

Multiple Endocrine Neoplasia Type 2A

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ease seemed to occur only in those patients with well-established medullary thyroid carcinoma or pheochromocytoma. Because more than 50% of affected individuals within the family eventually developed adrenal medullary abnormalities, screening in such families is mandatory.

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Editor's comment—*The potential for malignancy of multiple endocrine neoplasia type 2A is frightening, but these new chromosomal and metabolic screening techniques allow us to recognize family members at risk. The screening techniques also suggest clear and reliable methods to be used in following at-risk individuals.*

Judith G. Hall, M.D.

the thinness of the enamel and abnormalities of cusp formation. These dental abnormalities are unique to Morquio syndrome and are not found in any of the other mucopolysaccharidoses or spondyloepiphyseal dysplasias.

The authors studied the clinical and radiographic dental changes in 12 patients with MPS IV A and found varying degrees of the characteristic dental changes in all. These dental changes, however, are not present in either MPS IV B (beta-galactosidase deficiency) or MPS IV C (enzyme defect unknown). Although these dental abnormalities are present in all cases of MPS IV A, they may only be demonstrable radiologically in some clinically mild atypical cases. The dental changes are highly specific and can be extremely useful in the diagnosis of clinically atypical cases of MPS IV A.

(III) Odontoid Dysplasia

Spinal cord compression in the upper cervical region related to odontoid dysplasia is a major complication of Morquio syndrome. In addition to the odontoid hypoplasia, spinal cord compression is thought to be due to the associated ligamentous laxity and hypertrophy of the posterior longitudinal ligament. The pectus carinatum and sternal protrusion invariably found in these patients might act as a protective mechanism in some cases by limiting neck flexion.

The authors studied the cervical spine radiographically in 12 patients with Morquio syndrome; all showed evidence of odontoid dysplasia. In seven, it was defined as minor and in none of these was there evidence of instability. In five patients, the odontoid dysplasia was defined as major, with evidence of atlantoaxial instability in all five. The five patients with severe dysplasia and instability had classical Morquio syndrome, while the seven with minor dysplasia had milder atypical forms.

Clinical Findings in Twelve Patients with Mucopolysaccharidosis IV A (Morquio Syndrome): Further Evidence of Heterogeneity

(I) Clinical and Biochemical Findings

Morquio syndrome has long been known as a distinct mucopolysaccharidosis (MPS) characterized by short trunk dwarfism with skeletal radiographic changes quite distinct from those of the other mucopolysaccharidoses, as well as corneal clouding, enamel dysplasia, and urinary excretion of keratin sulfate. In recent years, heterogeneity in Morquio syndrome has been delineated, with three main types described: MPS IV A, associated with N-acetylgalactosamine-6-sulfate sulfatase deficiency; MPS IV B, with beta-galactosidase deficiency; and MPS IV C, with mild manifestations in which the enzyme defect has not been determined.

The authors describe the clinical findings in 12 cases of MPS IV A and document markedly variable clinical presentations, with some cases only mildly affected. Nevertheless, all cases show deficiency of N-acetylgalactosamine-6-sulfate sulfatase in fibroblasts. The patients with the mildest clinical presentation showed a high residual enzyme activity, although several

had markedly diminished enzyme activity.

The urinary glycosaminoglycans (GAGs) were also examined in all patients by a two-dimensional electrophoresis technique that proved to be highly reliable and efficient. In particular, no false-negative results were obtained, which is often a problem with routine screening methods.

The authors divided MPS IV A into three subgroups: the severe "classical" type, an intermediate type, and a mild type, all caused by N-acetylgalactosamine-6-sulfate sulfatase deficiency. Residual enzyme activity may be an important prognostic indicator for each subgroup.

(II) Dental Findings

Dental changes associated with Morquio syndrome have been recognized for some time. They are characterized by a thin enamel layer, with tooth surfaces marked by numerous, minute, irregularly distributed pits. The teeth, which are smaller than normal, are separated by spaces and the enamel appears to be structurally weak. Radiologic examination confirms

Long-term follow-up, with detailed neurological assessment, is essential in patients with Morquio syndrome. Any suggestion that the upper cervical cord is compromised by atlantoaxial instability should be investigated further by computerized tomography (with contrast dye) or by magnetic resonance imaging (MRI) so that the possibility of posterior fusion of the upper cervical spine can be considered in patients likely to benefit from this procedure. The degree of odontoid hypoplasia correlates well with the overall clinical severity of the condition, although the patients were of different ages when studied. Indeed, age-related variation in the dysplasia is another factor that must be taken into account.

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Editor's comment—These papers clearly demonstrate that, in addition to the known genetic heterogeneity in Morquio syndrome, there is significant clinical variability within individuals having the same enzyme deficiency state (N-acetylgalactosamine-6-sulfate sulfatase). These findings are similar to those that have been described in the other mucopolysaccharidoses: ie, in MPS I, deficiencies of alpha-1-iduronidase can be associated with typical Hurler syndrome, the very mild Sheie syndrome, or a variety of intermediate clinical states known as "compound heterozygotes"; the mild and severe forms of the Hunter syndrome associated with iduronate sulfate sulfatase deficiency; and the mild and severe forms of the Maroteaux-Lamy syndrome (MPS VI) associated with deficiency of arylsulphatase B. Thus, there appears to be both inter- and intramolecular heterogeneity in these disorders. Deficiencies of different enzymes due to mutations in different genes may produce similar clinical features:

ie, the San Filippo syndrome (MPS III A, B, C, and D) and Morquio syndrome (MPS IV A, B, and C). In contrast, different mutations along the same gene, resulting in variable deficiencies of the same enzyme, can produce marked clinical variability with severe and mild forms of the same phenotype.

The authors found that the enamel hypoplasia characteristic of Morquio syndrome is seen in all patients with MPS IV A, but is not present in MPS IV B or C. It therefore may be of diagnostic potential in cases of MPS IV, although in the mild forms of the disease, radiographs may be necessary to detect the enamel dysplasia. It is of interest that it is the enamel that is involved in Morquio syndrome, which is characterized by lysosomal vacuolization in epithelial-like cells. In osteogenesis imperfecta, where collagen is involved, it is the dentin that is abnormal.

Finally, the authors describe the variability in odontoid hypoplasia and atlantoaxial instability in pa-

tients with Morquio syndrome. Odontoid hypoplasia is characteristic of numerous skeletal dysplasias, including Morquio syndrome, the spondyloepiphyseal dysplasias, and metatropic dysplasia. Although it had been considered that all patients with Morquio syndrome have C1/C2 fusion of the spine because of the inevitability of atlantoaxial instability and spinal cord compression, the authors here demonstrate that in the mild forms of MPS IV A, there was no evidence of instability despite minor evidence of odontoid dysplasia. Nevertheless, all patients with Morquio syndrome must be followed longitudinally and with careful neurological and radiographic assessment of the C1/C2 area and cord. MRI, CT scanning, and neurophysiological studies should be done if there is any evidence of instability. If any evidence of spinal cord compression exists, fusion of the cervical spine is mandatory.

David L. Rimoin, M.D., Ph.D.

Genomic Imprinting— Genes Inherited From the Father May Act Differently Than the Same Genes When Inherited From the Mother: Four Reports

Research on embryogenesis in the mouse, utilizing transplantation and transgenic mice, indicates that maternally derived genes seem to play a greater role in the early development of the embryo, while paternally derived genes play a greater role in the development of the extraembryonic membranes. The pattern of DNA methylation is different and depends on whether the alleles on the mouse chromosomes are maternally or paternally derived. These observations have been interpreted to suggest that differential imprinting of the genome occurs during male and female gametogenesis. These

findings may help to explain why human diseases such as myotonic dystrophy and Huntington disease, both autosomal dominant disorders, may vary in severity depending on which parent passed on the gene.

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Editor's comment—This new work is startling, but "imprinting" has been observed by several groups. This suggests there are many such mechanisms at work in embryogenesis and early development that may be critical to normal growth.

Judith G. Hall, M.D.