

CARTILAGE-HAIR HYPOPLASIA

(Metaphyseal chondrodysplasia autosomal recessive)

DESCRIPTION :

Cartilage-hair hypoplasia is a constitutional bone diagnosis caused by mutations in the *RMRP* gene. Its name comes from the characteristic appearance of the hair of those affected; the hair grows slowly, is thin and sparse, and appears blond or pale.

The condition causes moderate to marked short stature; adult height is generally between 122 cm (4 ft) and 132 cm (4 ft 4 in). This type of dwarfism is inherited in an autosomal recessive fashion [refer to “genetics” factsheet]. Most prevalent within the Amish community (1 birth in 1,500) and among the Finnish population (1 birth in 23,000) however, it is observed in approximately 1 out of 200,000 births throughout the rest of the world.

CHARACTERISTICS AND DIAGNOSIS :

As the name suggests, Cartilage-hair hypoplasia mainly affects the cartilaginous bones and the hair. The main physical features include:

- Short stature;
- Typical hair;
- Short limbs;
- Little hands and little feet;
- Legs sometimes oriented in varus (knees turned outwards);
- Lordosis (hollow in the lower back) and/or moderate scoliosis (sideways curvature);
- Hyperlaxity of the joints (excessive mobility).

Although short stature is a characteristic already present at birth, the diagnosis is often made around the second year of life. X-ray imaging reveal lesions of the metaphyses (growth plates located under the heads of the bones), particularly in the knees and the epiphyses (heads of bones). The diagnosis is confirmed by sequencing the *RMRP* gene.

Also, of note is the observation that most people affected by cartilage-hair hypoplasia often have an immune deficiency, anemia (low red blood cell count) and/or lymphopenia (low white blood cell count) (see next section).

MAIN POSSIBLE COMPLICATIONS :

Disorders of intestinal absorption: About 8% of those affected have difficulty absorbing nutrients from food, which can lead to chronic diarrhea and can exacerbate growth impedance in the neonatal period. In addition, some individuals suffer from Hirschsprung's disease, which manifests itself from birth as severe constipation. Surgery is often needed to treat these complications.



Neck (cervical spine): Less than 10% of people have cervical instability (hypermobility of the neck vertebrae). If so, there is a risk of spinal cord compression, a serious problem that can cause slow and gradual myelopathy (damage to the spinal cord) and paralysis.

The first signs of myelopathy are: decreased endurance and muscle tone, hyperreflexia (exaggerated reflexes) and clonus (rapid contractions and reflexes of the limbs), especially in the legs and problems with bowel and/or bladder control (incontinence, etc.).

Because of these risks, radiographic examinations of the cervical region should be performed as soon as the diagnosis of cartilage-hair hypoplasia is made, then upon entering school, and every 5 years until adulthood. If instability is detected, an MRI (magnetic resonance imaging) will be required for a more detailed assessment.

In case of complications arising, it will be necessary to consult a surgeon specialized in the disorders of the spine. If the instability is severe, decompression with fusion of the cervical spine should be performed.

Immune Deficiency: The vast majority of people with cartilage-hair hypoplasia have an immune deficiency. Due to a decrease in the production of white blood cells (lymphopenia) and a decrease in the production of immune cells, immune deficiency will lead to an increase in infections, especially during infancy and/or childhood.

About 50 to 60% of individuals are prone to recurrent and serious infections. Serious attention should be paid to infections occurring in the first two years of life, as these can be fatal. Bacterial pneumonia, in particular, is the leading cause of death. Therefore, children (and adults) with immune dysfunction should be closely monitored for significant respiratory infection.

Because of these risks, affected children should undergo a comprehensive immunologic assessment to determine whether impaired T cell function or B cell function (immune deficiency) is present. Blood tests should also be done to check for lymphopenia. Evaluations must be done annually. For people with normal or near normal test results, an annual reassessment after 6 years of age is not necessary.

A small number of people (less than 5%) have severe combined immunodeficiency. For these patients, a bone marrow transplant is indicated. The transplant may also be considered for people who have severe recurrent infections or early bronchiectasis (see below).

Bronchiectasis: This diagnosis of the bronchioles can occur in people with a history of recurrent lung infections. They should perform lung function tests from the age of 5 to 7 years. The main signs of bronchiectasis are chronic cough, sputum, shortness of breath, wheezing and fatigue. If bronchiectasis is suspected, seek help from a pediatric pulmonologist who can perform a CT scan of the chest to confirm the condition.

Varicella (chickenpox): People with cartilage-hair hypoplasia are very vulnerable to chickenpox, which can be fatal. Therefore, affected children should not be vaccinated against chickenpox. Exposure to chickenpox should be avoided however, if the child is exposed, an



anti-varicella immunoglobulin (VariZIG) should be administered. In the case of infection, it is appropriate to use the antiviral drug Acyclovir.

Anemia (low red blood cell count): This affects about 80% of people with cartilage-hair hypoplasia, but is only significant in 15% of cases. Severe, life-threatening anemia occurs in 5% of cases.

Signs of anemia are paleness, fatigue, headache, unusual shortness of breath, tachycardia, dizziness and light-headedness. Because of the risks associated with anemia, blood tests should be done periodically. People with significant anemia should be referred to a pediatric hematologist. Bone marrow transplantation may be considered to treat persistent anemia. As for severe anemia, it requires periodic and permanent blood transfusions.

Autoimmune Diseases: Various autoimmune abnormalities can occur, especially in adults. Haemolytic anemia and thyroid dysfunction are thus sometimes observed.

Hashimoto's thyroiditis, which affects the thyroid, involves weight gain, drowsiness and intolerance to cold. Doctors managing adults with this diagnosis should watch for symptoms suggestive of a possible autoimmune disease.

Cancer: The risk of cancer from cartilage-hair hypoplasia is estimated to be around 11%. The most common cancers are non-Hodgkin lymphoma (cancer of the white blood cells), squamous cell carcinoma and basal cell carcinoma (cancers of the skin), as well as leukemia (cancer of the blood). Most of the cancers reported were seen in individuals aged 15 to 45 years.

Because of these risks, clinical monitoring, including careful examination of the skin, should begin in early adolescence. It is also advisable to protect oneself from the sun, for prevention.

TREATMENT:

The management of cartilage-hair hypoplasia is primarily symptomatic and requires the collaboration of a team of specialists, including pediatricians, orthopedists, dermatologists, immunologists, hematologists, gastroenterologists and physiatrists.

Regarding short stature, treatment with growth hormone shows only a limited effect in the case of cartilage-hair hypoplasia. As for limb lengthening, a controversial therapeutic practice, it is used very rarely.

List of the main elements to monitor and address [refer to the factsheet "Frequent interventions in little people"]:

- Intestinal disorders;
- Cervical instability with risk of spinal cord compression;
- Immune deficiency;
- Bronchial disease;
- Varicella;



- Anemia;
- Autoimmune diseases and cancer.

RESOURCES :

Association québécoise des personnes de petite taille

<https://www.aqppt.org/>

Little People of Ontario

<https://littlepeopleofontario.com/>

Regroupement québécois des maladies orphelines - Centre iRARE

<https://rqmo.org/centre-dinformation-et-de-ressources-en-maladies-rares/>

Orphanet

https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=FR&Expert=175

Little people of America

<https://www.lpaonline.org/assets/documents/NH%20Cartilage%20Hair%20Hyoplasia.pdf>

NORD – National Organisation for Rare Disorders

<https://rarediseases.org/rare-diseases/mckusick-type-metaphyseal-chondrodysplasia/>



Please contact us for more information

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