Hypochondroplasia

Overview

Hypochondroplasia, like achondroplasia, is a form of disproportionate dwarfism caused by a mutation in the fibroblast growth factor receptor 3 protein. It is the mildest dysplasia in the FGFR3 family. The frequency of the disease is unknown, but it is estimated to affect one in every 15,000 to 40,000 newborns. Children with hypochondroplasia are at a higher risk for cognitive delays, hydrocephalus and seizures but may also experience hearing difficulties and/or bowed legs. Our observations show that individuals with hypochondroplasia have normal life expectancies.

Heredity and genetics

The FGFR3 gene encodes the fibroblast growth factor receptor 3 on chromosome 4. In its functional state, FGFR3 is a membrane-spanning receptor that is active in slowing the production and development of cartilage. A mutation in the receptor causes the protein to be overexpressed, decreasing bone growth and causing disproportionately small stature. In 70 percent of cases, there is a common mutation in the gene, but mutations in other parts of the gene can also occur. The overexpression and enhanced ability of the protein to delay bone growth is known as a “gain-of-function” mutation.

Hypochondroplasia is inherited in an autosomal dominant pattern, meaning only one mutant copy of the gene must be present to have the disorder. As a result, affected individuals have a 50 percent chance of passing the abnormal gene to their offspring. However, hypochondroplasia can also appear in people with no prior family history of the disease. In these situations, a spontaneous mutation was introduced. The risk of having another child with a spontaneous mutation resulting in hypochondroplasia is near zero. The severity of the disease varies among individuals and can therefore have varying effects on stature.

Diagnosis and testing

Growth appears to be average during the first three years of life but begins to slow as the child ages. If the child is born to average-statured parents, a diagnosis may not take place until several years into childhood. At this point, genetic testing, radiologic imaging and clinical examinations may be used to confirm a diagnosis of hypochondroplasia. However, hypochondroplasia may be confirmed without a specific FGFR3 mutation, indicating there may be more genes involved in the disease. If there is a family history of the disease, similar techniques may be used to confirm a diagnosis at an earlier age.
Clinical features:

- Short stature
  - Adult height ranges from 3-foot-10 to 5-5
  - Median adult height: 4-8
- Mild macrocephaly
- Disproportionately short arms and legs
- Short, broad hands and feet
- Joint contractures
- Bowed legs

Radiographic features:

- Decrease interpediculate distance of the lumbar spine
- Shortened tubular bones
- Shortened, squared iliac bones and horizontal acetabula
- Broad femoral neck
- Mild metaphyseal abnormalities

**Orthopaedic problems and treatment**

**Growth monitoring**

There are no hypochondroplasia-specific growth charts, so there is no growth monitoring guidelines. Some may choose to monitor using achondroplasia growth charts, but due to the variability in stature for hypochondroplasia, one may outgrow the chart at some point.

Limb-lengthening can be used to increase stature but should only be performed by surgeons trained in skeletal dysplasias. Patients should be old enough to make an informed decision regarding lengthening and weigh the benefits versus the risks.

**Elbow contractures**

Limitation in fully extending the elbows is common and usually ranges between 20 and 60 degrees shy of extension. Adaptive devices may be needed for personal hygiene.

**Leg alignment abnormalities**

Genu varum, or “leg-bowing,” affects an estimated 10-20 percent of all children with hypochondroplasia and can arise from hypotonia, internal tibia torsion or twisting, and/or knee instability. A physical exam should be used to monitor genu varum, searching specifically for a lateral thrust (the appearance that the knee suddenly jumps out to the side while walking). A
series of X-rays called an “extremity alignment series” is also necessary to monitor the mechanical axis of the femoral head, knees and ankles.

Surgical intervention is typically not necessary but may be if the patient experiences extremity pain or in the case of a lateral thrust. Surgery may include 8-plate or derotational osteotomy.

Other common problems and treatment

Development

Existing literature indicates people with hypochondroplasia have an increased risk for learning disabilities and mental retardation. Learning disabilities may be present in an estimated 50 percent of people and may not be noticeable until the child is of school age. Cognitive disabilities are present in 10-12 percent of children. There are multiple areas of possible structural brain abnormalities, including enlarged temporal lobes, hippocampal dysplasia and temporal lobe dysgenesis. Intermittent developmental screening can assess if delays may be present. If there is concern for serious delays, a more formal assessment may be performed. If the child is determined to have learning disabilities or mental retardation, learning accommodations may be necessary for classroom purposes.

Seizures

Although the risks are relatively low — around 5-10 percent — seizures are possible. Seizures may present as apnea, so families should be aware of what apnea is and looks like so they can better recognize when seizures occur. Nearly all individuals with seizure have temporal lobe dysgenesis, a structural abnormality in the part of the brain responsible for hearing and language comprehension. Epilepsy treatments may be used to address seizures.

Risk for Hydrocephalus

Large head size occurs in about half the children with the common FGFR3 mutation. In children, this may be accompanied with excess fluid in the brain, which may or may not need treatment. Symptomatic hydrocephalus presents in less than 5 percent of children with hypochondroplasia. Ventricle size and extra-axial fluid volume should be assessed in infancy using neuroimaging to establish a baseline for those with macrocephaly. If head growth begins to accelerate more rapidly or symptoms of hydrocephalus are present, repeat neuroimaging is appropriate. Ventriculoperitoneal shunting is only necessary when symptomatic hydrocephalus is present. Parents should be aware and check for signs of increased intracranial pressure. Symptoms include, but are not limited to, the following:

- Rapid increase of head circumference
- Seizures
• Irritability
• Vomiting
• Headaches
• Blurred or double vision
• Poor coordination

Ears and hearing

Middle ear dysfunction and/or conductive hearing loss is common in individuals with hypochondroplasia. If not treated from an early age, language and speech developmental delays may occur. Middle ear dysfunction often isn’t manageable. Hearing tests (behavioral audiometric and tympanometric) should be completed around 9-12 months of age and then repeated annually. Myringotomy and pressure-equalizing tubes should be used. Ventilating tubes, should the child need them, should be used until age 6-8. After this age, the Eustachian tubes should be functioning well and ventilation tubes are usually no longer necessary.

Resources

General information

http://www.lpaonline.org/assets/documents/NH%20Hypochondroplasia1.pdf  
https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Hydrocephalus-Fact-Sheet

Little People of America

http://www.lpaonline.org/

Adaptive products

http://www.lpaonline.org/adaptive-products-