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X-linked spondyloepiphyseal dysplasia tarda: mucopolysaccharide excretion studies

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SUMMARY Sex linked spondyloepiphyseal dysplasia tarda is described in a family with four affected members. The characteristic features of short trunk, hip disease, and flattening of the vertebrae with a posterior "hump" were present. Urinary mucopolysaccharides were characterized both quantitatively and qualitatively and were within normal values.

Key words: Spondyloepiphyseal Dysplasia Tarda, Mucopolysaccharide Excretion.

A variety of skeletal anomalies are classified as spondyloepiphyseal dysplasia (SED), including the Morquio Syndrome (Type IV of the Mucopolysaccharidoses) (1,2). However, it is important for physicians to be aware of the different disease entities within the general class of SED, for prognosis is variable and genetic counseling quite different.

Recently we had the opportunity to study a family in which four members had the X-linked tarda form of SED. This entity has a good prognosis, and as the name implies, has sex-linked recessive inheritance. One of the affected individuals, however, had previously been mis-diagnosed as the Morquio Syndrome (poorer prognosis and autosomal recessive inheritance).

Thus, we feel it pertinent to describe the family and call attention to the clinical features of X-linked SED tarda. Moreover, since there is some similarity between the vertebral changes in X-linked SED and the mucopolysaccharidoses (especially Type IV), we investigated the mucopolysaccharide (glycosaminoglycan or GAG) excretion in this family. GAG excretion has not been previously described in X-linked SED tarda.

CASE REPORTS

Ji: The propositus presented at age 22 because of hip pain. He had become aware

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of short stature during early adolescence, when he also experienced mild, non-incapacitating back and hip pain. As a child he had had bilateral inguinal hernias repaired. After graduating from high school, he was employed with his brother in a dental laboratory.

Physical examination of Ji showed a height of 148.6 cm. The neck was short and the trunk shortened, producing a "barrel" chest (see Figure 1). Motion of the back was

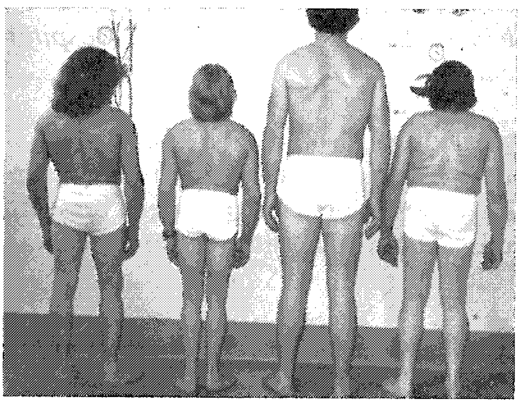

Fig. 1. Posterior view of affected boys (Ji, P and D) and their normal brother (Jo). Left to right: Ji (age 22 yrs.); P (age 21 yrs.); Jo (age 26 yrs); and D (age 28 yrs). Note the short neck, broad thorax, and short trunk (spine). Also the carriage of the hips suggests abnormality.

good in all ranges, but the right hip was painful on motion in all directions. Except for moderate hypertension (140/100 right arm sitting), the remainder of the physical examination was normal. There were no other skeletal anomalies, and corneas appeared normal.

D: Twenty-eight year old brother of Ji, also is a high school graduate and runs his own dental lab. He, too, had had bilateral inguinal hernias repaired. Physical examination showed hypertension (140/100 right arm sitting, on propranolol), height 149.9 cm., a short trunk, barrel chest and decreased motion in both hips. Slit lamp examination of the corneas was normal.

P: Twenty-one year old sibling, is a college student. In high school he was on the wrestling team. He is now experiencing mild back and hip pain. As a child he had had bilateral inguinal hernias repaired. On examination the blood pressure was 140/100, height 142.2 cm., with similar trunk changes as his brothers. He had mild discomfort on hip motion. Otherwise the examination was normal.

The family is of Polish-Finnish extraction. A maternal uncle, a college graduate electrical engineer, is similarly affected. The uncle is 152.4 cm. tall and at 60 years of age has had bilateral total hip arthroplasties. No one in the family is aware of any members similarly affected beyond the uncle and the three siblings described above.

Other siblings of the propositus include a 26 year old brother, Jo, who is 170.2 cm. tall and of normal build (Figure 1), with a normal physical examination. There are three sisters, ages 12,17 and 21 years all of whom are normal. Their mother had hypertension and died of a cerebrovascular accident at age 39. Their father of normal stature is alive and well.

X-ray studies of the axial skeleton showed similar changes in all three affected brothers. The spine (Figure 2) showed flattening of the vertebrae (platyspondylie), producing the short trunk, but also a peculiar and characteristic dorsal "hump" on the vertebral body, best seen in lateral projection. In addition, the hips showed bilaterally shallow acetabulae, with shortening of the femoral neck, and what was interpreted as "early degenerative changes" of the femoral head. Stained peripheral blood smears did not show basophilic (GAG) stippling.

Glycosaminoglycan (GAG) Excretion Studies

Twenty-four hour urine specimens were obtained from the three affected brothers and their uncle. Volume and creatinine content suggested complete collections. GAG was isolated using cetylpyridinium chloride

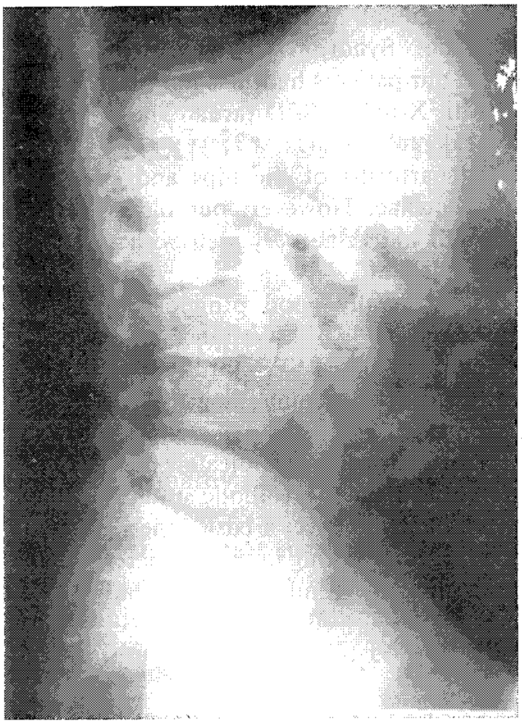

Fig. 2. Lateral x-ray of lumbar spine of Ji. Note the flattening of vertebra, suggestion of increased A-P length of vertebral bodies, with the characteristic posterior hump.

(3), and measured as uronic acid using a carbazole method (4). The values for the uncle, Ji, D and P were 19.3., 5.4, 5.7 and 7.7 mg/24 hours, respectively, all within the normal range. Assay by the orcinal method (5), which gives characteristically higher values with iduronic acid (dermatan sulfate) than does the carbazole method resulted in ratios of 1.4, 1.1, 1.3 and 1.4, (carbazole:orcinal) respectively, indicating that dermatan sulfate was not present. Hexosamine determinations (6), on purified material gave ratios of 1:1, (uronic acid:hexosamine), indicating the material studied was indeed a GAG.

To ascertain if keratan was present, ethanol molar ratio fractionation of the calcium salts was done, with a 50% and 80% fraction collected. All of the GAG except keratan should precipitate in the 50% fraction, leaving keratan in solution. The keratan should then precipitate in the 80% fraction. This latter fraction was then assayed for neutral sugar (7), and for galactose using the enzyme galactose oxidase (Galactostat, Worthington Biochem. Co.). Only negligible quantities were found by either method, indicating the presence of little or no keratan. We concluded that the GAG excretion (and hence metabolism) was normal in these patients.

DISCUSSION

Drs. Spanger and Langer (1) refer to the term, "Spondyloepiphyseal Dysplasia" as generic and descriptive, and one applied generally to patients with short trunk dwarfism. In the differential diagnosis they list in addition to X-linked SED tarda, other forms of spondyloepiphyseal dysplasia, chondrodysplasia punctata, the mucopolysaccharidoses (including the Morquio Syndrome), congenital hypothyroidism and the Dyggve-Melchior-Clausen Syndrome.

Prior to the work of Drs. Maroteaux, Lamy and Bernard (9) spondyloepiphyseal dysplasia tarda was thought to be a form of the Morquio Syndrome.

Perhaps because of training or exposure many rheumatologists first consider the mucopolysaccharidoses in the diagnosis of short-trunk dwarfism. Indeed, our patients were first, and incorrectly, so diagnosed. McKusick (11) has extensively described these various syndromes. The Hurler and Hunter Syndromes (MPSI and II) may be differentiated from X-linked SED tarda by abnormalities early in childhood; visceral organ involvement; large amounts of Dermatan and Heparan in the urine (due to lack of the enzyme iduronidase). Corneal clouding is often a feature as is mental retardation, but not in all variations (i.e., MPS I S or MPS II B). MPS IV, the Morquio Syndrome more closely resembles X-linked SED tarda, but the lateral view of the vertebra shows only platyspondylisis and not a dorsal "hump". Clouding of the cornea may occur, as do skin abnormalities, looseness of the joints and neurologic abnormalities secondary to the spinal defects. Two variations are recognized, that with excess Keratan sulfate in the urine and that without. In the former, with advancing age, the Keratan sulfaturia decreases.

The features previously described (8,9) for X-linked SED tarda include short stature, primarily truncal, with short neck, barrel chest and abnormal development of the hips. The vertebral bodies characteristically have a dorsal "hump" or thickening compared to the anterior surface, which is diagnostic (10). This is seen best in lateral X-ray views of the lumbar-spine. Our patients met all these criteria. In our family the mode of inheritance appears to be sex-linked recessive. Inguinal hernias (described with the Morquio Syndrome) and hypertension, which our patients had, has not been reported with X-linked SED tarda. These may be coincidental findings.

Osteoarthritis of the hips and spine are late sequelae. However, our oldest patient (age 60) has done very well with total hip arthroplasties.

The generally good prognosis, plus the sex-linked mode of inheritance, make recognition of X-linked SED tarda especially important when counselling parents and patients.

While our studies indicate normal GAG excretion, further metabolic studies of these families may uncover a basic inherited metabolic defect resulting in the characteristic abnormalities of X-linked SED tarda.

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