



Richard M. Pauli, M.D., Ph.D.,  
Midwest Regional Bone Dysplasia Clinics  
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## **MORQUIO SYNDROME NATURAL HISTORY**

### **INTRODUCTION:**

The following summary of the medical expectations in Morquio Syndrome is neither exhaustive nor cited. It is based upon the available literature as well as personal experience in the Midwest Regional Bone Dysplasia Clinics (MRBDC). It is meant to provide a guideline for the kinds of problems that may arise in individuals with this disorder, and particularly to help clinicians caring for a recently diagnosed child. For specific questions or more detailed discussions, feel free to contact MRBDC at the University of Wisconsin – Madison [phone – 608 262 6228; fax – 608 263 3496; email – [modaff@waisman.wisc.edu](mailto:modaff@waisman.wisc.edu)].

Morquio Syndrome is one of the mucopolysaccharide storage disorders. It affects around 1 in every 200,000 individuals, is pan ethnic, but varies in incidence quite markedly among different populations. Originally there were two subtypes distinguished as being caused by two different enzyme deficiencies. However, what had been termed “type B” is no longer considered to be Morquio Syndrome. Therefore Morquio Syndrome, Morquio Syndrome A, Morquio Syndrome Type A and mucopolysaccharidosis type IVA all refer to the same process.

As for most mucopolysaccharidoses, signs and symptoms are not present neonatally. Problems are usually first suspected by around 1-3 years of age and diagnostic confirmation is usually further delayed, most often occurring between 3 y and 10y of age (mean ~5 y). Typically first recognized features are gait abnormalities, abnormal leg position, chest deformity and/or slowing of growth.

Physical features that result in a recognizable phenotype include: disproportionate small stature with markedly foreshortened trunk; short neck; pectus carinatum; slender arms and legs; hip flexion contractures; knock knee deformity; facial coarsening (late in the course of the disorder and milder than in many mucopolysaccharidoses).

About 25% of affected individuals have what has been termed an “attenuated phenotype”. While they have defined and demonstrable mutations in the same gene, they have far milder phenotypic features than those with more typical Morquio Syndrome.

There is an International Registry from which additional natural history information should become available.

## **MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED**

### **PROBLEM: LIFE EXPECTANCY**

**EXPECTATIONS:** Historically most individuals suffered early death (in adolescence or early adulthood). Risks are clearly correlated with the severity of and effective management of cervical myelopathy, restrictive pulmonary disease and cardiac disease (see below). Even with optimal treatment, many affected individuals will die in early or mid-adulthood, although survival to the 6<sup>th</sup> or 7<sup>th</sup> decade is not rare.

**MONITORING:** -.

**INTERVENTION:** Sensitive counseling of the family and the affected individual is needed to address this issue.

### **PROBLEM: GROWTH**

**EXPECTATIONS:** Birth size is usually normal and growth remains normal for the first 1-2 years of life. Growth slowing then begins. Linear growth usually stops very early, most often between 7 and 12 years of age. (This fact has some relevance in the timing of various surgical interventions, since recurrence of deformity secondary to additional growth should not be expected after about 10 years of age.) Ultimate adult height ranges from about 80 cm to 140 cm (32" to 55") with mean heights of around 122 cm (48") in males and 113 cm (45") in females.

**MONITORING:** There are diagnostic growth grids (height, weight and BMI) available. These should be used to monitor growth.

**INTERVENTION:** There is no known treatment. Short stature means that there will be considerable adaptive needs in school and workplace etc.

### **PROBLEM: DEVELOPMENT**

**EXPECTATIONS:** Unlike most other mucopolysaccharidoses, intelligence is normal unless complications intervene. Variations in developmental patterns and, particularly, gross motor delays are to be expected because of the marked short stature and joint abnormalities.

**MONITORING:** Routine.

**INTERVENTION:** None.

### **PROBLEM: OPHTHALMOLOGIC**

**EXPECTATIONS:** Corneal clouding is a constant finding. It usually is not severe and usually causes little problem. Photophobia may be present. Experience suggests that surgical intervention is not appropriate even in the most severe cases, since recurrence is inevitable.

Rarely, other eye complications may develop – glaucoma (usually in adults); pigmentary degeneration of the retina (usually in adults and usually mild and clinically silent); cataracts (usually in adulthood but may be clinically significant).

**MONITORING:** Careful ophthalmologic evaluation every 1-2 years. In those older than around 10 y, assessment should include tonometry.

**INTERVENTION:** None is needed for corneal clouding or pigmentary retinopathy. Glaucoma and cataracts are treated as they would be in an otherwise average individual.

**PROBLEM: EARS AND HEARING**

**EXPECTATIONS:** Hearing loss often begins in mid-childhood. It is usually a mixed loss (both conductive and sensorineural components) and is frequently progressive. However, it rarely becomes worse than a moderate loss. Middle ear dysfunction is common.

**MONITORING:** Maintain a high level of clinical suspicion regarding middle ear disease. Hearing assessment, at least yearly, should be done beginning at diagnosis and continuing throughout life.

**INTERVENTION:** Aggressively treat middle ear dysfunction with use of pressure equalizing tubes as needed. Consider use of pneumococcal vaccine in hopes of reducing frequency of middle ear infections. Hearing aids, FM transmitter system in school, preferential seating etc. should be used in those with more than borderline loss.

**PROBLEM: DENTAL**

**EXPECTATIONS:** Enamel is uniformly abnormal – thin, rough and hypoplastic. This affects both the primary and secondary teeth. There is marked increased frequency of tooth fractures, flaking and caries.

**MONITORING:** All individuals should have early and aggressive dental care.

**INTERVENTION:** Consider early use of sealants, fluoride treatments. Orthodontia has been successful in those with Morquio Syndrome, but it must be done carefully because of the enamel abnormalities.

**PROBLEM: PULMONOLOGIC**

**EXPECTATIONS:** Breathing problems may arise either from restrictive or obstructive sequences. Restrictive pulmonologic disease can be secondary to the diminished chest size, anomalous chest shape with or without problems secondary to kyphoscoliosis. Obstructive symptoms are also multifactorial – intrinsically small airways, possibly accumulation of storage material in airways, and superimposed adenoidal and tonsillar hypertrophy. Breathing difficulties may also arise because of neurologic complications. Respiratory muscle paralysis secondary to cervical cord problems historically was a common cause of death; this should no longer be the case.

**MONITORING:** Involvement of a pulmonologist is almost always warranted. Careful clinical history and family observation of breathing in sleep should be followed by polysomnography if there is suspicion of obstruction. Pulmonary function testing should begin in late childhood, and should be repeated every 1-2 years.

**INTERVENTION:** If obstruction is identified, usual treatments are appropriate, e.g. tonsillectomy and adenoidectomy, use of cpap, etc. All individuals should receive influenza vaccine every year.

**PROBLEM: CARDIAC**

**EXPECTATIONS:** Mild heart disease is exceedingly common. It usually is valvular and usually left sided (aortic and mitral valves). It is remarkably benign in most children but may become important in adult life. Rarely, patients develop a cardiomyopathy.

**MONITORING:** Cardiologic and echocardiographic assessment should be completed at the time of diagnosis and probably every 2 to 3 years thereafter.

INTERVENTION: If valvular incompetence is present, should have SBE prophylaxis for dental work and surgeries.

**PROBLEM: CERVICAL SPINE**

EXPECTATIONS: This is one of the most critical issues in care of individuals with Morquio syndrome. High cervical myelopathy and/or sudden respiratory deaths may arise if not appropriately cared for. There appear to be three contributing factors to C-spine problems – odontoid hypoplasia, ligamentous laxity causing instability of C1-C2, and thickening of the soft tissues anterior to the upper cervical cord (presumably secondary to chronic movement-associated irritation). C-spine problems are virtually always present and are often progressive. C-spine compression may cause any of the following: slow, progressive myelopathy; sudden paralysis (particularly with injury); sudden death (probably secondary to ischemia of the respiratory control centers of the medulla); marked increased risks associated with anesthesia (see below). Early signs of myelopathy include: decreased endurance (for walking etc.); hyperreflexia and clonus, particularly in the legs; problems with bowel and/or bladder control. MONITORING: Lateral flexion, neutral and extension cervical spine x-rays should be obtained beginning at around 2 y of age and repeated yearly. Multiposition MRI with flow studies should be done if any instability is evident on C-spine films, or if any clinical suspicion of cervical myelopathy arises, and, in any event, beginning at around age 6 y and then repeated every 1-2 years.

INTERVENTION: There is a developing consensus that prophylactic fusion surgery is appropriate if there is any evidence for instability or compression. Surgical options that are most often recommended include the following: A. Occiput-C1-C2 posterior fusion in asymptomatic or minimally symptomatic individuals. This is often recommended at 6-8 y of age. This is less risky surgery than any other alternative and often allows for normalization of the os and the anterior soft tissues. B. Combined anterior and posterior approach with anterior decompression and combined fusion; this is appropriate in those who are already significantly symptomatic. (Note that posterior decompression is never indicated, is inappropriate, and has resulted in catastrophic outcomes.) Individuals who undergo fusion may develop instability just inferior to the terminus of the fusion and so need ongoing monitoring (neurologic reassessments, yearly C-spine plain films, multiposition MRI if symptoms recur).

**PROBLEM: KYPHOSIS AND KYPHOSCOLIOSIS**

EXPECTATIONS: This is common but highly variable in severity. There are no data in the literature about whether the curve can continue to progress after cessation of growth. However, early cessation of growth does mean that fusion surgery if needed can be done quite early without fear of development of disproportionate anterior growth of vertebrae. Kyphosis is sometimes sufficiently severe to cause neurologic abnormality secondary to cord tethering. MONITORING: Clinical spine assessment should be done yearly. If a curve is evident and progressive, then radiologic monitoring should be completed. In those with kyphosis, history of neurologic abnormality – increasing clumsiness, leg weakness, bowel and bladder incontinence, etc. should be sought.

INTERVENTION: The usual approaches to intervention are effective.

**PROBLEM: JOINT HYPERMOBILITY**

**EXPECTATIONS:** This particularly affects the small joints and, most severely, the wrists. It may be progressive. Wrist hypermobility may be sufficiently severe to affect activities of daily living, hand writing, etc.

**MONITORING:** Clinically assess severity of hypermobility and evaluate consequences on activities of daily living and school activities.

**INTERVENTION:** If wrist hypermobility is severe, wrist splinting may benefit fine motor functioning. Consider early keyboarding in school if hand writing is problematic.

**PROBLEM: COXA VALGA**

**EXPECTATIONS:** Hip changes are virtually constant. Coxa valga often progresses to complete disappearance of the femoral heads. Although one might expect that surgery for repositioning of the femoral heads would slow arthritic changes, this has not been demonstrated and surgery is not of any proven benefit.

**MONITORING:** -

**INTERVENTION:** -

**PROBLEM: GENU VALGUM**

**EXPECTATIONS:** Knock-knee deformity is virtually constant, usually severe and often debilitating.

**MONITORING:** Clinically assess severity of valgus deformity. Early referral to a pediatric orthopedist is appropriate.

**INTERVENTION:** Varus osteotomy surgery is clearly indicated. Timing of that surgery is often an issue. If done very early then there is a high probability of recurrence. However, since growth is completed in children with this disorder by around 10 y of age, this is a reasonable age to complete the surgery (if intervention is not essential before that time). There is general consensus that leg surgery should be done after cervical fusion is accomplished.

**PROBLEM: FOOT POSITION ABNORMALITIES**

**EXPECTATIONS:** Clubbed/splayed/skewed feet are common (but only occasionally requiring surgery). Pes planus is virtually constant.

**MONITORING:** Clinical.

**INTERVENTION:** If pes planus is associated with pain with walking then in-the-shoe orthotics can be used.

**PROBLEM: ARTHRITIS**

**EXPECTATIONS:** Development of degenerative arthritic changes of weight bearing joints is common in adults.

**MONITORING:** Query adolescents and adults regarding chronic pain.

**INTERVENTION:** This commends limitation of repetitive weightbearing (often self imposed for other reasons by affected individuals). Both total hip and total knee replacement surgery have been accomplished in adults who develop intractable pain and disability secondary to degenerative arthritis. However, it is very challenging surgery that should be undertaken only by orthopedists with extensive experience with special circumstances.

**PROBLEM: OBESITY**

**EXPECTATIONS:** Low activity level predisposes to excess weight gain. Obesity can exacerbate the respiratory and orthopedic problems.

**MONITORING:** Diagnosis-specific charts for weight and for BMI are available.

**INTERVENTION:** Weight management should include low impact or non-weight bearing aerobic exercise program; aquatic therapy is particularly helpful (and is also beneficial for orthopedic complications).

**PROBLEM: ANESTHESIA RISK**

**EXPECTATIONS:** Risks are increased secondary to pulmonologic, cardiologic and neurologic sequelae.

**MONITORING:** Careful assessment of cervical spine status, pulmonologic status and cardiologic involvement should be completed prior to any anesthetic episode.

**INTERVENTION:** Fiberoptic intubation is usually needed and compulsive postoperative pulmonologic care is essential.

## **GENETICS AND MOLECULAR BIOLOGY**

Morquio Syndrome is an autosomal recessive process. That means that a couple who has had one child affected by this disorder will have a 25% risk that any subsequent child will also be affected. In contrast, the affected individual has very little risk to have an affected child. This is of some relevance since fertility in affected individuals is normal. Females have carried pregnancies to term, although respiratory compromise late in pregnancy is likely, and Cesarean section inevitable.

Morquio Syndrome arises secondary to deficiency of an enzyme called N-acetylgalactosamine-6-sulfatase. This results from loss of function mutations in both copies of the gene, *GALNS*. Many different mutations have been detected in *GALNS* and there is some genotypic-phenotypic correlation – that is, the mutations present to some extent predict the severity of clinical manifestations.