Natural History

MORQUIO SYNDROME
[MUCOPOLYSACCHARIDOSIS, TYPE IVA]

GENERAL INFORMATION:

MORQUIO SYNDROME IS AN AUTOSOMAL RECESSIVE PROCESS ESTIMATED TO AFFECT ABOUT 1 IN 100,000 INDIVIDUALS. THERE ARE TWO SUBTYPES, SECONDARY TO TWO DIFFERENT ENZYMATIC DEFICIENCIES. TYPE A IS SECONDARY TO DEFICIENCY OF N ACETYLGALACTOSAMINE 6 SULFATASE. CLINICAL SYMPTOMS RESULT FROM GRADUAL ACCUMULATION OF STORAGE MATERIAL IN A VARIETY OF TISSUES.

AS FOR MOST MUCOPOLYSACCHARIDOSES, SIGNS AND SYMPTOMS ARE NOT PRESENT NEONATALLY. PROBLEMS USUALLY ARE SUSPECTED BY AROUND 1-3 Y OF AGE AND DIAGNOSTIC CONFIRMATION IS OFTEN DELAYED, MOST OFTEN OCCURRING BETWEEN AROUND 3 Y AND 10 Y OF AGE. TYPICALLY, FIRST RECOGNIZED FEATURES ARE AMONG THE FOLLOWING -- GAIT ABNORMALITY, ABNORMAL LEG POSITIONING, CHEST DEFORMITY, SLOWING OF GROWTH.

ISSUES OF RELEVANCE FOR ANTICIPATORY MEDICAL CARE:

GROWTH --

BIRTH SIZE IS USUALLY NORMAL AND GROWTH REMAINS NORMAL FOR THE FIRST COUPLE OF YEARS OF LIFE. LINEAR GROWTH USUALLY STOPS VERY EARLY, MOST OFTEN BETWEEN 7 Y AND 12 Y 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 Y OF AGE.]

ULTIMATE ADULT HEIGHT RANGES FROM 80 TO 120 CM (32 IN TO 48 IN).

NO GROWTH CURVES ARE AVAILABLE.

SMALL STATURE MEANS THAT THERE WILL BE CONSIDERABLE ADAPTIVE NEEDS, E.G. IN THE SCHOOL SETTING.

OPHTHALMOLOGIC --

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 MOST SEVERE CASES, SINCE RECURRENCE IS INEVITABLE.

RARELY, OTHER EYE COMPLICATIONS MAY DEVELOP, INCLUDING

GLAUCOMA: USUALLY ARISES IN ADULTHOOD. *TONOMETRY SHOULD BE PART OF OPHTHALMOLOGIC EXAMINATIONS BEGINNING IN EARLY ADOLESCENCE.*

PIGMENTARY DEGENERATION OF THE RETINA: USUALLY ARISES IN ADULTHOOD AND IS USUALLY MILD AND CLINICALLY SILENT.

CATARACTS: USUALLY ARISE IN ADULTHOOD BUT MAY BE CLINICALLY SIGNIFICANT

RECOMMENDATIONS:

- *ALL INDIVIDUALS SHOULD HAVE CAREFUL OPHTHALMOLOGIC EVALUATION (INCLUDING TONOMETRY IN THOSE OLDER THAN AROUND 10 Y) EVERY 1 TO 2 YEARS.*

OTOLOGIC --

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.

RECOMMENDATIONS:

- *FREQUENT HEARING ASSESSMENT, AT LEAST YEARLY, THROUGHOUT LIFE.*
- *AGGRESSIVE TREATMENT OF 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-MILD LOSS.*
- *SURGERY IS NOT INDICATED.*

DENTAL --

ENAMEL IS UNIFORMLY ABNORMAL. THERE IS MARKED INCREASE IN TOOTH FRACTURES, FLAKING AND CARIES.

RECOMMENDATIONS:

- *EARLY, AGGRESSIVE ROUTINE DENTAL CARE.*
- *CONSIDER EARLY USE OF SEALANTS.*

CERVICAL SPINE --

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.

RECOMMENDATIONS:

- *LATERAL FLEXION, NEUTRAL AND EXTENSION C-SPINE XRAYS BEGINNING AT AROUND 2 Y OF AGE AND REPEATED YEARLY.*
- *MULTIPOSITION MRI WITH FLOW STUDIES IF ANY INSTABILITY ON C-SPINE FILMS, OR IF ANY CLINICAL SUSPICION AND, IN ANY EVENT, BEGINNING AT AROUND AGE 6 Y.*

- *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. 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).*

KYPHOSCOLIOSIS

THIS IS COMMON BUT HIGHLY VARIABLE IN SEVERITY. SEVERE KYPHOSIS MAY CAUSE THORACIC CORD COMPRESSION. THERE IS 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 POSTERIOR FUSION IF NEEDED FOR SCOLIOSIS CAN BE DONE QUITE EARLY WITHOUT FEAR OF DEVELOPMENT OF DISPROPORTIONATE ANTERIOR GROWTH OF VERTEBRAE.

RECOMMENDATIONS:

- *CLINICAL SPINE ASSESSMENT YEARLY.*
- *IF CLINICAL CURVE IS APPARENT, RADIOLOGIC MONITORING.*
- *IF PROGRESSIVE, USUAL KINDS OF INTERVENTION ARE EFFECTIVE.*

PULMONOLOGIC

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, ?ACCUMULATION OF STORAGE MATERIAL IN AIRWAYS, ADENOIDAL AND TONSILLAR HYPERTROPHY.

RECOMMENDATIONS:

- *CAREFUL CLINICAL HISTORY AND OBSERVATION OF BREATHING IN SLEEP.*
- *POLYSOMNOGRAPHY IF ANY SUSPICION OF OBSTRUCTION.*
- *PULMONARY FUNCTION TESTING, PROBABLY BEGINNING IN LATE CHILDHOOD, AND REPEATED EVERY 1-2 YEARS.*
- *IF OBSTRUCTION IS IDENTIFIED, USUAL TREATMENTS ARE APPROPRIATE, E.G. TONSILLECTOMY AND ADENOIDECTOMY, USE OF CPAP ETC.*
- *INFLUENZA VACCINE EVERY YEAR.*

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.

CARDIAC

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.

RECOMMENDATIONS:

- *CARDIOLOGIC AND ECHOCARDIOGRAPHIC ASSESSMENT, PROBABLY EVERY 2 TO 3 YEARS.*
- *IF VALVULAR INCOMPETENCE IS PRESENT SHOULD HAVE SBE PROPHYLAXIS FOR DENTAL WORK AND SURGERIES.*

JOINT HYPERMOBILITY

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.

RECOMMENDATIONS:

- *IF WRIST HYPERMOBILITY IS SEVERE, WRIST SPLINTING MAY BENEFIT FINE MOTOR FUNCTIONING.*
- *CONSIDER EARLY KEYBOARDING IN SCHOOL IF HAND WRITING IS PROBLEMATIC.*

COXA VALGA

HIP CHANGES ARE VIRTUALLY CONSTANT. COXA VALGA OFTEN PROGRESSES TO COMPLETE DISAPPEARANCE OF THE FEMORAL HEADS. SURGICAL INTERVENTION HAS NOT SEEMED TO BE OF ANY BENEFIT. HIP REPLACEMENT CAN BE SUCCESSFULLY CARRIED OUT IN ADULTS WITH INTRACTABLE PAIN AND DISABILITY.

GENU VALGUM

KNOCK-KNEE DEFORMITY IS VIRTUALLY CONSTANT, USUALLY SEVERE AND OFTEN DEBILITATING.

RECOMMENDATIONS:

- *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).*
- *GENERAL CONSENSUS IS THAT LEG SURGERY SHOULD BE DONE AFTER CERVICAL FUSION IS ACCOMPLISHED.*

FOOT POSITION ABNORMALITIES

CLUBBED/SPLAYED/SKEWED FEET ARE COMMON. ONLY OCCASIONALLY IS SURGERY REQUIRED.

PES PLANUS IS VIRTUALLY CONSTANT. USUALLY THIS REQUIRES NO INTERVENTION. IF SYMPTOMATIC, *IN-THE-SHOE ORTHOTICS* CAN BE USED.

LATE ONSET ARTHRITIS

DEGENERATIVE ARTHRITIC CHANGES OF WEIGHT BEARING JOINTS IS COMMON IN ADULTS. THIS WOULD COMMEND *LIMITATION OF REPETITIVE WEIGHT BEARING* (OFTEN SELF IMPOSED FOR OTHER REASONS BY AFFECTED INDIVIDUALS).

BOTH *TOTAL HIP AND TOTAL KNEE REPLACEMENT* SURGERY HAS BEEN ACCOMPLISHED IN ADULTS, ALTHOUGH IT IS VERY DIFFICULT SURGERY THAT SHOULD BE UNDERTAKEN ONLY BY ORTHOPEDISTS WITH EXTENSIVE EXPERIENCE WITH SPECIAL CIRCUMSTANCES.

OBESITY

LOW ACTIVITY LEVEL PREDISPOSES TO EXCESS WEIGHT GAIN. OBESITY CAN EXACERBATE THE RESPIRATORY AND ORTHOPEDIC PROBLEMS.

RECOMMENDATIONS:

- *LOW IMPACT OR NON WEIGHTBEARING AEROBIC EXERCISE PROGRAM .*
- *AQUATIC THERAPY (WHICH IS ALSO BENEFICIAL FOR ORTHOPEDIC COMPLICATIONS).*

LIFE EXPECTANCY

HISTORICALLY MANY INDIVIDUALS SUFFERED EARLY DEATH (ADOLESCENCE OR EARLY ADULTHOOD). *RISKS ARE CLEARLY CORRELATED WITH THE SEVERITY OF AND EFFECTIVE MANAGEMENT OF CERVICAL MYELOPATHY*, RESTRICTIVE PULMONARY DISEASE AND CARDIAC DISEASE.

MISCELLANEOUS

FERTILITY IS NORMAL.

FEMALES HAVE CARRIED PREGNANCIES ALTHOUGH RESPIRATORY COMPROMISE IS LIKELY AND C-SECTION INEVITABLE.

ANESTHESIA RISKS REQUIRE FIBEROPTIC INTUBATION AND COMPULSIVE POSTOPERATIVE PULMONOLOGIC CARE.