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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 Clinic. 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 clinic at the University of Wisconsin – Madison [phone – 608-915-0680; fax – 608 263-0530.

Hypochondroplasia is one of a 'family' of bone dysplasias caused by gain of function variants in the *FGFR3* gene that codes for the type 3 fibroblast growth factor receptor. This family of conditions includes achondroplasia, SADDAN syndrome, and thanatophoric dysplasia, all resulting from different variants in the FGFR3 gene. FGFR3 is involved in bones that grow through cartilage which are 90% of the bones in our bodies. The variant resulting in hypochondroplasia causes bone growth to slow. It also causes different cognitive (thinking and learning) features. Hypochondroplasia is the mildest in this series of related disorders from a physical standpoint, but cognitive features may be more significant.

MEDICAL ISSUES AND PARENTAL CONCERNS TO BE ANTICIPATED

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

GROWTH
EXPECTATIONS: There is marked variability of growth potential with ultimate adult height ranging from about 4 feet 2 inches to 5 feet 5 inches (128-165 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 variant.
MONITORING: Recent growth curves from a British cohort have been published by Cheung et al. A blunted pubertal growth spurt is to be expected.
INTERVENTION: Recent clinical trials in children with hypochondroplasia have shown improved growth with vosoritide with between 1.8 and 2cm/year of additional growth. Vosoritide is a daily CNP injection with was initially approved for increasing growth in children with achondroplasia. 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. Complications of extended limb lengthening do occur, though more infrequently than they did initially, and they do not appear to be diagnosis specific.

HEAD GROWTH AND RISK FOR HYDROCEPHALUS

EXPECTATIONS: Macrocephaly is common, Mild findings of midface hypoplasia may be seen, but true midface retrusion and bossing are usually not seen. 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 ventriculoperitoneal 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 extra-axial fluid.
INTERVENTION: Repeat neuroimaging if head growth acceleration or signs/symptoms of hydrocephalus arise. Ventriculoperitoneal shunting should only be performed for symptomatic hydrocephalus.

CRANIOCERVICAL JUNCTION ASSOCIATED RISKS

EXPECTATIONS: The foramen magnum is narrower than in average stature individuals, but not so narrow that there is a significant risk of stenosis requiring decompression in the early years. Anecdotally, there is increased occurrence of Chiari malformation.
MONITORING: Do complete neurological exam every time patient is seen to look for hypotonia, hyperreflexia, clonus, or asymmetries. If there are concerns, consider neuroimaging and polysomnography looking for sleep disordered breathing. In children with interest in participating in higher-impact sports or wrestling, an MRI is warranted to look at the upper cervical spinal cord.
INTERVENTION: Suboccipital decompression surgery may be considered in severe cases, especially if Chiari is seen.

SPINAL STENOSIS

EXPECTATIONS: Increased likelihood of spinal stenosis in adulthood, but milder than in achondroplasia.
MONITORING: Good neurologic exam with every encounter. Assess distance able to be walked without pausing.
INTERVENTION: Surgery (laminectomy) in severe cases. Sometimes fusion is necessary.

SEIZURES

EXPECTATIONS: Seizures are more common in patients with hypochondroplasia, These can present as seizure-precipitated apnea in the newborn period. Seizures almost always have onset during childhood. See CNS DIFFERENCES below
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. There may be an increased risk of persistent seizures if medicines are weaned off.

CNS DIFFERENCES

EXPECTATIONS: macrocephaly is common. Temporal lobe folding differences are also common and present in the majority of patients with FGFR3+ hypochondroplasia.
MONITORING: Baseline MRI with particular attention to the temporal lobes.
INTERVENTION: Monitor for learning and cognitive differences.

DEVELOPMENT – INCLUDING NEURODEVELOPMENT

EXPECTATIONS: Neurodevelopmental differences occur. Intellectual disability and learning disabilities are higher in children with hypochondroplasia than in children with average stature or achondroplasia. Learning disabilities (not recognizable until school age) may be present in as many as ½ of children with this diagnosis.
MONITORING: Developmental screening at routine encounters. If concerns arise, referral to developmental pediatrics is warranted. If concerns arise during school age, early neuropsychological evaluation is recommended.
INTERVENTION: An individualized education plan (IEP) may be considered and implemented.

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, they are usually required until about 6-8 years of age which is a later age than in average stature individuals.

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.

KNEE 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 (hemiepiphysiodesis) and derotational osteotomies. Most often 8 plates (hemi-epiphysiodesis) with constriction across one half of the growth plate are used.

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 can all be obtained with a written 504 plan. Little People of America and Little Legs Big Heart are two support organizations for people with skeletal dysplasia.

GENETICS AND MOLECULAR BIOLOGY

Hypochondroplasia appears almost 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 the pathogenic FGFR3 variant (although special risks are present if both parents are affected). Many times, an individual with hypochondroplasia 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.

About 70 % of those with Hypochondroplasia have a specific variation in the Fibroblast Growth Factor Receptor type 3 (*FGFR3*) gene, with about 50% of children having the same change at the same site.

Prenatal diagnosis with ultrasound, amniocentesis for FGFR3, and fetal MRI has been done. Pre-implantation genetic screening has also been done.

Medications are in development to improve growth in children with Hypochondroplasia including injectable medications and oral medications.