deformity.

<*Next x-ray*> Another feature which we will see in MPS 6, also sometimes in MPS 1H, are changes in the jaws. This is an orthopantomogram showing the whole of the mandible. You can see there is a hypoplasia of the condylar process of the mandible, the molar tooth is in the ascending ramus, the first dentition teeth have not been shed and then there are cysts on this side. And another feature is that the molar teeth are far too close to the inferior border of the mandible. They are impinging on the cortical bone of the inferior surface of the mandible.

<Sutcliffe to camera>

So, in conclusion, one can say that radiology will allow a positive diagnosis in MPS 4. It will differentiate the other mucopolysaccharidoses from all, or almost all, the hundreds of other bone dysplasias one encounters in childhood. I will now introduce Dr Brian Lake who will talk on the examination of the blood films and their part in the diagnosis of these diseases.

<Lake to camera>

Thank you. In 1938 Alder described an unusual granulation in the white blood cells of a nine year old girl who presented with scarlet fever. There were no other clinical signs, but a younger well brother also had the granules, whilst neither abnormality could be detected in their two other siblings or in either parent. Alder followed these two cases and six years later the brother developed a waddling gait. Radiological studies at that time showed changes which were consistent with a diagnosis of Perthes disease, and there were clear disturbances of skeletal growth and development.

Alder granules can be demonstrated in blood films by the standard Romanowsky type of stain used in all routine haematology laboratories.

<Lake narrates over series of slides using indicator>

In this slide of a normal neutrophil from a normal film from a normal patient, the nucleus stains darkly and the cytoplasm contains only a few fine granules. <*Next slide*> However in cells with Alder granulation, numerous cytoplasmic granules staining darkly are present throughout the cytoplasm, and these give the cytoplasm a reddish lilac colour. <*Next slide*> The granules are present in practically every neutrophil and can be seen in the other nucleated cells but to a lesser extent. This type of granulation we have learnt to associate with <*Next slide*> Maroteaux-Lamy disease that is mucopolysaccharidosis type VI, and it is now clear that Alder's two cases represent the mild variant or type VI B.

<Lake to camera>

Similar granulation occurs in the mucosulphatidosis where there is a deficiency of sulphated A, B or C, and it is also reported in β-glucuronidase deficiency. In discussion following one of Alder's presentations in 1950, Gasser described inclusions present in the lymphocytes only of a patient aged ten months, who probably had Hurler's disease. These cells, now known as Gasser cells, are present in most of the mucopolysaccharidoses and their characteristic appearance is not, however, specific for any particular type.

<Lake narrates over series of slides using indicator>

Here you can see in a routinely stained blood film, the distinct inclusion within a vacuole in the cytoplasm of a lymphocyte. Inclusions are not present in every vacuole <*next slide*> and not every lymphocyte is affected. This one for example has no vacuoles in it at all. Gasser mentioned that using his special toluidine blue stain, he could demonstrate that the inclusions in the lymphocytes show metachromasia, a theme which Mittwoch pursued. She showed that metachromatic inclusions could be found in the lymphocytes of patients with a variety of mucopolysaccharidoses, but in those days the identification of individual glycosaminoglycans was not easy. Enzyme assays were not available and the type of mucopolysaccharidosis was often in doubt.

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For the past ten years, we have been using the technique described by Mittwoch of staining to demonstrate metachromasia in patients in whom the diagnosis is now firmly established. <*Next slide*> The metachromasia must be searched for using an oil immersion lens and a minimum of 100 lymphocytes should be examined. Cells may contain one metachromatic granule or may contain a cluster of granules. In no instance have we found metachromatic inclusions in normal patients, though the converse is true for example in Morquio's disease, no chromatic inclusions are found.

The percentage of lymphocytes containing metachromatic inclusions is often a good indication of the type of mucopolysaccharidosis your patient has. <*Next slide – table*> We have found in general that patients with Sanfilippo disease have more than 20% of lymphocytes with metachromatic inclusions. Patients with Hurler or Hunter disease have in general less than 20% positive lymphocytes. In the Scheie and Hurler-Scheie compound, less than 5% of metachromatic lymphocytes were present in the two patients we have seen.

<Lake to camera>

Examination of blood films by these simple techniques can thus be a valuable aid to the diagnosis of these diseases. For studies of urinary glycosaminoglycans and their part in diagnosis, I will now hand you back to Dr Paul Whiteman.

<Whiteman to camera>

Thank you. Abnormal mucopolysaccharide urea is one of the cardinal features of a mucopolysaccharidosis and the type of glycosaminoglycans excreted depends on the nature of the enzyme defect. Initial investigations should include a measurement of total acid glycosaminoglycans excretion. In a child, a normal level of excretion virtually excludes a diagnosis of mucopolysaccharidosis. However if mistakes are to be avoided, care must be exercised in the choice of analytical technique and in the method of expressing results.

<Whiteman narrates over series of diagrammatic slides>

For instance the concentration of glycosaminoglycans in the urine of patients with mucopolysaccharidosis tends to be higher than that in the urine of age-matched control subjects. But, as shown here, there is a moderate degree of overlap between the two groups, particularly in infants and young children. The discrimination between patients and normal subjects is considerably enhanced when glycosaminoglycans excretion is expressed in terms of creatinine excretion, that is as a glycosaminoglycans:creatinine ratio.

<*Next slide*> The glycosaminoglycans:creatinine ratio is normally high in infancy and falls with advancing age. The control range is given here as + and -2 standard deviations from the mean. <*Next slide*> Patients with mucopolysaccharidosis give glycosaminoglycans:creatinine ratios which are considerably elevated above the control range. In Morquio's disease, represented in this diagram as squares, this increase in glycosaminoglycans excretion is generally less marked than that seen in other types of mucopolysaccharidoses. And in the older patients with this disease, levels of glycosaminoglycans excretion may approach normal values.

<*Next slide – table*> The combination of a normal level of glycosaminoglycans excretion and some of the clinical and radiological features of Hurler's disease should alert one to the possibility of another type of lysosomal storage disorder, such as GM1 gangliosidosis, I cell disease or mannosidosis.

<Whiteman to camera>

The qualitative analysis of urinary glycosaminoglycans is useful for confirming a diagnosis of mucopolysaccharidosis and in differentiating the various forms, particularly in young children who might not have developed the full clinical syndrome. Chondroitin sulphate is the major glycosaminoglycan in the urine of normal subjects and accounts for more than 80% of the total in children.

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<Whiteman narrates over series of slides, using indicator>

Vesler's[?] method of electrophoresis in barium acetate solutions is particularly useful for the separation of individual urinary glycosaminoglycan components. This photograph shows the typical patterns obtained in different types of mucopolysaccharidoses. Here are standard preparations of chondroitin sulphate, dermatan sulphate and heparan sulphate. These act as markers for the identification of the urinary glycosaminoglycan components. It is worth remarking at this stage that

dermatan sulphate was formerly known as chondroitin sulphate B; it is, in fact, chemically distinct from the chondroitin sulphate.

In Sanfilippo disease, there is a grossly elevated secretion of heparan sulphate with little or no increase in dermatan sulphate excretion. This pattern is diagnostic and does not occur in any other condition. In Morquio's disease, there is no increase in heparan or dermatan sulphate excretion, however there is an increase in chondroitin and keratan sulphate excretion. These two components run together in this system of electrophoresis but can be separated by other techniques. Some studies have shown that chondroitin sulphate keratan-sulphate hybrid molecules are excreted in the urine of these patients.

Hurler's disease, Hunter's disease and Maroteaux-Lamy disease are all characterised by a grossly elevated dermatan sulphate excretion, but differ from one another with respect to heparan sulphate excretion. By simple measuring of these components and calculating a heparan sulphate:dermatan sulphate ratio, it is possible to differentiate these disorders.

<*Next slide*> Values for the heparan sulphate:dermatan sulphate ratio are highest in Hunter's disease and lowest in Maroteaux-Lamy disease. Patients with Hurler's disease give values in between these two groups. These differences are maintained irrespective of age or severity of clinical involvement. The absolute values of these ratios depend on the method of analysis used.

<Whiteman to camera>

By assessing the clinical and laboratory findings as outlined in this programme, it is usually possible to make an accurate diagnosis in an individual case. Final confirmation can in several instances be obtained from appropriate enzyme studies on cultured skin fibroblasts or white blood cells. In the second programme on mucopolysaccharidosis we shall be covering biochemical aspects and looking at recent research.

<End credits>