

Case study # 39

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ACHONDROPLASIA

LEARNING OBJECTIVES

- 1) Explain the epidemiology and prevalence of Achondroplasia.
- 2) Describe the typical presentation of Achondroplasia.
- 3) Describe the prognosis and treatment for Achondroplasia.
- 4) Name the genes involved and mode of inheritance for Achondroplasia.
- 5) Create a genetic counseling plan for a patient and the family members of a person with Achondroplasia.

PRETEST QUESTIONS

1. Achondroplasia is a hereditary disorder with which of the following symptoms?
 - a) short stature
 - b) large head with prominent forehead
 - c) spinal kyphosis or lordosis
 - d) shortening of proximal limbs
 - e) all of the above
2. The prevalence of Achondroplasia is approximately?
 - a) 1:25000
 - b) 1:10000
 - c) 1:6000
 - d) 1:290
 - e) 1:100
3. Through what mode of inheritance is Achondroplasia acquired?

- a) Autosomal dominant
- b) Autosomal recessive
- c) X-linked
- d) Incomplete penetrance
- e) Multivariant inheritance

4. What percentage of patients with Achondroplasia have phenotypically normal parents?

- a) 10%
- b) 25%
- c) 50%
- d) 80%
- e) 100%

5. A person with Achondroplasia has what chance of passing it along to his/her child?

- a) 25%
- b) 50%
- c) 66%
- d) 75%
- e) 100%

Answers: 1. e 2. a 3. a 4. d 5. b

CASE STUDY

A mother gives birth to a 4 lb, 3 ounce baby boy. The birth was an uncomplicated spontaneous vaginal delivery. On initial physical exam after birth, it is noticed that the baby has a large head, extremely short stature, as well as shortening of both arms. The baby is also noticed to have facial hypoplasia and a saddle nose. Prenatal genetic testing was not performed on the couple. The father is of normal height, while the mother is slightly under average height at 4 ft 11 inches. The mother reports no drug or alcohol abuse during pregnancy. She took appropriate prenatal vitamins throughout pregnancy. The remaining physical exam is unremarkable.

DIFFERENTIAL DIAGNOSIS

Congenital hypophosphatasia, achondrogenesis, Rickets, osteomalacia, congenital brittle bones with joint contractures (Bruck syndrome), congenital brittle bones with craniosynostosis and ocular proptosis (Cole-Carpenter syndrome), juvenile Paget disease, juvenile osteoporosis and child abuse.

SYNONYMS

- ACH
- Achondroplastic dwarfism
- Chondrodystrophia fetalis
- Chondrodystrophy syndrome
- Congenital osteosclerosis
- Osteosclerosis congenita

EPIDEMIOLOGY AND PREVALENCE

Achondroplasia follows an autosomal dominant inheritance pattern, however most cases are due to spontaneous mutations. Its incidence rises with increasing paternal age.

Achondroplasia is the most common form of inherited disproportionate short stature. Its prevalence is approximately 1 in 15,000-40,000 live births.

PRESENTATION OF ACHONDROPLASIA

Achondroplasia is usually diagnosed based on characteristic clinical and radiographic findings. Achondroplasia is often diagnosed at birth or infancy. Common presenting clinical characteristics include a short stature, shortened arms and legs, along with a large head and characteristic hypoplastic facial features. Other features may include bowing of the legs, long thin trunk, decreased muscle tone, spinal stenosis, and limited elbow extension. Radiographic findings include narrowing of the interpediculate distance of the caudal spine, sacroiliac groove notching, and shortening and thickening of the long bones with metaphyseal flaring.

PROGNOSIS AND TREATMENT OF ACHONDROPLASIA

Prognosis for achondroplasia varies depending on the severity of the patient's disease. Approximately 5% of newborns with achondroplasia will not survive the first year of life. These are considered to be the extremely severe forms of the disease because the majority

of patients with the disease will live a normal life span. Patients diagnosed with achondroplasia will usually have a normal intelligence level. However, they will rarely ever reach 5 feet in height. Severity of the disease is usually determined by whether the patient is homozygous or heterozygous for the abnormal FGFR3 gene.

Currently, there is no cure or specific treatment for achondroplasia, but many treatments have been used with varied success. Pharmacologic, as well as surgical therapies are available if needed. It is important to monitor the patient's growth, especially during the first year of life. This includes height, weight, head circumference, and upper to lower extremity ratio. Therapies are often targeted at the clinical manifestations of the disease instead of a cure for achondroplasia. It is very important to control weight in these patients in order to avoid obesity. Growth hormone therapy has been used in an attempt to promote growth in achondroplasia patients. Study results from GH use in achondroplasia have been mixed. Some studies have shown an increase in growth velocity in the first 2 years of use. Safety concerns have arisen with the concern that GH therapy increases the deposition of abnormal bone leading to complicated orthopaedic problems for the patients. Anti-inflammatory agents have had success in those patients with degenerative joint disease. Surgical procedures that have shown success include leg lengthening procedures, lumbar laminectomy, spinal fusion, and surgery to release craniomedullary compression can improve neurologic function. Patients should also seek referrals for neurosurgeons, ENT specialists, orthopaedists, and pulmonologists as needed for clinical complications of the disease. Genetic testing and counseling is also advised as means of patient education for this familial disorder and for future prenatal recommendations. Support groups are also available for those families affected by the disease.

GENES ARE INVOLVED WITH ACHONDROPLASIA

Mutations in the FGFR3 gene cause achondroplasia. FGFR3 stands for Fibroblast Growth Factor Receptor gene. The mutation involved is an autosomal dominant mutation. The FGFR3 gene offers instructions for making a protein that is involved in the development and maintenance of bone and brain tissue. This protein limits the ossification of cartilage, especially in the long bones. Two specific mutations in the FGFR3 gene are responsible for almost all cases of achondroplasia. In about 98% of cases, a G to A point mutation at nucleotide 1138 of the FGFR3 gene causes a glycine to arginine substitution. About 1%

of cases are caused by a G to C point mutation at nucleotide 1138. It is hypothesized that these mutations cause the protein to be overly active, which interferes with skeletal development and leads to the disturbances in bone growth seen with this disorder.

People with achondroplasia have one normal copy of the fibroblast growth factor receptor 3 gene and one mutant copy. Two copies of the mutant gene are invariably fatal before or shortly after birth. Only one copy of the gene needs to be present for the disorder to occur. In the majority of cases, however, people with achondroplasia are born to parents who do not have the condition (carry the gene). This is the result of a new mutation. New gene mutations are associated with increasing paternal age. Studies have demonstrated that new gene mutations are exclusively inherited from the father and occur during spermatogenesis.

GENETIC COUNSELING IN ACHONDROPLASIA

Achondroplasia is inherited in an autosomal dominant manner. As previously stated, over 80% of individuals with achondroplasia have parents of normal stature and have achondroplasia as the result of a de novo gene mutation. Such parents have a low risk of having another child with achondroplasia. An individual with achondroplasia, who has a reproductive partner without achondroplasia, has a 50% risk in each pregnancy of having a child with achondroplasia. When both parents have achondroplasia, the risk to their offspring of having achondroplasia is 50% and of having homozygous achondroplasia which is a lethal condition, 25%. Prenatal molecular genetic testing is available for all couples interested but physicians should use their experience as to when testing should be ordered.

PATIENT INFORMATION RESOURCES

Quick References and Fact Sheet

http://www.marchofdimes.com/professionals/14332_1204.asp

Support Groups

<http://www.achondroplasia.co.uk/>
<http://www.cafamily.org.uk/Direct/a14.html>

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