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## **HYPOCHONDROPLASIA NATURAL HISTORY**

### **INTRODUCTION:**

The following summary of the medical expectations in Hypochondroplasia 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 children 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)].

Hypochondroplasia is one of a ‘family’ of bone dysplasias caused by gain of function mutations in the *FGFR3* gene that codes for the type 3 fibroblast growth factor receptor. Other members of this family (which share many features but which vary markedly in severity) include, for example, achondroplasia, SADDAN syndrome and thanatophoric dysplasia. This gene codes for a protein essential for recognition of growth stimuli and signal transduction in those cells normally stimulated. This particular growth factor receptor appears to be particularly crucial in cartilage and bone growth. Hypochondroplasia is the mildest in this series of related disorders. Medical complications are, in general, fewer and milder than in achondroplasia. However, as outlined below, there are a couple of exceptions.

An international collaborative study of hypochondroplasia was undertaken a few years ago. Unfortunately, none of the clinically relevant data that was collected has been published.

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

#### **PROBLEM: LIFE EXPECTANCY**

**EXPECTATIONS:** No mortality studies have been done, but it appears that individuals with hypochondroplasia have completely normal life expectancy.

**MONITORING:** -

**INTERVENTION:** -

**PROBLEM: GROWTH**

**EXPECTATIONS:** There is marked variability of growth potential with ultimate adult height ranging from about 3 feet 10 inches to 5 feet 5 inches (118-165 cm) and a median adult height of around 4 feet 8 inches. Note that growth in the first 1-3 years may be near normal, and, in relatively mildly affected individuals, this may result in delay in diagnosis. Rare individuals have been identified who have body disproportion but ultimate height within the normal range who have the usual, common hypochondroplasia mutation.

**MONITORING:** No diagnostic specific growth grids have been generated. One might elect to monitor growth using achondroplasia-specific growth grids keeping in mind that both growth velocity and growth potential may exceed these standards in some.

**INTERVENTION:** No known treatment. Growth hormone trials show only very limited effect as would be anticipated since this disorder is secondary to intrinsic abnormality of bone growth. Limb lengthening is chosen by a small minority of affected individuals. Extended limb lengthening is a complex process and, if chosen, should only be performed in a multidisciplinary setting. When done in the U.S., in general, extended limb lengthening is performed in teenage years.

**PROBLEM: HEAD GROWTH AND RISK FOR HYDROCEPHALUS**

**EXPECTATIONS:** In about 50% of children macrocephaly will be present. This is far more frequent in those with the common mutation in *FGFR3* (see below under Genetics and Molecular Biology). In most this macrocephaly is secondary to benign ventriculomegaly and excess extraaxial fluid accumulation. In an unknown but probably very tiny minority (i.e. less than 5%) symptomatic hydrocephalus requiring shunting will develop.

**MONITORING:** Those with macrocephaly (above +2 standard deviations on regular head circumference growth grids) should have baseline neuroimaging in infancy or early childhood to assess ventricle size and volume of extraaxial fluid.

**INTERVENTION:** Repeat neuroimaging if head growth acceleration or signs/symptoms of hydrocephalus arise. Ventriculoperitoneal shunting should only be performed for symptomatic hydrocephalus.

**PROBLEM: SEIZURES**

**EXPECTATIONS:** A small minority – perhaps 5-10% – of individuals with hypochondroplasia have seizures. Often these will present as seizure-precipitated apnea. It appears that most (perhaps nearly all) individuals with seizures also have a structural abnormality of the brain termed temporal lobe dysgenesis.

**MONITORING:** Parents should be apprised of this risk so that they will recognize seizures should they occur. Any child with hypochondroplasia who has apneic episodes or seizure-like events should have both electroencephalography and magnetic resonance imaging of the brain.

**INTERVENTION:** Standard treatments for epilepsy can be used.

**PROBLEM: DEVELOPMENT**

**EXPECTATIONS:** Cognitive abilities are usually normal unless complications intervene. However, there appears to be an unexplained increased risk for both learning disabilities and mental

retardation. Learning disabilities (not recognizable until school age) may be present in as many as ½ of children with this diagnosis. Combining the larger series available in the literature suggests that 10-12% of children with hypochondroplasia have a secondary diagnosis of mental retardation. It appears that temporal lobe dysgenesis also is correlated with presence of mental retardation, but how strong this relationship is remains unknown at this time.

**MONITORING:** Periodic screening of development and more formal assessment should suspicion of serious delays arise.

**INTERVENTION:** Usually only reassurance is needed. Special programming will be required for those 10-12% with mental retardation and for some of those with specific, isolated learning disabilities.

**PROBLEM: EARS AND HEARING**

**EXPECTATIONS:** Many infants and young children with hypochondroplasia will develop recurrent or persistent middle ear dysfunction with conductive hearing loss (although this risk is considerably less than in children with achondroplasia). If not aggressively treated, this may contribute to delays in language and speech development. Middle ear dysfunction is often resistant to medical management.

**MONITORING:** Behavioral audiometric and tympanometric assessment, first at 9-12 months of age and at least yearly throughout early childhood. One should have a high level of suspicion that middle ear problems are present.

**INTERVENTION:** Aggressive use of myringotomy and tube placement. If a child needs ventilation tubes, then they should be maintained until 6-8 years of age, since it appears that eustachian tube autonomy typically does not develop until then.

**PROBLEM: LIMITED ELBOW EXTENSION**

**EXPECTATIONS:** Limitation ranging from 20° to 60° is common. When present this may further limit functionally effective reach (e.g. for toileting).

**MONITORING:** Clinical assessment.

**INTERVENTION:** Use of adaptive devices (e.g. bottom wiper) as needed.

**PROBLEM: VARUS DEFORMITY**

**EXPECTATIONS:** Progressive varus at the knees and of the mesial segments of the legs arises in around 10-20% of affected children.

**MONITORING:** Clinical monitoring for position and determination if the three weight-bearing joints of the leg remain in plumb. Clinical history should inquire about pain with ambulation, decreased endurance, decreased activity level etc.

**INTERVENTION:** If joints become significantly out of plumb or if position is associated with marked pain, then surgical intervention is needed. A variety of surgical options are available including use of 8-plates, epiphysiodesis and open osteotomies. Most often correction is by proximal tibial and fibular valgus and derotational osteotomies, with either internal or external fixation.

**PROBLEM: ADAPTIVE**

**EXPECTATIONS:** Considerable psychological and physical adaptive needs may arise later in childhood in those with severe small stature.

**MONITORING:** Assess for age appropriate needs.

**INTERVENTION:** School adaptations, stools, adaptations for toileting, teacher involvement, Little People of America involvement etc. may all be appropriate.

## **GENETICS AND MOLECULAR BIOLOGY**

Hypochondroplasia appears always to be caused by an autosomal dominant gene abnormality. This means that an adult with this disorder will have a 50% chance to pass this poorly functional gene on to each child (although special risks are present if both parents are affected). Not infrequently an individual with this disorder will be born to average statured parents. When this happens it is because of a new chance change (mutation). This means that the risk for recurrence in a next pregnancy is virtually zero.

In around 70% of those with Hypochondroplasia have a specific mutation of the Fibroblast Growth Factor Receptor type 3 (*FGFR3*) gene. Preliminary information suggests that medical expectations in those with and those without this 'common mutation' may differ.